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Mitochondrial Membrane Permeabilization in Cell Death

GUIDO KROEMER, LORENZO GALLUZZI, AND CATHERINE BRENNER

Institut Gustave Roussy, Institut National de la Santé et de la Recherche Médicale Unit "Apoptosis, Cancer and Immunity," Université de Paris-Sud XI, Villejuif; and Centre National de la Recherche Scientifique UMR 8159, Université de Versailles/Saint-Quentin en Yvelines, Versailles, France

Kroemer G, Galluzzi L, Brenner C. Mitochondrial Membrane Permeabilization in Cell Death. *Physiol Rev* 87: 99–163, 2007; doi:10.1152/physrev.00013.2006.—Irrespective of the morphological features of end-stage cell death (that may be apoptotic, necrotic, autophagic, or mitotic), mitochondrial membrane permeabilization (MMP) is frequently the decisive event that delimits the frontier between survival and death. Thus mitochondrial membranes constitute the battleground on which opposing signals combat to seal the cell's fate. Local players that determine the propensity to MMP include the pro- and antiapoptotic members of the Bcl-2 family, proteins from the mitochondrial

permeability transition pore complex, as well as a plethora of interacting partners including mitochondrial lipids. Intermediate metabolites, redox processes, sphingolipids, ion gradients, transcription factors, as well as kinases and phosphatases link lethal and vital signals emanating from distinct subcellular compartments to mitochondria. Thus mitochondria integrate a variety of proapoptotic signals. Once MMP has been induced, it causes the release of catabolic hydrolases and activators of such enzymes (including those of caspases) from mitochondria. These catabolic enzymes as well as the cessation of the bioenergetic and redox functions of mitochondria finally lead to cell death, meaning that mitochondria coordinate the late stage of cellular demise. Pathological cell death induced by ischemia/reperfusion, intoxication with xenobiotics, neurodegenerative diseases, or viral infection also relies on MMP as a critical event. The inhibition of MMP constitutes an important strategy for the pharmaceutical prevention of unwarranted cell death. Conversely, induction of MMP in tumor cells constitutes the goal of anticancer chemotherapy.

I. INTRODUCTION

Throughout the second half of the 20th century, mitochondria were exclusively considered as the cell's powerhouse, organelles whose particular architecture and biochemical composition would serve one major purpose, namely, maximization of energy production by oxidative phosphorylation. While many graduate students in chemical, biological, and medical sciences discretely abhorred mitochondria as a site of major metabolic pathways, it became clear around 1995 that mitochondria have a second crucial function, namely, the control of cell death. The discovery that mitochondria control cell death has revitalized the fields of mitochondrial bioenergetics and genetics and has revolutionized the field of cell death research. At first, the idea of mitochondrial cell death control appeared counterintuitive. Specialists in bioenergetics and inveterate biochemists wondered how it is possible that the cell's vital forces concentrated in mitochondria could be perverted to serve a lethal purpose. Similarly, cell death researchers were initially reluctant to accept that an organelle that during apoptosis does not suffer any major alterations in its ultrastructure, for instance, compared with the nucleus, would control the fate of the cell.

Today, the initial resistance against the concept of mitochondrial cell death control has been overcome. Since 2001, more than 13,000 articles that simultaneously mention the keywords *apoptosis* and *mitochondrion* have been published in the Medline database. Nowadays, it is difficult to ignore that cell death, in both its physiological and pathological occurrence, is closely linked to mitochondrial structure and (dys)function. The flood of information running through mitochondrial cell death control is so important that it has become an arduous task to understand the complexity of mitochondrial death/life decision making without getting lost in details. The purpose of this review is to provide an ordered vision of mitochondrial cell death control.

In healthy cells, the inner mitochondrial membrane (IM), the frontier between the intermembrane/intercristae space and the matrix, is nearly impermeable to all ions, including protons. This allows complexes I–IV of the respiratory chain to build up, across IM, the proton gradient that is required for oxidative phosphorylation (521, 522). The charge imbalance that results from the generation of an electrochemical gradient across the IM forms the basis of the inner mitochondrial transmembrane potential ($\Delta\Psi_m$). Finally, the proton gradient is exploited by complex V of the respiratory chain to drive ATP synthesis. Therefore, the maintenance of the proton gradient is of vital importance for cellular bioenergetics (521, 522), meaning that all constituents of the mitochondrial matrix and all metabolites that cross the IM do so in a tightly regulated fashion, with the help of highly selective channels and transport proteins. Although a transient loss of the $\Delta\Psi_m$, through the "flickering" of one or several IM pores, may occur in physiological circumstances (404, 896), a long-lasting or permanent $\Delta\Psi_m$ dissipation is often associated with cell death (488, 880), as discussed in this review.

The permeability of the outer mitochondrial membrane (OM), which delimits the outer contour of mitochondria, is also well regulated, both in normal life and during cell death. It has been assumed that OM is freely permeable to small metabolites and solutes up to ~5 kDa, due to the presence of an abundant protein, the voltage-dependent anion channel (VDAC), that would allow for the diffusion of such solutes through the OM. However, this view has been challenged during recent years, because real-time measurements of mitochondrial Ca^{2+} concentrations coupled to manipulations of the OM protein composition revealed the existence of Ca^{2+} microdomains in which VDAC and a variety of additional OM proteins control and limit the diffusion of Ca^{2+} (152, 631). For a comprehensive and detailed analysis on this specific topic, the reader is referred to the excellent review by Rizzuto and Pozzan (648). In cell death, the OM permeability often increases, allowing for the release of soluble proteins that usually are retained within mitochondria, in the intermembrane space (IMS). The death-associated OM permeabilization is not only an accidental process but also a tightly regulated phenomenon, with major consequences for health and disease, as detailed in this review.

II. AN OVERVIEW OF CELL DEATH PATHWAYS

A. Apoptosis

In a pioneering study on ischemic liver injury, published in 1972, Kerr et al. (377) observed a novel type of cell death, dubbed "apoptosis," which appeared different from toxin-induced necrotic hepatocyte death. As revealed by electron microscopy, apoptotic cells form small round bodies that are surrounded by membranes and contain intact cytoplasmic organelles or parts of the nucleus. These bodies result from progressive cellular condensation and budding, and eventually are engulfed by resident phagocytic cells (e.g., epithelial cells or fibroblasts). The morphological changes that define apoptosis are nuclear pyknosis (chromatin condensation) and karyorhexis (nuclear fragmentation) (405). The phenomenon of apoptosis has been documented as a prominent player in normal embryonic and postembryonic development, as well as in pathological and therapeutic settings (638, 766). Indeed, apoptosis can be viewed as a process that eliminates superfluous, ectopic, damaged, or mutated cells according to the rule "better death than wrong." Disabled apoptosis is a pathogenic event that contributes to oncogenesis and cancer progression. Unwarranted apoptosis of postmitotic cells (such as neurons or cardiomyocytes) also causes disease. Acute massive apoptosis participates in the pathophysiology of infectious diseases, septic shock, and intoxications (638, 766).

Apoptosis is a genetically predetermined mechanism that may be elicited by several molecular pathways (Fig. 1). The best characterized and the most prominent ones are called the extrinsic and intrinsic pathways. In the extrinsic pathway (also known as "death receptor pathway"), apoptosis is triggered by the ligand-induced activation of death receptors at the cell surface. Such death receptors include the tumor necrosis factor (TNF) receptor-1, CD95/Fas (the receptor of CD95L/FasL), as well as the TNF-related apoptosis inducing ligand (TRAIL) receptors-1 and -2. In the intrinsic pathway (also called "mitochondrial pathway"), apoptosis results from an intracellular cascade of events in which mitochondrial permeabilization plays a crucial role (677).

Both routes to apoptotic death can be divided at least in three distinct phases: initiation, integration/decision, and execution/degradation (409). The initiation phase is highly heterogeneous and depends on the nature of the death-inducing signal, be it an extrinsic one (the ligation of a death receptor) or an intrinsic one [which may affect any cellular organelle including the nucleus, the endoplasmic reticulum (ER), lysosomes, or mitochondria]. The integration/decision phase involves the near-to-simultaneous activation of caspases and mitochondrial death effectors in a complex molecular interplay that will be dissected in this review. During this phase, the "decision to die" is taken and the "point of no return" is trespassed. The execution/degradation phase, which is essentially a post mortem process, is common to distinct types of apoptosis, meaning that the morphological and biochemical alterations that accompany late-stage apoptosis are independent of the initiating stimulus. Both the extrinsic and the intrinsic routes to apoptosis ultimately lead to cell shrinkage, chromatin condensation, nuclear fragmentation (which is frequently accompanied by internucleosomal DNA fragmentation), blebbing, and phosphatidylserine exposure on the surface of the plasma membrane (Fig. 1) (882).

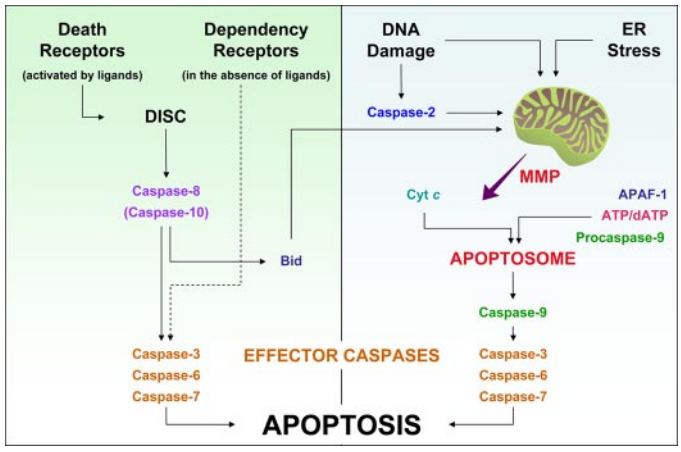


FIG. 1. Extrinsic versus intrinsic caspase activation cascades. *Left:* extrinsic pathway. The ligand-induced activation of death receptors induces the assembly of the death-inducing signaling complex (DISC) on the cytoplasmic side of the plasma membrane. This promotes the activation of caspase-8 (and possibly of caspase-10), which in turn is able to cleave effector caspase-3, -6, and -7. Caspase-8 can also proteolytically activate Bid, which promotes mitochondrial membrane permeabilization (MMP) and represents the main link between the extrinsic and intrinsic apoptotic pathways. The extrinsic pathway includes also the dependency receptors, which deliver a death signal in the absence of their ligands, through yet unidentified mediators. *Right*: intrinsic pathway. Several intracellular signals, including DNA damage and endoplasmic reticulum (ER) stress, converge on mitochondria to induce MMP, which causes the release of proapoptotic factors from the intermembrane space (IMS). Among these, cytochrome *c* (Cyt *c*) induces the apoptosis protease-activating factor 1 (APAF-1) and ATP/dATP to assemble the apoptosome, a molecular platform which promotes the proteolytic maturation of caspase-9. Active caspase-9, in turn, cleaves and activates the effector caspases, which finally lead to the apoptotic phenotype. DNA damage may signal also through the activation of caspase-2, which acts upstream mitochondria to favor MMP. See section II*A* for further details.

It appears that the activation of a specific class of proteases, the caspases ("cysteine protease cleaving after Asp"), is required for the rapid and full-blown manifestation of these features of apoptosis. However, not all caspases are required for apoptosis and the process generally results from the activation of a limited subset of caspases, in particular, caspases-3, -6, and -7 (231). These are the "executioner" caspases, and they mediate their effects by the cleavage of specific substrates in the cell.

Activation of the executioner caspases-3 and -7 by initiator caspases-8, -9, and -10 define the best understood apoptotic pathways (Fig. 1).

In the extrinsic pathway, ligation of death receptors [a subset of the TNF receptor (TNFR) family, including TNFR1, Fas/CD95, the TRAIL receptors -1 and -2, and probably the death receptor 3, also known as TRAMP, i.e., translocating chain-association membrane protein] causes the recruitment and oligomerization of the adapter molecule FADD (Fas-associating death domain-containing protein) within the death-inducing signaling complex (DISC). Oligomerized FADD binds the initiator caspases-8 and -10, causing their dimerization and activation (Fig. 1) (167). As an alternative, the extrinsic pathway can be activated by the so-called dependency receptors, which are believed to be connected to rapid caspase activation as well. In the absence of ligand, these receptors trigger cell death, thus generating a state of cellular dependence from their ligands. The prototype dependency receptors are the netrin-1 receptors DCC (deleted in colorectal cancer) and UNC5H-1, -2 and -3 (for a review, see Ref. 509).

Most cell death in vertebrates proceeds via the intrinsic or mitochondrial pathway of apoptosis (264). Here, the executioner caspases are cleaved and activated by the initiator caspase-9, which is activated by multimerization on the adapter molecule apoptosis protease activating factor 1 (APAF-1) within a multiprotein complex called "apoptosome." APAF-1 preexists in the cytosol as a monomer, and its activation depends on the presence of cytochrome *c* (Cyt *c*) and ATP/dATP (Figs. 1 and 2) (82). The release of Cyt *c*, which normally resides only in the IMS where it functions as an electron shuttle in the respiratory chain (49), is rate-limiting for the generation of the apoptosome. Hence, mitochondrial membrane permeabilization (MMP) is the critical event responsible for caspase activation in the intrinsic pathway. MMP can even commit a cell to die when caspases are not activated. This "caspase-independent death" (129, 407) can occur because of an irreversible loss of mitochondrial function as well as because of the mitochondrial release of caspase-independent death effectors including apoptosis-inducing factor (AIF) (742), endonuclease G (EndoG) (448), and others (Fig. 2) (129, 407).

The cross-talk between the extrinsic and intrinsic pathway has been extensively investigated for death receptors. In the so-called type 1 cells, ligation of death receptors causes the activation of effector caspases without the necessity of MMP. In contrast, in type 2 cells, a complex signaling cascade (caspase-8 activation → cleavage and activation of Bid → Bid-mediated Bax activation → MMP → Cyt *c*-dependent caspase-3 activation) critically depends on MMP as a conditio sine qua non for cell death induction (402, 677).

Because apoptosis is involved in the maintenance of tissue homeostasis, it is strictly controlled at multiple,

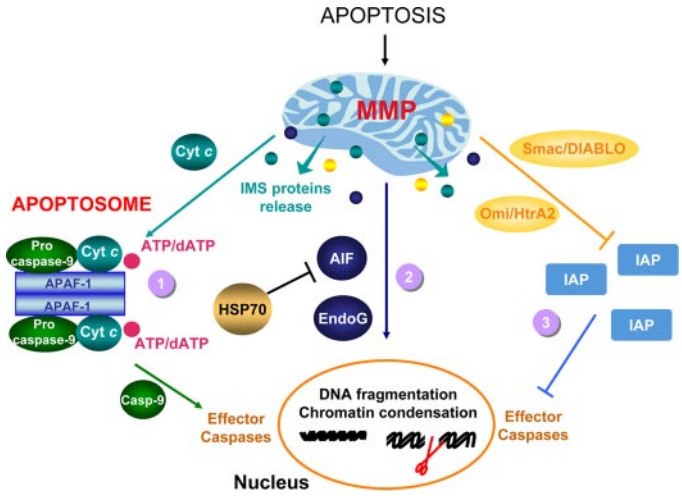


FIG. 2. Release of IMS proteins. Proapoptotic signals resulting in mitochondrial membrane permeabilization (MMP) provide intermembrane space (IMS) proteins with a route for release. Once in the cytosol, IMS proteins follow different fates. *1*) Cytochrome *c* (Cyt *c*) promotes the formation of the so-called "apoptosome," a molecular platform for the activation of caspase-9 (Casp-9) including also the apoptosis protease activating factor 1 (APAF-1) and ATP/dATP. In turn, active Casp-9 catalyzes the proteolytic activation of the effector caspases, which ultimately contribute to the appearance of the morphological hallmarks of apoptosis (e.g., DNA fragmentation and chromatin condensation). See sections IIA and VIIIA as well as Figure 1 for further information. *2*) The caspase-independent death effectors apoptosis-inducing factor (AIF) and endonuclease G (EndoG) translocate from the cytosol to the nuclear compartment where they favor DNA fragmentation and chromatin condensation. Members of the heat shock protein (HSP) family, like HSP70 (i.e., heat shock protein of 70 kDa), antagonize AIF proapoptotic activity by preventing its nuclear import. For additional details, see sections VIII, *C* and *D*, as well as Figure 11. *3*) Second mitochondria-derived activator of caspase/direct IAP binding protein with a low pI (Smac/DIABLO) and the Omi stress-regulated endoprotease/high temperature requirement protein A2 (Omi/HtrA2), promote apoptosis indirectly, by binding to and antagonizing members of the IAP (inhibitor of apoptosis protein) family. Under normal circumstances, IAPs would exert antiapoptotic effects by preventing the caspase activation. See section VIII*B* for more detailed information.

crucial levels (264). In numerous models, mitochondria represent a central checkpoint of apoptosis control by integrating various signals including endogenous factors [e.g., cytosolic and organellar concentrations of protons, Ca^{2+}, Mg^{2+}, K^+, and Na^+, metabolites such as ATP, ADP, NAD(P), glutathione, lipid second messengers, and multiple proteins including kinases and phosphatases] as well as exogenous factors (e.g., specific viral proteins or xenobiotics). These organelles collect the sum of death-inducing and life-preserving signals at the level of their membranes and, when the lethal signals predominate over the vital ones, mitochondria undergo MMP. MMP is characterized by several hallmarks that include *1*) the release of Cyt *c*, second mitochondria-derived activator of caspase/direct inhibitor of apoptosis binding protein (IAP) with a low pI (Smac/DIABLO), Omi stress-regulated endoprotease/high temperature requirement protein A2 (Omi/HtrA2) through the OM and the subsequent activa-

TABLE 1. *Consequences of MMP*

Examples	Mode of Action	Reference Nos.
	Apoptogenic proteins released from mitochondria	
AIF	Translocates to nucleus, where it interacts with DNA, activates cyclophilin A (latent DNase), and presumably recruits other proteins into the "degradosome"	83, 526, 742
AMID	AIF homolog	842
ARTS	Inactivates XIAP, a caspase inhibitor	261
	Translocates to nucleus and activates caspase-3	420
Bit1	AES, part of an integrin-controlled pathway of death (anoikis)	342
Cyt *c*	Activates apoptosome and, consequently, caspase-9 and caspase-3	78
	Deinhibits IP_3 receptor, thereby increasing cytosolic Ca^{2+}	62
	Its absence from mitochondria inhibits electron flow along the respiratory chain, thus favoring ROS generation, uncoupling, and mitochondrial dysfunction	890
EndoG	Translocates to nucleus, where it induces caspase-independent internucleosomal DNA cleavage	448
HSP10	Coactivates apoptosome	668
	Its absence from mitochondria favors the disruption of mitochondrial integrity and ATP generation	458
HSP60	Coactivates apoptosome	668
	Its absence from mitochondria favors the disruption of mitochondrial integrity and ATP generation	458
IκBα	Inhibits NFκB	64
Omi/HtrA2	Inhibits IAPs	744, 794
	Serine protease, actively contribute to caspase-independent cell death	744, 794
Pro-caspase-2	Caspase	741
Pro-caspase-3	Caspase	487
Pro-caspase-8	Caspase	627
Pro-caspase-9	Caspase directly activated by ROS	368, 741
Smac/DIABLO	Inhibits IAPs and indirectly activates caspases	187, 793
	Metabolic alterations	
Cessation of ATP synthesis	Bioenergetic crisis, mitochondria become net consumers of ATP	645
Ca^{2+} release	Loss of $\Delta\Psi_m$	897
	Can participate in intracellular intermitochondrial amplification loops	323, 580
ROS generation	Uncoupling and inhibited electron transfer; PTPC opening	400
	Can participate in intracellular intermitochondrial amplification loops	898
	Morphological alterations of mitochondria	
Change from filiform to punctuate network	Mitochondrial fission/fusion impairment	365
Targeting of mitochondria to autophagic removal	CsA-sensitive PT may target mitochondria for autophagy	107

See text for definitions.

tion of effector caspases (Fig. 2); *2*) the release of caspase-independent apoptogenic death effectors, such as AIF and EndoG (Fig. 2); *3*) an alteration of the $\Delta\Psi_m$ of the IM; and *4*) a bioenergetic catastrophe including the arrest of oxidative phosphorylation, as well as the accumulation of reactive oxygen species (ROS) (Table 1). The multiple relationships existing between apoptosis and bioenergetics are depicted in Figure 3. The kinetic order in which these alterations occur depends on the mechanisms of MMP and in particular whether these mechanisms primarily affect IM or OM, as discussed later in this review.

Defects in initial signal transduction (initiation phase) or in the integration/decision phase of apoptosis can arrest the lethal process. On the contrary, defects in the execution/degradation phase will not affect the fatal outcome, yet change the phenotypic manifestations of cell death, shifting it to a subapoptotic, necrotic, or autophagic appearance. Accordingly, inhibition of caspases has often negligible or little cytoprotective effects, although it drastically affects the morphological appearance of cell death.

B. Autophagic Cell Death

While apoptosis involves the explosive activation of catabolic enzymes leading to the demolition of cellular structures and organelles, autophagy is a slow, circumscript phenomenon in which parts of the cytoplasm are sequestered within double-membraned vacuoles and finally digested by lysosomal hydrolases (406). The functional relationship between apoptosis and autophagy is complex, and autophagy may either contribute to cell death (710) or constitute a cellular defense against acute stress, in particular induced by deprivation of nutrients or

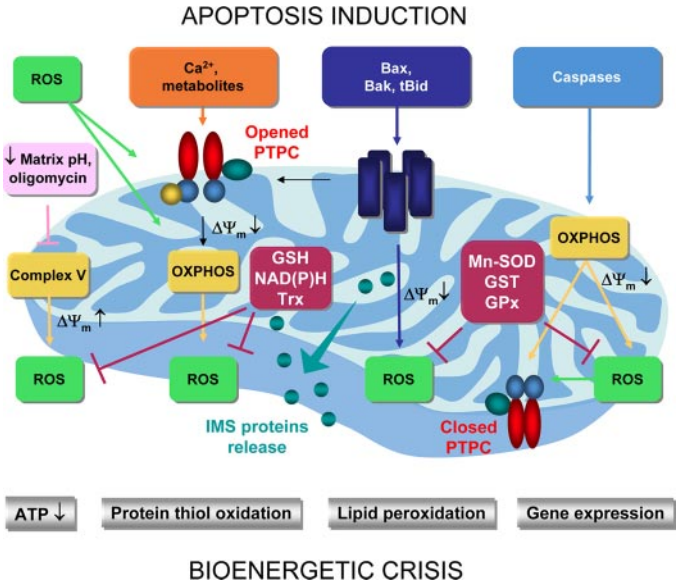


FIG. 3. Multiple intersections between apoptosis and bioenergetics. Mitochondria are the cell's powerhouse, the site where the vast majority of ATP is synthesized. ATP synthesis is driven by the electrochemical gradient built across the inner mitochondrial membrane (IM) by the oxidative phosphorylation complexes (OXPHOS). To generate this electrochemical gradient, OXPHOS pump protons from the matrix to the intermembrane space (IMS), thus leading to the formation of a transmembrane potential ($\Delta\Psi_m$) as well as to the generation of reactive oxygen species (ROS). In healthy cells, ROS are kept at harmless levels by the activity of both nonenzymatic and enzymatic antioxidant systems. Among the former, a prominent role is played by nonoxidized glutathione (GSH), thioredoxin (Trx), and NAD(P)H. On the other hand, glutathione-*S*-transferase (GST), glutathione peroxidase (GPx), and the manganese-dependent superoxide dismutase (Mn-SOD) represent redox-active enzymes. This delicate equilibrium breaks down when apoptosis is induced, following distinct but sometimes overlapping mechanisms. $\Delta\Psi_m$ dissipation is promoted by proapoptotic stimuli as diverse as members of the Bcl-2 family of proteins (Bax, Bak, tBid), Ca^{2+} and cytosolic metabolites (all of which promote the opening of the PTPC, i.e., the permeability transition pore complex), and the activation of caspases (that may degrade OXPHOS subunits). The progressive loss of $\Delta\Psi_m$ is often accompanied by an increased generation of ROS, which quickly saturate the antioxidant systems and induce the functional impairment of mitochondria, by arresting oxidative phosphorylation and via feed-forward mechanisms on the PTPC. ROS may accumulate also upon an increase of $\Delta\Psi_m$, as induced by inhibitors of the ATP synthase (complex V) like oligomycin or by the acidification of the mitochondrial matrix. Finally, decreased ATP production, protein thiol oxidation, lipid peroxidation, and the activation of stress response genes intervene, in the scenario of a bioenergetic crisis that progressively leads the cell to death.

obligate growth factors (28, 67). Cells that are deprived from exogenous energy sources catabolize part of their cytoplasm to generate ATP and other intermediate metabolites that allow them to meet their essential energetic demand. Moreover, autophagy allows for the turnover of cytoplasmic regions including protein aggregates and damaged organelles. Thus autophagy prevents the accumulation of misfolded proteins in inclusion bodies, a function that may exert neuroprotective effects. As an example, mice expressing mutant huntingtin protein develop an Huntington-like neurodegenerative disease, which can be prevented by the administration of rapamycin, an inducer of autophagy (634).

Enhanced autophagic vacuolization is observed in some instances of cell death, which has been named "autophagic cell death." It is an ongoing conundrum, however, in which cases autophagic cell death truly occurs through autophagy (meaning that inhibition of autophagy would prevent cell death) and in which cases it occurs with autophagy (meaning that inhibition of autophagy would only affect the morphology of the process, but not the fate of cells). Recently, several loss-of-function studies of autophagy (*atg*) genes have been performed, and these knock-out (KO) models will clarify the contribution of autophagy to physiological (developmental) and pathological cell death. As it stands, it appears that the essential autophagy gene beclin 1 (also known as *atg6*) plays an important role in endogenous tumor suppression (444). This tumor suppression may be related to a beclin 1-dependent autophagic control that would avoid the accumulation of cells with damaged organelles, including mitochondria. Beclin 1 was originally identified as a Bcl-2 interacting protein from a mouse brain library (455) and functions in the lysosomal degradation pathway of autophagy (454). Recently, it has been demonstrated that the binding of beclin 1 by Bcl-2 at the ER results in the inhibition of beclin 1-dependent autophagy. According to a rheostat model for the function of the beclin 1-Bcl-2 complex, the relative amounts of the two proteins ensure that autophagy operates at homeostatic levels, sufficient for the cells to cope with starvation or other forms of stress but not enough to promote cell death (602). This scenario, which highlights beclin 1-dependent autophagic cell death as an additional mechanism against tumor progression, raises the possibility that Bcl-2 and the other antiapoptotic members of the Bcl-2 family may function as oncogenes not only by directly blocking apoptosis but also by blocking autophagy (601). It has not yet been demonstrated whether beclin 1 could neutralize the antiapoptotic functions of Bcl-2. Manipulations of other autophagy genes also revealed the importance of autophagy in the elimination of invading microbial pathogens (272).

For the purpose of the present discussion, it is important to note that autophagy is essential for the removal of damaged mitochondria. Thus, when MMP occurs only in a minor subset of mitochondria, in response to a subapoptotic insult, autophagy may constitute the mechanism responsible for the removal of damaged (and permeabilized) organelles. In this scenario, suppression of autophagy will facilitate the induction of apoptosis through the intrinsic pathway (406). The detailed mechanisms through which damaged mitochondria are sequestered in phagosomes for degradation ("mitophagy") remain to be elucidated. According to some studies, mitochondria that undergo permeability transition (PT) with loss of $\Delta\Psi_m$ are preferentially targeted by "mitophagy" (196).

C. Necrosis

The cell's decision to die from necrosis or apoptosis is dictated at least in part by the abundance of intracellular energy stores. Indeed, whereas apoptosis requires a minimal amount of intracellular ATP, necrosis is generally accompanied by its total depletion (550). Thus necrosis may be viewed as an accidental type of cell death. Necrosis is not genetically predetermined and normally occurs within a short period following the triggering insult (2–4 h). The final phenotypic appearance of necrotic cells is highly dependent on the severity of the injury. The main features of necrosis include a gain in cell volume (oncosis) that finally leads to rupture of the plasma membrane and the unorganized dismantling of swollen organelles. Hence, necrosis lacks a specific biochemical marker, apart from the presence of plasma membrane permeabilization, and can be detected only by electron microscopy. Necrosis is considered to be harmful because it is often associated with pathological cell loss and because of the ability of necrotic cells to promote local inflammation that may support tumor growth (782). Importantly, cell death that usually occurs with an apoptotic morphology can be shifted to a more necrotic phenotype when caspase activation is inhibited by pharmacological inhibitors or by the elimination of essential caspase activators such as APAF-1 (257, 407).

Recently, the molecular events occurring during TNF-induced cell death have been investigated in more detail, revealing a contribution of caspase activation and protein synthesis to necrosis (407, 664). These observations as well as recent KO studies (540) argue against the concept of necrosis as a merely accidental cell death and rather suggest that the susceptibility to undergo necrosis is partially determined by the cell (and not only by the stimulus) and that the necrotic process involves an active contribution of cellular enzymes, implying that it is subjected to regulation. A recent study has demonstrated that the kinase RIP (receptor interacting protein), which is essential for TNF-induced necrosis, can inhibit ATP/ADP exchange on mitochondrial membranes by a direct interaction with the adenine nucleotide translocase (ANT), thereby causing mitochondrial dysfunction and cell death (760). Thus mitochondrial alterations may constitute a rate-limiting step of necrotic cell death, at least in some instances.

In accord with this idea, in several paradigms, overexpression of Bcl-2, an antiapoptotic protein that stabilizes mitochondrial membranes, can prevent or retard necrotic cell death. This applies, for instance, to necrosis induced by cyanide or by the simultaneous treatment with chemotherapeutic agents and the caspase inhibitor *N*-benzyloxycarbonyl-Val-Ala-Asp.fluoromethylketone (Z-VAD.fmk) (305, 404). Similarly, the KO of cyclophilin D (CypD), a protein that is required for some modes of MMP (29, 36), has been shown to prevent necrotic cell death of hepatocytes responding to the Ca^{2+} ionophore A23187 or to H_2O_2 (540). These results demonstrate that MMP can be rate-limiting for necrotic cell death.

D. Mitotic Catastrophe

Mitotic catastrophe represents a type of cell death that occurs during mitosis. Thus the morphological aspect of cells dying during mitosis is different from that of cells dying from classical apoptosis (that mostly occurs in the interphase). Mitotic catastrophe often involves micronucleation and multinucleation events that occur before cell death. Mitotic catastrophe results from a combination of deficient cell cycle checkpoints (in particular the DNA structure and the spindle assembly checkpoints) and cellular damage (for a review, see Ref. 96). Failure to arrest the cell cycle before or at mitosis triggers an attempt of aberrant chromosome segregation, which culminates in the activation of the apoptotic pathway and ultimately leads to the cellular demise. Cell death occurring during the metaphase/anaphase transition is often characterized by the activation of caspase-2 (which can occur in response to DNA damage) (96) and/or MMP with release of cell death effectors such as AIF and the caspase-9 and -3 activator Cyt *c* (553).

When cell death resulting from mitotic catastrophe is inhibited (for instance by overexpression of Bcl-2), the abortion of irregular mitoses is avoided and cells divide asymmetrically resulting in the generation of aneuploid daughter cells (397). Thus mitotic catastrophe may be viewed as a mechanism that protects against unwarranted (and possibly oncogenic) aneuploidization (96, 397). As it stands, mitotic catastrophe is a complex process that is controlled by numerous molecular players including kinases involved in cell cycle control (e.g., the cyclin-dependent kinase Cdk1, polo-like kinases, and Aurora kinases), cell cycle checkpoint proteins, survivin, p53, caspases, and members of the Bcl-2 family. Nonetheless, as the other cell death modalities, the fatal outcome of mitotic catastrophe depends, at least in part, on mitochondrial permeabilization.

III. DETECTION OF MITOCHONDRIAL MEMBRANE PERMEABILIZATION

MMP is a universal feature of cell death and is often considered as the "point of no return" in the cascade of events leading to apoptosis (263, 264). In general, it represents a defining stigma of death affecting cells as diverse as lymphocytes, cardiomyocytes, hepatocytes, neurons, osteoblasts, keratinocytes, or kidney epithelial cells. The mechanisms underlying MMP are complex and probably result from the coordinate execution of several in-

terdependent steps. Before we discuss the intricate mechanisms of MMP, we recapitulate here the technologies that can be used to detect permeabilization events affecting the IM or OM of mitochondria. These technologies are very different. OM is normally permeable to metabolites but not to proteins, meaning that OM permeabilization is mostly assessed by determining the translocation of proteins through OM, from the IMS to the extramitochondrial compartment. In contrast, IM is usually impermeable to ions and water, so its permeabilization is measured by physicochemical methods assessing the capacity of IM to maintain an electrochemical gradient or to separate low-molecular-weight solutes from each other.

A. Signs of Outer Mitochondrial Permeabilization

OM permeabilization is generally detected by determining the subcellular localization of proteins that are normally retained within the IMS by the protein-impermeable OM. Immunoblot detection of such proteins [including Cyt *c*, AIF, or adenylate kinase (ADK)], in an extramitochondrial compartment (cytosol, nuclei) purified according to subcellular fractionation procedures is interpreted as a reliable sign of OM permeabilization. Similarly, two-color immunofluorescence experiments can be performed to detect the presence of AIF, Cyt *c*, or ADK outside of mitochondria, by visualizing them in a separate localization from sessile mitochondrial markers such as heat shock protein 60 (HSP60) (394, 450, 741). Based on microinjection experiments with recombinant proteins, Cyt *c* and AIF are considered the prototypes of apoptogenic proteins released upon MMP, since each of them suffice to trigger nuclear apoptosis (466, 742, 891). However, proteomic analysis of the supernatants of mitochondria with permeabilized OM revealed that Cyt *c* and AIF are released together with numerous other key proteins, including but not limited to procaspases, Smac/DIABLO, Omi/HtrA2, and EndoG (5, 394, 600, 665, 741). While all these proteins are released to the cytosol, some additionally translocate to the nucleus (e.g., AIF, EndoG) or interact with receptors on the ER (e.g., Cyt *c*).

Thus multiple IMS proteins can be used as markers of OM permeabilization. It should be noted, however, that not all IMS proteins are released from mitochondria simultaneously. Depending on the apoptotic model that is studied, it has been found that the release of Cyt *c* can occur before or after that of AIF (526). Similarly, Smac/DIABLO may be released from mitochondria before Cyt *c* and AIF (22). This has been interpreted as an indication of differential release mechanisms (for instance distinct OM pores) (666), yet may also be explained by distinct mechanisms of mitochondrial retention. For instance, Cyt *c* must be desorbed from its interaction with the IM lipid cardiolipin (see also Fig. 10), presumably through cardiolipin oxidation (573), while AIF must be cleaved by a non-caspase protease to remove its anchorage in the IM (see also Fig. 11) (615). Thus it may be an advantage to monitor the subcellular localization of several IMS proteins rather than a single one to detect OM permeabilization.

To visualize OM permeabilization in living cells, they can be transiently or stably transfected with chimeric cDNA constructs that contain a mitochondrial IMS localization sequence (MLS) linked to a green fluorescent protein (GFP) moiety (Fig. 4). With the use of this system, it is possible to generate cells that express a fluorescent fusion protein (such as Cyt *c*-GFP or AIF-GFP chimeras) in the IMS until they receive an apoptotic stimulus (Fig. 4). Videomicroscopy revealed that the mitochondrial release of AIF-GFP or Cyt *c*-GFP chimeric proteins occurs in a rapid, coordinate fashion affecting all mitochondria of a cell in usually <5 min (256, 466).

In selected cases, OM permeabilization has been detected by electron microscopy, by the visualization of gaps in OM, through which IM herniation may occur (762, 785). Osmotic matrix swelling due to the influx of water may culminate in OM rupture. This is possible because the surface area of the IM with its folded cristae largely exceeds that of the OM. Obviously, this mode of OM permeabilization is irreversible and so are the associated mitochondrial dysfunction and release of apoptogenic factors. Indeed, according to immunoelectron microscopy determinations, upon physical rupture of the OM following PT induction, VDAC and the subunit F1 of ATPase remain associated with mitochondrial membranes, while Cyt *c* staining is lost (762). Nonetheless, there is no consensus on the contribution of OM ruptures to OM permeabilization. Confocal fluorescence microscopy has been used to visualize large Bax/Bak pore-forming oligomers assembled within or in the vicinity of OM (417, 546), and such complexes have been suggested to explain OM permeabilization without permanent membrane rupture.

Also, biochemical tests have been used to measure the OM integrity. For instance, the diffusion of metabolites generated by IMS enzymes (e.g., phosphocreatine produced by creatine kinase) can be used to determine the permeability of OM (and that of the metabolite channel in OM, VDAC) (659). Similarly, the accessibility of the enzymes of the respiratory chain (e.g., NADH oxidase, Cyt *c* oxidase) to exogenously administered substrates (e.g., NADH or Cyt *c*) can be quantified to determine the opening state of VDAC (which is responsible for the diffusion of NADH). Moreover, there have been attempts to measure the permeability of OM to Cyt *c* in cells after the permeabilization of their plasma membranes (528). These methods, however, have not yet been established for the routine monitoring of OM permeabilization in cell death research.

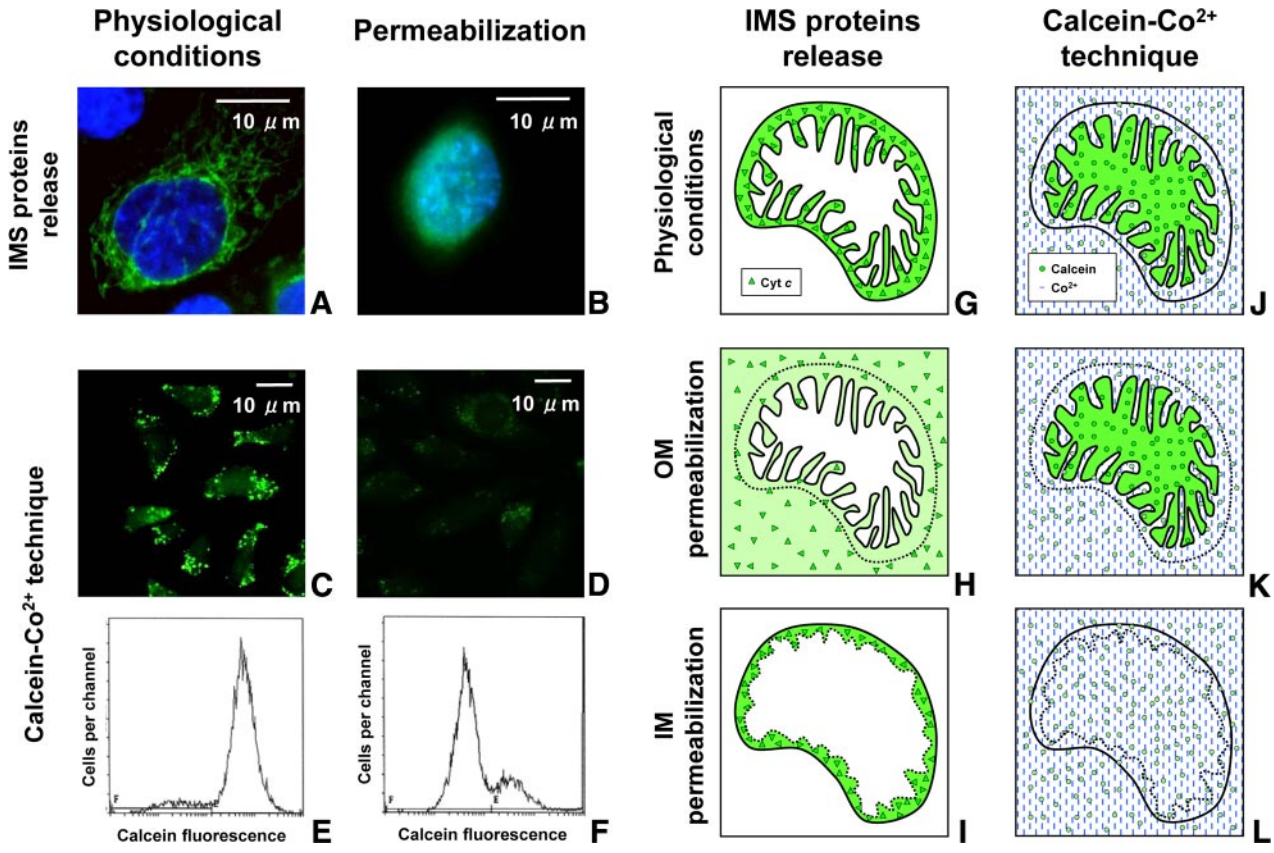


FIG. 4. Detection of OM and IM permeabilization. Mitochondrial outer membrane (OM) permeabilization (*A*, *B*, *G*, *H*): under physiological conditions *(A, G)*, cytochrome *c*-green fluorescent protein (Cyt *c*-GFP) fusions are retained in mitochondria, thanks to the diffusional barrier provided by the OM. This is visualized as a tubular pattern of green fluorescence by fluorescence microscopy *(A)*. Upon OM permeabilization *(B, H)*, intermembrane space (IMS) proteins, including Cyt *c*-GFP chimeras, redistribute to the cytoplasm, resulting in a diffuse green fluorescence of lower intensity. In *A* and *B*, blue fluorescence identifies the nucleus (Hoechst DNA staining). Mitochondrial inner membrane (IM) permeabilization (*C–F*, *J*, *L*): under physiological conditions *(C, E, J)*, calcein loaded into cells as its acetoxymethyl ester freely diffused to all subcellular compartments, whereas its quencher (Co^{2+}) is excluded from the mitochondrial matrix due to the fact that IM is impermeable to this ion. As a consequence, fluorescence microscopy may be employed to identify functional mitochondria, which appear as brightly fluorescent spots (*C*). This corresponds to an intense cellular fluorescence, as assessed by monoparametric fluorescence-activated cell sorter (FACS) analysis (*E*). When cells are treated with calcimycin (a Ca^{2+} ionophore which promotes IM permeabilization) (*D*, *F*, *L*), Co^{2+} gain access to the mitochondrial matrix, where they quench the calcein signal, as assessed by fluorescence microscopy (*C*), as well as by monoparametric FACS analysis (*D*). As schematized in *K*, the calcein-Co^{2+} technique does not identify OM permeabilization. Similarly, whereas IM permeabilization results in osmotic swelling of the mitochondrial matrix, IMS proteins are not released so far as the OM remains intact *(I)*. See section III for further details.

B. Signs of Inner Mitochondrial Permeabilization

IM permeabilization implies the formation of pores or channels that cause the dissipation of the $\Delta\Psi_m$ built across IM. Lipophilic cations accumulate in the mitochondrial matrix, driven by the $\Delta\Psi_m$ according to the Nernst equation, which states that (at +37°C) a hyperpolarization by 61.5 mV corresponds to a 10-fold increase in the intramitochondrial concentration of monovalent cations. Since in physiological conditions the $\Delta\Psi_m$ ranges from 120 to 180 mV (the intramitochondrial side being electronegative), the concentration of such cations is normally 2 to 3 logs higher in the mitochondrial matrix than in the cytosol. As a result, several different cationic fluorochromes can be employed to measure the $\Delta\Psi_m$ (95, 513). These markers include 3,3′-dihexyloxacarbocyanine iodide [$DiOC_6(3)$] (which emits in green, ~552 nm), chloromethyl-X-rosamine (CMXRos, also known as MitoTracker Red) (emitting in red, at 599 nm), tetramethylrhodaminemethylester (TMRM) (emitting in orange, with a peak at ~580 nm), and 5,5′,6,6′-tetrachloro-1,1′,3,3′-tetraethylbenzimidazolcarbocyanine iodide (JC-1) (which emits in red or green, according to its oligomerization status). Compared with rhodamine-123, which we do not recommend for cytofluorometric analyses, TMRM and $DiOC_6(3)$ offer the important advantage that they can be used at relatively low concentrations that do not cause major quenching effects (513). JC-1 incorporates into mitochondria where it either forms monomers (emitting in green, at 527 nm) or, at higher dye concentrations (implicating a high $\Delta\Psi_m$), aggregates (emitting in red, at 590 nm). Thus the ratio between green and red JC-1 fluorescence provides an estimate of $\Delta\Psi_m$ that is (relatively)

independent of mitochondrial mass. These $\Delta\Psi_m$-sensitive fluorochromes may be used to assess the apoptosis-associated $\Delta\Psi_m$ loss. For a critical evaluation of the methods currently available to measure $\Delta\Psi_m$, the reader may refer to Ref. 189.

As a caveat, it has to be taken into account that $\Delta\Psi_m$ dissipation may result from inhibited respiration not followed by IM permeabilization. Moreover, IM pore opening may be transient, leading to a transient $\Delta\Psi_m$ loss. To measure such a transient IM permeabilization event ("flickering pores"), one may use the calcein quenching method. This method relies on the loading of cells with the fluorescent probe calcein (molecular mass 620 Da) and its quencher, cobalt (Co^{2+}) (321). When loaded into cells in its acetoxymethyl ester form, calcein is trapped in all subcellular compartments including mitochondria, whereas Co^{2+} is excluded from the mitochondrial matrix due to the IM impermeability to this ion. As a consequence, when the barrier provided by IM is functional, a distinct punctuate fluorescence signal from calcein clearly identifies mitochondria (Fig. 4*C*). Conversely, upon IM permeabilization induced by Ca^{2+} overload or oxidative stress (551, 607), Co^{2+} enters the mitochondria matrix, and quenches the calcein signal (Fig. 4*D*). In most models of apoptosis induced by DNA damage and p53 activation, IM permeabilization, as measured by either of these methods, occurs at the same time or shortly after mitochondrial translocation of Bax (599, 691, 822).

Following IM permeabilization, an increase in mitochondrial matrix volume occurs as a consequence of the massive entry of solutes and water (320). This is the result of the colloid osmotic pressure of the matrix, which is tightly packed with metabolically relevant enzyme complexes. This swelling gives rise to a distension and disorganization of the cristae as well as to a reduction of the electron density of the matrix. In vivo, such an alteration has been observed for the first time in hepatocytes undergoing apoptosis induced by Fas or glutathione depletion and later confirmed in several models (209, 286). Thus electron microscopy constitutes an additional means to investigate the contribution of mitochondria to cell death.

IV. MECHANISMS OF MITOCHONDRIAL OUTER MEMBRANE PERMEABILIZATION

A. Bax/Bak-Mediated Permeabilization

Bcl-2 is the prototype member of a family of proteins containing at least one Bcl-2 homology (BH) region. For classification purposes, the family may be divided into antiapoptotic multidomain proteins (prototypes: Bcl-2, Bcl-X_L), which contain four BH domains (BH1234); proapoptotic multidomain proteins (prototypes: Bax, Bak), which contain three BH domains (BH123); and proapoptotic BH3-only proteins (prototypes: Bid, Bad) (442). Some members of all the subgroups share an additional COOH-terminal transmembrane domain, which mediates their insertion into the OM and other intracellular membranes (e.g., the ER membrane). The main site of action of Bcl-2-like proteins is probably the mitochondrial membrane (408). As a rule, BH1234 proteins mainly reside in OM, where they protect mitochondria against MMP, presumably by binding to and neutralizing other proapoptotic proteins from the Bcl-2 family, which on the contrary induce MMP. However, some BH1234 proteins act also at the ER membrane. The same has been reported also for some BH123 proteins, and the effect of Bcl-2-like proteins on the ER is discussed in section VII*B*, when the impact of lethal signals emanating from the ER is mentioned.

In healthy cells, the BH123 protein Bak is associated with the OM, whereas the other BH123 protein Bax resides in the cytosol, under normal circumstances. The expression of at least one of the two BH123 proteins (Bax or Bak) is required for MMP, in a series of different models of apoptosis induction (823). Accordingly, fibroblasts from mice that lack both Bax and Bak (but not cells from animals deficient solely for Bax or Bak) are highly resistant against MMP induction and against the activation of cell death by the intrinsic pathway (823). The genetic invalidation of Bax and Bak proved their determining role in the disruption of mitochondrial function promoted by a plethora of stimuli including, but not limited to, staurosporine, ultraviolet irradiation, growth factor deprivation, etoposide, and the ER stress inducers thapsigargin and tunicamycin (823). Although it has been assumed that mitochondria from Bax/Bak double KO fibroblasts would be completely resistant to MMP, it appears that such mitochondria can be permeabilized by alternative mechanisms such as high Ca^{2+} concentrations, which can induce the phenomenon known as "permeability transition" (PT) (174), or by a hexokinase/VDAC-dependent mechanism (477), which is discussed below.

As just mentioned, in physiological conditions Bax is a cytosolic protein. However, upon apoptosis induction, Bax inserts into the OM (836), where it is thought to form supramolecular openings, alone or in association with other proapoptotic members such as Bak or tBid (truncated Bid) (417). Such openings might result from the formation of homooligomeric Bax-containing pores or from the destabilization of the lipid bilayer, resulting in transient discontinuities within OM (Fig. 5). Relocalization of Bax is required for its proapoptotic function. Indeed, if Bax is retained in the cytosol by interaction with the Ku autoantigen of 70 kDa (Ku70), as well as with Ku70-derived peptides, mitochondrial damage and apoptosis are efficiently prevented (674). Although the precise mechanisms of MMP are debated (878), MMP can

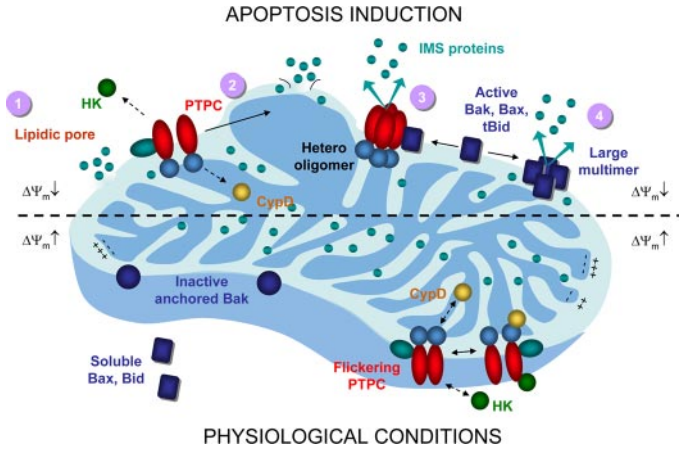


FIG. 5. Mechanisms for OM permeabilization. Under physiological conditions, mitochondria exhibit a high mitochondrial transmembrane potential ($\Delta\Psi_m$), intermembrane space (IMS) proteins are retained in IMS, proapoptotic members of the Bcl-2 family are in their inactive state (either soluble in the cytoplasm, as Bax and Bid, or anchored to the mitochondrial OM, as Bak) and the permeability transition pore complex (PTPC) ensures the exchange of metabolites between the cytosol and the matrix, in virtue of its "flickering" activity. In these circumstances, interactions of hexokinase (HK) and cyclophilin D (CypD) with the scaffold structure of the permeability transition pore complex (PTPC) are likely to inhibit OM permeabilization. OM permeabilization, which leads to the release in the cytosol of the IMS proteins and eventually to cell death, may occur through several mechanisms. *1*) Proapoptotic signals may directly promote the destabilization of mitochondrial lipids, thus favoring the formation of pores which allow for the release of IMS proteins. *2*) Long-lasting opening of the PTPC, associated with the loss of antiapoptotic interactions with HK and CypD, may lead to the dissipation of $\Delta\Psi_m$, followed by an osmotic imbalance that induces the swelling of the mitochondrial matrix. Due to the surface area of the mitochondrial IM, largely exceeding that of the OM, swelling may culminate in the physical rupture of the OM. See sections IIIA and IV as well as Figure 6 for additional information. *3*) Upon activation, proapoptotic members of the Bcl-2 family may translocate from the cytosol to OM (e.g., Bax and Bid) or undergo conformational changes (e.g., Bak) to bind to components of the PTPC. The resulting heterooligomers may provide IMS proteins with a route for release. See section IVA for further details. *4*) Alternatively, activated proapoptotic proteins of the Bcl-2 family may assemble into large multimers, allowing for the release of IMS proteins. See section IVA for further details.

result from a conformational change of Bax or Bak (with exposure of their NH_2 terminus), their full insertion into mitochondrial membranes as homooligomerized multimers, and formation of giant protein-permeable pores (Fig. 5) (417). It is an ongoing conundrum, however, how Bax (and Bak) "find their way" to mitochondria and whether they are attracted through specific properties of the lipid or protein composition of OM. Reportedly, large Bax oligomers organize in clusters near the mitochondria shortly after its translocation to mitochondria (546). Bak colocalizes in these apoptotic clusters, in contrast to other Bcl-2 family members, including Bid and Bad. Formation of these complexes has been reported to occur in a caspase-independent fashion and to be inhibited completely and specifically by Bcl-X_L (546).

BH3-only proteins can exert their proapoptotic action by two different mechanisms. Some BH3-only proteins (the "facilitators," prototype: Bad) preferentially interact with BH1234 proteins, dissociating them from other BH3-only or from BH123 proteins, which in turn promote MMP. Others (the "activators," prototype: tBid) directly activate BH123 proteins to initiate MMP, either by stimulating the translocation of Bax to mitochondrial membranes or by local effects on Bak (442). As a result, it is possible to generate two different types of "BH3 mimetics," a class of pharmacological agents that bind to multidomain Bcl-2 family proteins or so-called "BH3 receptors." One type of BH3 mimetics (prototype: ABT-737) only binds to BH1234 proteins (and hence facilitates apoptosis induction by neutralizing the antiapoptotic proteins of the Bcl-2 family) (570), while a second type of BH3 mimetics also binds to BH123 proteins and directly induces apoptosis in a Bax/Bak-dependent fashion (805).

How the molecular openings induced by Bax/Bak and/or Bax/tBid mediate Cyt *c* release is still a highly controversial issue. Indeed, some discrepancies between in vitro models based on purified cellular components (e.g., reconstituted proteoliposomes, black lipid membranes) and cell cultures have been reported. Evidence supporting the importance of lipid-protein interactions has started to accumulate (259, 469, 878), and it remains formally possible that Bax or Bak simply destabilize lipid bilayers instead of forming specific "pores" (35). Nonetheless, further studies are needed to completely elucidate the Bax/Bak- and/or Bax/tBid-mediated OM permeabilization.

According to some reports, Bax engages in a close molecular cooperation with proteins from the permeability transition pore complex (PTPC), such as ANT and/or VDAC, to induce MMP (Fig. 5). This has been demonstrated, for instance, by electrophysiological experiments involving purified recombinant Bax and purified ANT or VDAC (for a review, see Ref. 264). However, experiments on isolated mitochondria and liposomes suggest that Bax can permeabilize OM and release Cyt *c* in a fashion that does not involve any of the critical components of the PTPC, including VDAC, ANT, or CypD (201, 417). The two modes of Bax-mediated MMP (PTPC dependent versus PTPC independent) are not mutually exclusive, and they may coexist in specific proapoptotic settings. Indeed, the contribution of the PTPC to Bax-mediated MMP may be dictated by the concentration of Bax and its oligomerization status (599). Accordingly, when added to isolated mitochondria, Bax promotes cyclosporin A (CsA)-sensitive PT, depolarization, swelling, and release of Cyt *c* and of matrix-entrapped calcein only when used above a certain concentration threshold. Conversely, when lower amounts of Bax are used, mitochondrial swelling and depolarization are not detected (599).

The way the antiapoptotic members of the Bcl-2 family inhibit MMP is also a matter of debate. According to some authors, antiapoptotic members of the Bcl-2 family would simply act as inhibitors of their proapoptotic coun-

terparts, without any independent effects on other mitochondrial proteins. This suppression of MMP could be either achieved by direct interaction with the pore-forming members of the Bcl-2 family, or indirectly by neutralizing BH3-only proteins (442). However, some data indicate that Bcl-2 and Bcl-X_L can interact with sessile mitochondrial proteins including ANT (495) and VDAC (711). In vitro, the overexpression of Bcl-2 in cells or the addition of Bcl-2 to isolated mitochondria reduces the PT probability (495, 708). Moreover, recombinant Bcl-2 can inhibit the formation of pores by purified ANT or VDAC reconstituted into artificial membranes (71, 708), while enhancing the ADP/ATP antiporter activity of ANT (71). Accordingly, chemical inhibitors of Bcl-2 that have been designed to block a hydrophobic pocket within its BH3-binding domain can sensitize isolated mitochondria to permeability transition in vitro (518). One possible interpretation of these data would require the assumption that Bcl-2-like proteins have two functions on mitochondria, namely, the inhibition of pore formation by Bax and Bak as well as the inhibition of pores formed by proteins from the PTPC, such as VDAC and ANT.

In summary, the proapoptotic members of Bcl-2 family like Bax and Bak can induce MMP either independently or in coordination with PTPC proteins, by means of interactions occurring before or after PTPC opening (171, 621, 822, 830). Therefore, as depicted in Figure 5, two MMP mechanisms may coexist: a Bax-mediated OM permeabilization that occurs independently of any early and direct effect on the IM (214, 215) and a PTPC-mediated permeabilization, which on the contrary involves IM. The possible cooperation between these pathways and their relative weight in different cell death settings are still debated. Nonetheless, both routes eventually lead to the permeabilization of both mitochondrial membranes, release of proapoptotic proteins from IMS, and functional collapse of the organelle and apoptosis, irrespective of the initial trigger. It appears plausible that either of the two mechanisms may prevail, depending on the cell type and the apoptosis inducer.

Another subject of debate regards the relationship between Bax-mediated MMP and mitochondrial dynamics. Theories explaining the mechanisms of MMP are formulated, debated, and modified on a regular basis, and one of the recurrent discussions in the field concerns the question of whether mitochondrial fission would be required for Bax-induced MMP (605). An emerging consensus in this area suggests that mitochondrial fission is not required for apoptotic MMP, yet it may contribute to MMP induction, in some circumstances, as an accelerating factor (10, 99).

B. VDAC-Mediated Permeabilization

The voltage-dependent anion channel (VDAC) is the most abundant protein of the OM. It functions as a low-specificity molecular sieve of exclusion, with a cut-off at ~5 kDa. Recently, it has been shown that opening of VDAC is a regulated process and that VDAC may exhibit some degree of specificity in the mitochondrial import/export of molecules (e.g., ATP, Ca^{2+}, and other ions). Its implication in apoptosis was first proposed by Tsujimoto and co-workers in 1999 (Fig. 6) (713, 773). This group showed that recombinant Bax and Bak accelerate the opening of VDAC in reconstituted proteoliposomes. Moreover, VDAC1-deficient mitochondria isolated from a mutant yeast strain failed to exhibit the Bax/Bak-induced $\Delta\Psi_m$ loss and Cyt *c* release that was observed with VDAC1-expressing control mitochondria. In the same model, VDAC opening and Cyt *c* release were prevented by recombinant Bcl-X_L, Bcl-2, or peptides corresponding to the BH4 domain of these proteins (711, 714). Furthermore, synthetic cell-permeable BH4 peptides have been shown to exert cytoprotective effects both in vitro and in vivo. More precisely, the intraperitoneal delivery of BH4 peptides greatly inhibited X-ray-induced apoptosis and partially suppressed Fas-induced fulminant hepatitis in mice (737). Moreover, the same peptides markedly suppress heart failure after ischemia/reperfusion injury in isolated rat hearts (737) and protect lymphocytes from sepsis-induced apoptosis in mice (312). Also the microinjection of neutralizing anti-VDAC antibodies into cells prevents Bax-induced Cyt *c* release and $\Delta\Psi_m$ loss (712, 714). Taken together, these results suggest that the Bcl-2 family of proteins bind to VDAC to regulate the $\Delta\Psi_m$ and the release of Cyt *c* during apoptosis.

An alternative model implicating VDAC as a mediator of OM permeabilization has been proposed (Fig. 6). The comparison between intact mitochondria isolated from cells undergoing apoptosis and the same organelles treated by a detergent that solubilizes specifically the OM, and not the IM, led Thompson and colleagues to propose that apoptosis induction could favor the closed conformation of VDAC and that closed VDAC, in turn, would cause OM rupture (784–786). Conversely, BH1234 proteins such as Bcl-X_L would prevent cell death by promoting VDAC opening (785, 786). However, this interpretation is not consistently supported by electrophysiological experiments (for a critical review, see Ref. 659). The two models for OM permeabilization are compared in Figure 6.

Independent evidence supporting the implication of VDAC in apoptosis control is furnished by the observation that hexokinase I and II (HKI and HKII) may bind to a not yet defined VDAC isoform, thus hindering its interaction with Bax. Accordingly, HKI and HKII would prevent apoptosis in hepatocytes and tumor cells by impeding the formation of the proapoptotic VDAC-Bax complex (595, 597, 652, 874). Moreover, it has been reported that overexpression of VDAC1 suffices to induce apoptosis in a variety of cells (874). It has been suggested that distinct VDAC isoforms interact differentially with proapoptotic

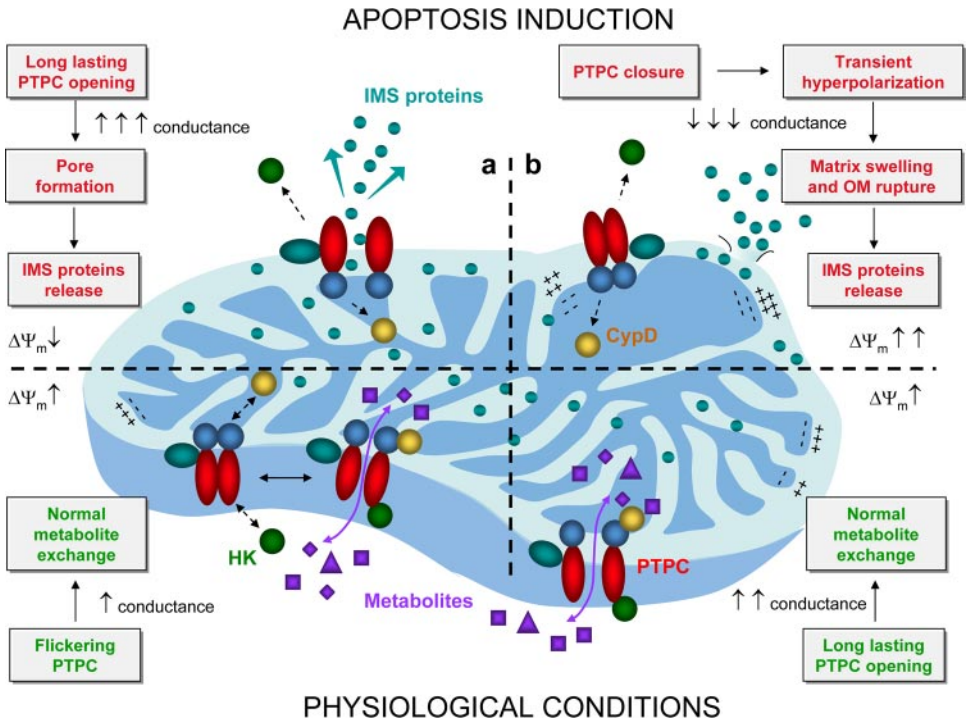


FIG. 6. Role of the voltage-dependent anion channel (VDAC) in OM permeabilization. Two models have been put forward to explain the role of VDAC in the mitochondrial OM permeabilization. According to Tsujimoto and co-workers (*a*) (713, 773), in physiological conditions VDAC would exist prominently in a low conductance state, within a "flickering" permeability transition pore complex (PTPC), to ensure the exchange of metabolites between mitochondria and cytosol. Upon apoptosis induction, VDAC would exhibit an increased conductance associated with long-lasting PTPC opening, thus leading to dissipation of mitochondrial transmembrane potential ($\Delta\Psi_m$), efflux of IMS proteins, and eventually cell death. On the contrary, Thompson and colleagues (*b*) (784–786) proposed that the physiological role of VDAC would be exerted by its high conductance state and that under proapoptotic conditions the closed state of VDAC would be favored. This would bring about a transient mitochondrial hyperpolarization, followed by osmotic imbalance, OM rupture, release of the IMS proteins, and ultimately cell death. See section IV*B* for more detailed information.

members of Bcl-2 family. For instance, VDAC2 reportedly sequesters Bak by a direct molecular interaction, thus preventing Bak activation and apoptosis (121), whereas VDAC1 may serve as a receptor for Bax (597). In conclusion, the current literature suggests that VDAC1 may exert preponderantly proapoptotic functions, whereas VDAC2 may be mainly antiapoptotic. However, thus far no direct comparisons between VDAC1 and VDAC2 have been carried out in the same experimental system, meaning that the hypothesis of a diametrically opposed role for VDAC1 and VDAC2 remains to be validated.

V. PUTATIVE CONTRIBUTION OF INNER MITOCHONDRIAL PERMEABILIZATION

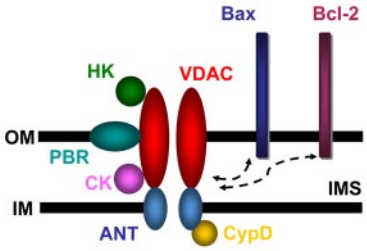
A. Controversy About Inner Mitochondrial Permeabilization

It is a matter of intense debate whether IM contributes to MMP or whether the regulation of MMP is entirely localized at the OM, without any contribution of IM. In several paradigms of MMP, the $\Delta\Psi_m$ collapses shortly after (within minutes) OM permeabilization, and in some cases, this $\Delta\Psi_m$ dissipation requires caspase activation. Indeed, one report indicates that caspase activation resulting from Cyt *c* release can lead to the cleavage of a subunit of respiratory chain complex I (see also Fig. 10) (645). However, in most examples of apoptosis induction, $\Delta\Psi_m$ dissipation occurs in a caspase-independent fashion (264, 407). This indicates that two pathways leading to MMP can be distinguished, one in which the $\Delta\Psi_m$ is lost early during the process, in a caspase-independent fashion, and a second one in which IM is not affected until the degradation phase of apoptosis starts. As a caveat against this distinction, however, it should be mentioned that the $\Delta\Psi_m$ is not a stringent criterion to assess IM permeabilization (in part because the $\Delta\Psi_m$ can recover after transient permeabilization) and that the calcein/Co^{2+} method should be used to distinguish between these two possibilities.

In support of an essential role of IM to MMP, four observations may be enumerated. *1*) Kinetic analyses suggest that IM permeabilization can precede Bax/Bak/Bid activation (400, 897). *2*) Some lethal stimuli involve the obligate contribution of IM or matrix proteins interacting

with IM. This applies, for instance, to CypD (29, 36, 540). *3*) Several antiapoptotic proteins exert their effects in part through interactions with IM proteins (e.g., Bcl-2; see sect. v*B*). *4*) Some pharmacological inhibitors acting on IM proteins such as CsA (which acts on CypD) or bongkrekic acid (BA; which acts on ANT) can inhibit cell death, at least in some models of apoptosis (488, 881).

Taken together, these observations suggest that IM (or IM proteins) contribute to MMP. According to current knowledge, the principal mechanism leading to IM permeabilization is the so-called "permeability transition."



	MMP inhibitors	MMP facilitators
ANT	ADP/ATP Bongkrekic acid NADPH	Atractyloside Ca^{2+} Palmitate Thiol oxidation
CK	Creatine Cyclocreatine	Anion superoxide ($O_2^{\bullet-}$)
CypD	Cyclosporine A Sanglifehrin A	
HK	Glucose	Glucose-6-phosphate
PBR		PK11195
VDAC	DIDS König polyanion NADH UTP	Anion superoxide ($O_2^{\bullet-}$) Ca^{2+}

FIG. 7. PTPC architecture. Although the exact molecular composition of the permeability transition pore complex (PTPC) has not been clearly established yet, a consensus has started to emerge about the proteins involved in its scaffold structure, which builds up at the contact sites between the mitochondrial outer and inner membranes (OM and IM, respectively). In addition to the VDAC and the adenine nucleotide translocase (ANT), which represent the main PTPC components, these include hexokinase (HK, interacting with VDAC from the cytosol), creatine kinase (CK, interacting with PTPC from the intermembrane space, IMS), peripheral-type benzodiazepine receptor (PBR, interacting with PTPC from OM), and cyclophilin D (CypD, interacting with ANT from the mitochondrial matrix). HK and CK seemingly associate with the PTPC scaffold in a mutually exclusive fashion. Both anti- and proapoptotic members of the Bcl-2 family modulate the activity of PTPC, through direct interactions with ANT or VDAC. The table reports some inhibitors and facilitators of mitochondrial membrane permeabilization (MMP) for which the target within PTPC has been identified. PK11195, 1-(2-chlorophenyl)-*N*-methyl-*N*-(1-methylpropyl)-3-isoquinoline-carboxamide.

B. Mitochondrial Permeability Transition

Permeability transition (PT) is a sudden increase of the IM permeability to solutes with molecular mass up to 1.5 kDa. This phenomenon is caused by the opening of a voltage-dependent, high-conductance channel located in the IM that is known as the permeability transition pore (PTP). In isolated mitochondria, PT is usually detected thanks to the change in the diffraction/absorption of light (measured at 540 nm) that results from matrix swelling or as a reduction of the organellar retention of potential-sensitive fluorochromes (896). The exact molecular nature of the PTP is still a matter of debate, although an emerging consensus considers a multicomponent protein complex, the PTPC, and not a single protein, as being responsible for the opening of PTP. One among the possible models for PTPC is proposed in Figure 7. It is believed that PTPC is assembled at the contact sites of the mitochondrial membranes and that its scaffold structure is based on the dynamic interaction between VDAC, ANT, and CypD (895, 896) (for recent reviews, see Refs. 72, 151). This idea is mainly based on the analysis of the ANT interactome (795) as well as on in vitro experiments in which semi-purified PTPC reconstituted into proteoliposomes were depleted from distinct components or highly purified PTPC proteins were incorporated into artificial membranes (71, 495, 496, 804).

PTPC may exhibit several distinct opening states, ranging from a low-conductance conformation, characterized by a very limited permeability, to a high-conductance state that allows the free passage of solutes and molecules with a molecular mass <1.5 kDa (see also Fig. 6) (896). In intact healthy cells, PTPC likely fluctuates with a rapid kinetics between the open and closed states (607). Only large and long-lasting openings, in the presence of an adequate amount of ATP, would lead to cell death induction by Ca^{2+}, as shown by measurements of mitochondria-entrapped calcein. PTPC opening is indeed highly sensitive to Ca^{2+} as well as to prooxidant agents, proapoptotic Bcl-2 family members (e.g., Bax, Bak, and Bid), and some chemotherapeutic agents (for a review, see Ref. 72). Conversely, PTP opening can be inhibited by ligands of CypD such as CsA (277) and sanglifehrin A (138), ANT ligands such as BA (275), and antiapoptotic members of the Bcl-2 family including Bcl-2 and Bcl-X_L (45, 421, 495, 496, 633).

Several mechanisms have been put forward to account for PTPC opening: *1*) chemical modifications of a peculiar protein of PTPC, such as the cross-linking of ANT thiols (146) or the phosphorylation of VDAC1; *2*) changes in protein-to-protein interactions, such as the switch from Bcl-2 to Bax binding observed within the ANT interactome (795); *3*) modulation of the expression levels of pro- or antiapoptotic components of PTPC (40, 178, 876); *4*) modifications of the lipidic microenvironment, notably involving cardiolipin, induced by Ca^{2+} accumulation in mitochondria (77).

ANT has been proposed to be a major player of the process of IM permeabilization during apoptosis, since it can switch from a vital function (stoichiometric ADP/ATP exchange on IM) to a lethal one, corresponding to its pore-forming activity (for a review, see Ref. 275). However, the requirement for ANT in MMP and apoptosis has been questioned. Wallace and colleagues (395) engineered mice whose hepatocytes lack both ANT1 and ANT2, two ANT isoforms encoded by the mouse genome. Mitochondria isolated from ANT1/ANT2 double KO hepatocytes are relatively resistant against Ca^{2+}-induced

swelling (395). Accordingly, they exhibit an increase in the amount of Ca^{2+} required for the induction of mitochondrial swelling, yet conserve the ability to undergo CsA-inhibitable PTP opening in vitro (395). Unfortunately, in the meantime an additional ANT isoform has been identified in mice (653), casting some doubts on the conclusion that ANT at large would be irrelevant for PTP opening (395). ANT belongs to a large family of structurally related proteins, namely, the family of mitochondrial carriers (835). Several among these proteins share the capacity to convert into nonspecific pores. For instance, the treatment of the ornithine/citrulline carrier with mercurial reagents results in the induction of an additional, porelike transport mode (770). This suggests that ANT1 and -2 could be replaced in their pore-forming activity by other similar carriers.

Several groups independently reported the phenotype of mitochondria isolated from mice lacking CypD (gene name *Ppif*, for peptidylprolyl *cis-trans* isomerase f). Liver mitochondria from *Ppif*$^{-/-}$ mice display a desensitization of the PTP to Ca^{2+}, meaning that they require twice the Ca^{2+} load than wild-type (wt) mitochondria for PTP opening (29, 36, 540). *Ppif*$^{-/-}$ hepatocytes thus display a phenotype similar to cells deficient for both ANT1 and -2 with regard to Ca^{2+}-induced PTP opening (395). Ca^{2+}-induced PTP opening of *Ppif*$^{-/-}$ liver mitochondria, moreover, is insensitive to CsA (36), corroborating the notion that CypD is the pharmacological target of CsA in mitochondria. However, the PTP response to $\Delta\Psi_m$ dissipation, ubiquinone, pH, adenine nucleotides, and thiol oxidants is similar in mitochondria from wt and *Ppif*$^{-/-}$ mice (36). Moreover, liver mitochondria from *Ppif*$^{-/-}$ and wt mice release Cyt *c* in the supernatant with a similar kinetics, when treated with recombinant Bax or tBid (29, 540). Fibroblasts from *Ppif*$^{-/-}$ mice are resistant against PTP opening and cell death induced by H_2O_2. The reintroduction of wt CypD (but not that of a mutant that has lost the peptidylprolyl *cis-trans* isomerase activity) restores the capacity of *Ppif*$^{-/-}$ fibroblasts to die in response to H_2O_2 (29). Fibroblasts from *Ppif*$^{-/-}$ mice are also resistant to cell death induced by thapsigargin (which causes Ca^{2+} release from the ER) (29). CypD-deficient hepatocytes are protected against necrotic cell death induced by A23187 or H_2O_2 (540). Finally, overexpression of CypD in B50 cells facilitates necrosis induction by the nitric oxide (NO) donor sodium nitroprusside and sensitizes their mitochondria to PT induced by Ca^{2+} and oxidative stress (452).

These in vitro data have been extrapolated to the in vivo physiology. Heart infarction induced by ischemia/reperfusion is strongly reduced in *Ppif*$^{-/-}$ mice (29, 540). Conversely, overexpression of a *Ppif* transgene under the control of a heart-specific promoter induces an elevated propensity of mitochondria to PTP opening in vitro and signs of cardiomyocyte apoptosis (Cyt *c* release, caspase-9 activation, TUNEL positivity) in vivo (29). *Ppif*$^{-/-}$ mice also display a dramatic reduction in brain infarct size after acute middle cerebral artery occlusion and subsequent reperfusion (681). These data confirm previous observations that CsA injections can attenuate ischemia-associated cell death in vivo (212, 278).

These genetic experiments confirm the implication of the PTPC in cell death regulation. However, there is also abundant evidence that CypD is not universally required for cell death induction. For instance, fibroblasts from *Ppif*$^{-/-}$ mice are not protected against cell death induced by Bax (29) or Bid (540). *Ppif*$^{-/-}$ and wt thymocytes die at a similar rate in response to etoposide, staurosporine, TNF-α plus cycloheximide, or the Ca^{2+} ionophore A23187 (540). These data suggest that there are two different pathways leading to MMP: one that partially relies on CypD expression (which is CsA inhibitable) and another one that is CypD independent (CsA resistant). Nonetheless, it would be premature to conclude that PTP opening is irrelevant to cell death in those circumstances in which removal of CypD fails to modulate cellular demise. Indeed, the PTP from *Ppif*$^{-/-}$ mitochondria opens normally in response to arsenicals (36), which act on ANT (and perhaps other similar proteins from the mitochondrial transporters family) (146). In conclusion, there is no clear evidence to exclude a CypD-independent PTP opening.

There have been some attempts to simplify the debate on MMP by saying that the "necrotic" modality of MMP would rely on the PTPC, whereas the "apoptotic" modality would be regulated by the Bcl-2 family in a PTPC-independent fashion (29, 540). However, there are dozens of examples of apoptotic cell death that are inhibited by CsA and BA (880), suggesting that such a simple distinction represents an oversimplification.

VI. REORGANIZATION OF CRISTAE

The conventional view of mitochondria distinguishes two submitochondrial compartments: the matrix (surrounded by IM) and IMS (between IM and OM). Electron microscopic tomography performed by Mannella and coworkers (225, 486) has changed this view, leading to the identification of an additional compartment, the intracristae space (ICS). Convoluted folds of the IM, cristae, may form lamellar and tubular structures that create a compartment (i.e., ICS) that communicates with IMS through bottleneck-like junctions so tight that they create a diffusion barrier. Most Cyt *c* (~85%) is contained in the ICS, meaning that its release from mitochondria through the permeabilized OM is favored by an additional process that affects the internal structure of mitochondria. This process has been baptized "cristae remodeling" and results in the widening of the junctions that delimitate ICS, the removal of the diffusion barrier, and the mobilization of the Cyt *c* from ICS to IMS (Fig. 8) (690).

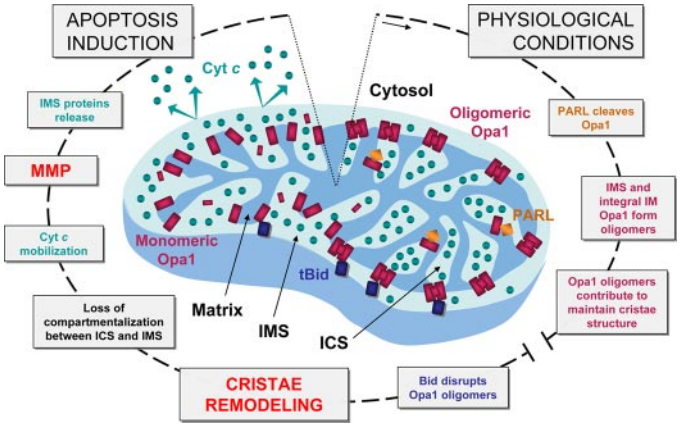


FIG. 8. Cristae remodeling. Under physiological conditions, mitochondrial membranes define the boundaries of at least three submitochondrial compartments: the mitochondrial matrix is enclosed within the mitochondrial IM, the intermembrane space (IMS) is located between the IM and the mitochondrial OM, the intracristae space (ICS) is delimited by the convoluted folds of the IM, namely, cristae. Most cytochrome *c* (Cyt *c*) resides in the ICS, which communicates with IMS via tight bottleneck-like junctions, forming a diffusional barrier. It appears that ICS undergoes deep structural rearrangements during apoptosis to promote the complete release of Cyt *c* and other IMS proteins. In healthy cells, cristae structure is maintained with the help of Opa1 (optic atrophy 1) oligomers, which are constituted by both the IM integral form of Opa1 and by its IMS soluble counterpart. The serine protease PARL (presenilin-associated rhomboid-like) is responsible for the production of the soluble form of Opa1 that is required for the assembly of Opa1 oligomers. Upon apoptosis induction, Opa1 oligomers are disrupted (for instance following the translocation of truncated Bid, i.e., tBid). Then profound rearrangements of the submitochondrial structure take place, resulting also in the loss of the diffusion barrier between IMS and ICS. Taken together, these rearrangements have been called "cristae remodeling" and promote the mobilization of the pool of IMS proteins, including Cyt *c*, previously sequestered in ICS. Finally, mitochondrial membrane permeabilization (MMP) allows for the release of the mobilized IMS proteins. For further details see section VI.

Several proteins that are involved in mitochondrial dynamics (fusion and fission) may play a major role in the proapoptotic reorganization of cristae. For instance, Drp1 (dynamin-related protein 1) participates in mitochondrial fission and is required for the optimal release of Cyt *c*, presumably through its contribution to cristae remodeling (248). Moreover, recent work suggests that the junctions between ICS and IMS are maintained by Opa1 (optic atrophia 1) (226), an integral protein of the IM with established roles in mitochondrial dynamics (113, 605). The proteolytic activation of Opa1 is mediated by PARL (presenilin-associated rhomboid-like), a serine protease localized in the IM and whose yeast ortholog is implicated in mitochondrial fusion (136).

Upon cleavage, truncated Opa1 is released in the IMS as a soluble protein. Both forms of Opa1 (i.e., the integral IM protein and the soluble form) build up oligomers that are disrupted during cristae remodeling, for instance, when mitochondria are exposed to the BH3-only protein Bid or upon osmotic swelling (Fig. 8). These oligomers may constitute (part of) the structure that preserves the junctions between ICS and IMS in a bottleneck configuration (136, 226). Given the multiple relationships that have been already characterized between mitochondrial dynamics and apoptosis (605, 870), it will be interesting to learn in the future also the more specific molecular liaisons between mitochondrial fission (which often occurs during apoptosis) and cristae remodeling. Moreover, it will be a challenge for further investigation to determine how different proapoptotic effectors, including proteins of the Bcl-2 family and PTPC constituents, interact with the molecular machinery that mediates cristae remodeling.

VII. AFFERENT SIGNALS FROM OTHER ORGANELLES

Mitochondria occupy a central position in apoptotic signaling and integrate various types of proapoptotic signals incoming from other organelles (e.g., nucleus, cytosol, lysosomes, and autophagic vacuoles). Interorganellar cross-talk may have a prominent role in the determination of cell fate by favoring survival or death pathways. This interorganellar communication is mediated by a plethora of factors such as entire transcriptional programs, metabolite and ion fluxes, redox reactions, and posttranslational protein modifications [including translocation, proteolysis, as well as (de)phosphorylation]. Intriguingly, most organelle-specific death responses hardwire either to MMP or to caspase activation, both of which may function as central integrators of the apoptotic program, thereby streamlining nucleus-, lysosome-, Golgi apparatus-, or ER-elicited responses into a common pathway. The central position occupied by mitochondria in the integration of pro- and antiapoptotic signals emanating from other subcellular compartments is illustrated in Figure 9. For an extensive list of proteins and nonproteinaceous factors that favor or inhibit MMP, see Tables 2 and 3, respectively.

A. Nuclear DNA Damage

Under normal conditions, cells that experience DNA damage to a degree that is beyond repair either undergo apoptosis or enter a senescent state, namely, a near-to-irreversible cell cycle arrest. The tumor suppressor gene product p53 mediates part of the response of mammalian cells to DNA damage, either by stimulating DNA repair or, beyond a certain threshold of DNA damage, by initiating apoptosis (Fig. 9). p53, which among its several roles is a transcription factor, *trans*-activates a large series of proapoptotic proteins from the Bcl-2 family (in particular Bax, Bid, Puma, Noxa) (803), which induce MMP and therefore the release of apoptogenic factors from the IMS. p53 upregulates the apoptosis-associated specklike adaptor protein (ASC, which favors the activation of Bax and

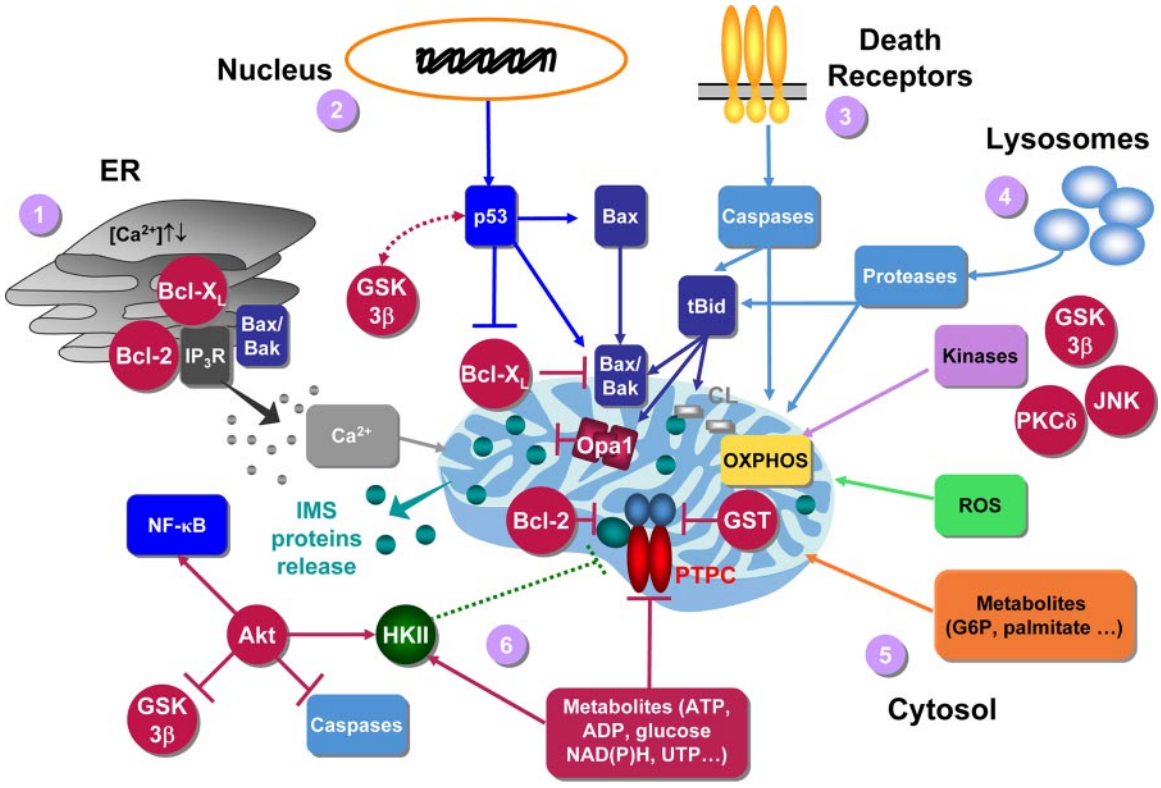


FIG. 9. Signals converging on mitochondria to induce MMP. Mitochondria represent crucial checkpoints of apoptosis control, where lethal and vital signals emanating from different intracellular compartments, as well as from the extracellular microenvironment, converge and are integrated to decide the cell's fate. *1*) Pro- and antiapoptotic members of the Bcl-2 family exert their activities not only at mitochondria but also at the endoplasmic reticulum (ER), where they have been shown to regulate the size of the intra-ER Ca^{2+} pool. The amount of Ca^{2+} available for release upon activation of the inositol 1,4,5-trisphosphate receptor (IP_3R) determines the mitochondrial response to this ion, which may range from metabolic activation to mitochondrial membrane permeabilization (MMP), release of intermembrane space (IMS) proteins, and apoptosis. For further details, see section VII*B*. *2*) p53 controls part of the response of mammalian cells to DNA damage, by means of both transcriptional (for instance by upregulating the expression of proapoptotic members of the Bcl-2 family like Bax) and transcription-independent mechanisms. Among the latter, p53 may favor MMP by direct interactions with Bak, Bax, Bcl-2, and Bcl-X_L at the outer mitochondrial membrane (OM). p53 transcriptional and transcription-independent activities may be promoted by the binding of glycogen synthase kinase 3β (GSK-3β). For further details, see section VII*A*. *3*) Death receptors transduce proapoptotic signals from the extracellular environment, along the extrinsic pathway, into the activation of the caspase cascade. The extrinsic pathway is linked to mitochondria by caspase-8, which mediates the proteolytic maturation of Bid. tBid favors MMP by promoting the pore-forming activity of Bak and Bax, the dismantling of Opa1 (optic atrophy 1) oligomers (a process that results in cristae remodeling), and mitochondrial dysfunctions through interactions with cardiolipin (CL) in the IM. For further details on the extrinsic pathway of apoptosis, see section II*A* and Figure 1. For additional information on cristae remodeling, see section VI and Figure 8. *4*) When lysosomal membranes break down, cathepsins and other hydrolases are released into the cytoplasm, where they promote apoptosis and/or necrosis. Some cathepsins are able to activate Bid, as well as to induce mitochondrial dysfunctions by cleaving specific subunits of the oxidative phosphorylation complexes (OXPHOS), thus enhancing reactive oxygen species (ROS) generation. The same has been reported for caspase-3, which may enter IMS upon limited OM permeabilization and participate in amplificatory loops for MMP. For further details on the cross-talk between lysosomes and mitochondria, see section VII*C*. For additional information about the involvement of caspases in amplification loops MMP, see Figure 10 and Ref. 242. *5*) Multiple signals coming from the cytosol lead to MMP. These include but are not limited to the following: ROS, metabolites (e.g., glucose-6-phosphate, palmitate) and the activation of specific kinases [e.g., GSK-3β; PKCδ, i.e., protein kinase C, δ isoform; members of the c-Jun NH_2-terminal kinase (JNK) family]. *6*) On the other side, numerous endogenous modulators inhibit the permeability transition pore complex (PTPC) and protect mitochondria from MMP. These include metabolites [e.g., NAD(P)H and UTP], the antiapoptotic members of Bcl-2 family, antioxidant enzymes (e.g., glutathione-*S*-transferase) and several prosurvival kinases, like Akt. Akt inhibits apoptosis via multiple distinct pathways, such as the activation of NFκB, the inhibition of caspases and of GSK-3β, and through hexokinase II (HKII)-dependent mechanisms (activated also by glucose). See section VII*D* for more detailed information.

its interaction with mitochondria) (563), as well as several proteins that localize to mitochondria where they favor MMP through oxidative reactions (ferredoxin reductase, proline oxidase) (186, 322) or unknown mechanisms (p53AIP1, i.e., p53-regulated apoptosis-inducing protein 1; mtCLIC/CLIC4, i.e., mitochondrial chloride intracellular channel/chloride intracellular channel 4) (211, 500, 561). p53 also *trans*-represses the anti-apoptotic protein Bcl-2 (which acts on mitochondria to prevent membrane permeabilization) (844). In addition, p53 may initiate apoptosis through proteins that are normally resident in the ER (Scotin) (65) or in the plasma membrane (Fas/CD95; death receptor-4 and -5, i.e., DR4 and DR5, PERP, i.e., p53 apoptosis effector related to PMP-22) (325, 464, 879). It is important to note, however, that these genes may be *trans*-activated by p53 but that their induction does not

TABLE 2. *Protein factors and second messengers that favor MMP*

Molecules	Putative Target: Mode of Action	Reference Nos.
	Sessile membrane proteins	
ANT	Bax, Bcl-2, NFκB	45, 496, 877
Bak	Ca^{2+} flux from ER, VDAC1, VDAC2	121, 691, 713
Bcl-X_S	Bak(?), Bcl-2, Bcl-X_L	106, 459
CypD	ANT	29, 275, 540
ITM2B$_S$	Bcl-2, others(?)	219
PLS-3	Cardiolipin transported to OM	293
Siva-1	Bcl-X_L	850
VDAC	Bak, Bax, Bcl-X_L, Ca^{2+} flux	711, 713, 714, 773
ΔN Bcl-X_L	VDAC	352
	Proteins translocating to mitochondria: proapoptotic Bcl-2-like proteins	
BH123 proteins		
Bax	ANT, inhibition of ADP/ATP exchange; Ca^{2+} release from the ER; cardiolipin (CL); VDAC opening	45, 417, 495, 691, 709, 773
MAP-1	Bax	31, 753
BH3-only proteins		
Bad	Bcl-2, Bcl-X_L, glucokinase, VDAC2, competition for Bak binding	121, 159, 442
Bik/Blk/Nbk	Bak, Bax	499
Bim	Bcl-2, Bcl-w, VDAC opening, VDAC2, competition for Bak binding?	121, 122
Hrk/DP5	Bcl-2, Bcl-X_L, Mcl-1, p32	327, 740
Noxa	A1/Bfl-1, Mcl-1, competition for Bak binding and proteasome degradation targeting, PTPC	114, 560, 697, 833
Puma	Bax, Bcl-X_L, competition for p53 binding, Mcl-1, ROS generation	93, 128, 465
tBid	Bak, Bax, Bok/Mtd, carnitine palmitoyltransferase 1, CL, HK, iPLA2, lipid microdomains, mitochondrial carrier homolog 2, ROS generation, VDAC closure, VDAC2, competition for Bak binding	93, 121, 241, 259, 268, 478, 823
BH3-related proteins		
Bnip3	Bcl-2, Bcl-X_L, Bok/Mtd, PTPC, involved in autophagic cell death	239, 364, 785
Bnip3L	Bcl-2, Bcl-X_L	326
	Inducible proteins translocating to mitochondria	
E2F1-inducible proteins		730
BH3-only proteins		300
Bid, Bim, Hrk/DP5, Noxa, Puma	See above	87, 300
Caspase-8	See below	87
Siva-1	See above	220
HIF-1-inducible proteins		91, 266
Bnip3, Bnip3L	See above	27, 76
HGTD-P	VDAC	431
Noxa	See above	382
p53-inducible proteins		290, 802
ASC	Bax	563
Bak	See above	603
Bax	See above	523, 603
BH3-only and BH3-related proteins		
Bid, Noxa, Puma, Bnip3L	See above	208, 675, 800
Ferredoxin reductase	Locally generates ROS	322
Maspin	Bax, Bcl-2: control on protein stability, GST: activation, HSP70, HSP90	423, 862, 886
mtCLIC/CLIC4	Is a chloride channel	211
p53AIP1	Bcl-2	500, 561
p66Shc	Mitochondrial HSP70, ROS generator	252, 574
Proline oxidase	Locally generates ROS	186
Siva-1	See above	220
TSAP6	Bnip3L	594
	Proteins translocating to mitochondria: p53-regulated proteins	
LKB1	Serine/threonine kinase	367
	Proteins translocating to mitochondria: transcriptional factors	
Nur77/TR3/NGFIB	Bcl-2	457
p53	Bak, Bax, Bcl-2, Bcl-X_L, GSK-3β, Mn-SOD	131, 443, 516, 820, 889
	Proteins translocating to mitochondria: fission regulatory proteins (517)	
Dap3	Involved in caspase-dependent cell death	534
Drp1	Endophilin B1/Bif-1	223, 366
Endophilin B1/Bif-1	Bax	366, 747

TABLE 2—*Continued*

Molecules	Putative Target: Mode of Action	Reference Nos.
Fis1	Positive regulator of mitochondrial fission	340, 436
	Proteins translocating to mitochondria: cytoskeleton regulators	
Cofilin	Upon apoptosis, it translocates to mitochondria before cytochrome *c* release	134
	Proteins translocating to mitochondria: kinases	
c-Abl	Phosphorylation of mitochondrial substrates	413
GSK-3β	elF2B, p53	584, 820
JNK	Bcl-2, Bcl-w, Bim, Bmf, Hrk/DP5	13, 437
PKC-δ	Bad, ERKs, PLS-3	293, 537
SEK1	JNK(?)	13
	Proteins translocating to mitochondria: proteases	
Calpain	AIF release, Bcl-X_L cleavage	541, 615
Caspase-2	Bid(?)	270
Caspase-3	Bcl-X_L, Bim_{EL}, complex I and II, Mcl-1	386, 644, 827, 851
Caspase-8	Mcl-1	299, 851
Caspase-9	Mcl-1	299, 851
	Proteins translocating to mitochondria: cytotoxic granule components	
Granulysin	Negatively charged lipids	586
Granzyme A	Promotes caspase-independent mitochondrial damage	493
Granzyme B	Bid, Mcl-1	279, 821
Granzyme C	Induces PT in intact cells and in isolated mitochondria	351
	Nonproteinaceous factors: (sphingo)lipid messengers	
Arachidonic acid	Facilitates PT	692
Ganglioside GD3	Lipid microdomains (?)	241, 646
Palmitate	ANT	179
	Nonproteinaceous factors: divalent cations	
Ca^{2+}	ANT, Drp1, VDAC	248, 251
	Nonproteinaceous factors: pro-oxidants	
4-Hydroxyhexenal	ANT	796
NO	ANT, Bcl-2, Bnip3	81, 796, 799
Superoxide	ANT, CK, VDAC	476, 682, 799
	Nonproteinaceous factors: metabolites	
Glucose	Locally generates ROS, at high concentrations	181
Glucose-6-phosphate	HKI	25

See text for definitions.

necessarily require p53 and may result from the activity of other transcription factors. For instance, in some experimental settings Fas/CD95 expression is regulated by members of the Jun, Egr (early growth response), and Nur77 (neural orphan nuclear receptor NUR77) subfamilies of transcription factors (346). In response to double strand breaks, p53 can somehow stimulate the nuclear release of histone H1.2, which then acts on mitochondria to favor MMP (396). Moreover, p53 can stimulate the expression of the p53-induced protein with a death domain (PIDD), thus contributing to the nuclear activation of caspase-2. Indeed, this caspase can be activated in the nucleus by the "PIDDosome," a molecular complex that contains PIDD and the caspase-2 and RIPK1 domain containing adaptor with death domain (CRADD, also known as RAIDD, RIP-associated ICH1/CED3-homologous protein with death domain) (51). In isolated mitochondria, caspase-2 has been shown to trigger MMP in a direct fashion, through a mechanism that does not rely on its proteolytic activity (at least in the cell-free system) (650). It remains to be established, however, which is the actual contribution of caspase-2 (and in particular of its "caspase-independent" function) to p53-induced apoptosis.

As outlined above, it appears that p53 can engage in multiple, in part cell-type-specific, proapoptotic pathways and promotes a sort of "overkill" by *trans*-activating a wide array of apoptosis-inducing genes (803). The transcriptional activity of p53 relies on complex mechanisms, which seem to depend on the levels of p53, its affinity for the regulated promoters, and interactions with several coactivators. For instance, Bax possesses a weak promoter and requires high amounts of p53 (358) or, alternatively, coactivation by STAT-1 (771). Moreover, p53 is able to activate Fas/CD95 via an effect on Golgi transport, i.e., via transcription-independent mechanisms (46).

TABLE 3. *Protein factors and second messengers that repress/prevent MMP by a direct effect on mitochondria*

Molecules	Putative Target: Mode of Action	Reference Nos.
	Sessile membrane proteins	
BH1234 proteins		
A1/Bfl-1	BH3-only proteins (Bim, Bik/Blk/Nbk, Hrk/DP5, Noxa, Puma, t-BID), Bok/Mtd	114, 832
Bcl-2	ANT, enhancement of ADP/ATP exchange, BH3-only proteins (Bad, Bim, Bmf, Puma, t-BID), ITM2B_L, VDAC	45, 122, 338, 832
Bcl-w	BH3-only proteins (Bad, Bim, Bik/Blk/Nbk, Bmf, Hrk/DP5, Puma, t-BID)	832
Bcl-X_L	Bak, Bax, BH3-only proteins (Bad, Bim, Bik/Blk/Nbk, Bmf, Hrk/DP5, Puma, t-BID), p53, VDAC, opening and enhancement of metabolite exchange	122, 714, 787, 832
Mcl-1	Bak, BH3-only proteins (Bim, Noxa, Puma, t-BID)	114, 443, 833
Bcl-X_{ES}	Bak, Bax: interferences with oligomerization	684
Dicarboxylate carrier (DCC)	Maintain mitochondrial GSH pool	422
FKBP38	Bcl-2, Bcl-X_L	363, 716
Oxoglutarate carrier (OGC)	Maintains mitochondrial GSH pool	846
Parkin	E3 ubiquitin ligase, promotes the degradation of mitochondrial substrates involved in apoptosis	169
PBR	ANT, VDAC	52, 236
VDAC2	Bak	104, 121
	Cytosolic proteins	
Associated with the PTPC		
HKI	Maintenance of the $\Delta\Psi_m$, reduction of ROS generation, VDAC	25, 804
HKII	VDAC, competition for Bax binding	596, 597
Chaperons (41)		
HSP60	Bak; Bax; Bcl-X_L	271
HSP70	AIF, Bax; MUC1 C-ter	642, 685
HSP90	Bid, MUC1 C-ter	642, 888
Translocating to the mitochondria		
Glucokinase	Bad	159
MUC1 C-ter	Bcl-2(?), Bcl-X_L(?)	641, 642
	Intermembrane space proteins	
Associated with the PTPC		
CK	ANT, VDAC, reduction of the affinity for Bax and competition for ANT binding	682, 792
	Matrix proteins	
Associated with the PTPC		
CypD	ANT, HKII	474, 688
	Components of the fission-fusion machinery (113)	
Opa1	Fis1	436, 566
Mfn2	Bax, reduces susceptibility to ROS-induced PT	549
	Antioxidant proteins	
Grx2	Promotes disulfide reduction	197
GST	ANT	795
Mn-SOD	Buffers oxidative insults, buffers lipid peroxidation, stabilizes mitochondrial membranes	531, 828
PHGPx	Buffers oxidative insults, prevents cardiolipin (CL) peroxidation	552
Prdx3	Trx2	554
Trx2	Controls ROS increases	755
	Components of the cytoskeleton	
G-actin	VDAC closure	262, 848
Tubulin	Bim_{EL}: sequestration	111
	Signal transducers	
Kinases		
Akt	Bad, Bax, GSK-3β, HKII, Mcl-1	173, 478, 852
c-Src	MUC1 C-ter	642
Casein kinase I and II	Bid	180
p70S6K	Bad	287
Pak5	Bad	148
PKA	Bad	288, 892
PKC-ε	ANT1, Bax, HKII, VDAC2	30, 508
PKG	PTPC	748
Pim-2	Bad	221

TABLE 3—*Continued*

Molecules	Putative Target: Mode of Action	Reference Nos.
Raf1	Bad, Bcl-2, VDAC	348, 426
RSK	Bad	192
Phosphatases		
Calcineurin	Bad	726, 810
PP2A	Bcl-2, Bid	155, 751
Others		
Gelsolin	VDAC closure	416
	Metabolites	
ADP	ANT	53, 798
ATP	ANT	53, 658
Cyclocreatine	CK	183
Creatine	CK	183
Glucose	Glucokinase, HK	159, 161, 478
GSH	Grx2, GST	197, 896
NADH	VDAC closure, buffers oxidative insults	896
NADPH	ANT, buffers oxidative insults	440a, 896
UTP	VDAC	658

See text for definitions.

p53 may also induce apoptosis via transcription-independent mechanisms (130), although it remains controversial to which extent this is important for DNA damage-induced apoptosis (Fig. 9). For instance, p53 can bind to OM and antagonize the antiapoptotic function of Bcl-2 and Bcl-X_L (516). Importantly, some p53 mutants simultaneously lose the capacity of binding to DNA and to Bcl-2/Bcl-X_L (516). p53 might also activate the pore-forming, MMP-inducing function of Bax (131) or Bak (443). Bax activation by p53 occurs in a direct fashion, without the requirement for additional factors, in a cell-free system (131). Moreover, the interactions among Bcl-X_L, cytoplasmic p53, and Puma (p53-upregulated modulator of apoptosis) coordinate the differential p53 roles, i.e., cytoplasmic versus nuclear (128). Indeed, after genotoxic stress, Bcl-X_L is able to sequester p53, thus preventing both its transcription-dependent and -independent activities. Puma is a proapoptotic BH3-only protein target of p53 transcriptional activity. When induced, it displaces p53 from Bcl-X_L and restores/enhances its proapoptotic effects (128). Thus distinct proteins of the Bcl-2 family and p53 may engage in a complex network of regulatory interactions that determine the cell fate through both transcriptional and nontranscriptional mechanisms.

The proapoptotic and cell-cycle-arresting (senescence-inducing) functions of p53 have been attributed to distinct transcriptional profiles (for example, Bax for apoptosis induction versus p21 for cell cycle arrest), which correlate, to some extent, with the phosphorylation of p53 on serine-46 (which augments its proapoptotic potential) (803). Whether such phosphorylation events also affect the nontranscriptional effects of p53 is currently unknown. Interestingly, it has been demonstrated that glycogen synthase kinase 3β (GSK-3 β) is able to bind to p53 and to promote p53-mediated transcription as well as its direct MMP-inducing effects (820).

The orphan nuclear receptor Nur77 (also known as TR3, i.e., thyroid hormone receptor 3) is an important coordinator of the equilibrium between proliferation and apoptosis and contributes to the maintenance of tissue architecture, notably in the colon mucosa. TR3 can translocate from the nucleus to mitochondria, to induce Cyt *c* release and apoptosis (445). Moreover, TR3 seems able to promote Cyt *c* release and apoptosis from a cytosolic localization, possibly through the activation of Bax and/or by changing the conformation of Bcl-2, thus switching it from an anti- to a proapoptotic, pore-forming function. This specific nucleus-to-cytoplasm translocation has been reported in colon carcinoma cells treated with selected proapoptotic compounds, such as butyrate, the nonsteroidal anti-inflammatory drug sulindac, or the chemotherapeutic drug 5-fluorouracil (834).

Thus several transcription factors can participate in the regulation of apoptosis upon translocation to mitochondria.

B. Endoplasmic Reticulum

ER stress can be induced by defective folding of ER proteins, as well as by perturbation of the Ca^{2+} gradient built up across the ER membrane. Cell death induced by ER-targeted toxins such as thapsigargin and tunicamycin is suppressed when MMP is avoided by overexpression of mitochondrial membrane-stabilizing proteins such as Bcl-2 or the viral mitochondrial inhibitor of apoptosis (vMIA) from cytomegalovirus (CMV) (66). There are numerous ways how ER Ca^{2+} or the so-called unfolded protein response (UPR) can induce MMP.

ER constitutes the main intracellular store for Ca^{2+}, a bivalent cation that contributes to a wide range of processes as diverse as proliferation, fertilization, and cell death (for reviews, see Refs. 70, 648). The strategic location of mitochondria close to the main source of intracellular Ca^{2+} allows them to be exposed to so-called Ca^{2+} "microdomains" (i.e., localized increases of Ca^{2+} that do not involve the totality of the cytoplasm but remain confined to part of it) which allow for the rapid and large accumulation of the cation in the matrix, despite the low affinity of mitochondrial transporters (614, 648, 745).

At physiological levels, Ca^{2+} released from the ER during cell activation is taken up by mitochondria to promote oxidative phosphorylation (through Ca^{2+}-stimulated reactions catalyzed by tricarboxylic acid cycle dehydrogenases) (188), to enhance metabolite flow on the OM (37), and hence to increase ATP production. Sustained and complete release of Ca^{2+} from the ER stores, in combination with additional stress signals, may initiate Ca^{2+}-dependent forms of apoptosis via the induction of MMP (274).

Ca^{2+} concentrations within the ER are tightly modulated by Ca^{2+}-regulated transporters, namely, inositol 1,4,5-trisphosphate receptor (IP_3R), of which three isoforms have been described, and ryanodine receptor (RYR) for release and sarcoplasmic and endoplasmic reticulum Ca^{2+}-activated ATPase (SERCA) for uptake. Due to the capacity of mitochondria to accumulate Ca^{2+} and to undergo Ca^{2+}-induced PT in some models of apoptosis, the cross-talk between the two organelles has been under intense investigation (Fig. 9). However, physiological stimuli (e.g., histamine, IP_3) that trigger the IP_3R-dependent release of Ca^{2+} are generally not sufficient per se to induce MMP, and require the participation of one or more coactivators. As a matter of fact, Bak, Bax, and Bcl-2 have been found to regulate MMP and apoptosis also by direct actions on ER membranes, presumably via the modulation of Ca^{2+} fluxes or by means of direct interactions with the above-mentioned Ca^{2+} transporters (101, 558, 765, 894).

As demonstrated by several laboratories, Bcl-2 lowers the Ca^{2+} loading of the ER stores (222, 581, 612), possibly by increasing Ca^{2+} leakage under resting conditions (581), although this may be a cell-specific effect (182, 614). In the absence of Bcl-2, the reduction of intra-ER Ca^{2+} obtained by different pharmacological and molecular approaches protects cells from ceramide-induced apoptosis (613). Because ceramide promotes apoptosis via a Bcl-2-sensitive pathway, these results support the idea that the antiapoptotic functions of Bcl-2 may be (at least in part) due to the depletion of ER Ca^{2+} (613). Thus it seems that Bcl-2 and other antiapoptotic proteins would inhibit lethal signals also by decreasing ER Ca^{2+}, thus indirectly reducing mitochondrial Ca^{2+} uptake (which can promote MMP) (Fig. 9).

Recent data support a model in which Bcl-X_L physically interacts with all three IP_3R isoforms and acts as a direct regulator of the transporter, by increasing its sensitivity to IP_3 and enabling Ca^{2+} release from the ER to be more sensitively coupled to extracellular signals (829). Within physiological Ca^{2+} ranges, this would enhance mitochondrial ATP generation and increase resistance to apoptosis. Accordingly, Bcl-X_L would not stimulate an unregulated leakage of Ca^{2+} from the ER, which would be energetically costly, but rather modulate an exquisitely regulated permeability (829). Bcl-2 has been suggested to control the phosphorylation state of type I IP_3R, which in turn influences the Ca^{2+} release rate through the channel (558). Moreover, the reduced resting concentrations of Ca^{2+} in the ER of $Bax^{-/-}/Bak^{-/-}$ fibroblasts (691) were raised to the normal levels of wt cells by small interfering RNA (siRNA)-mediated knock-down of type I IP_3R (558), again suggesting that IP_3R may be the downstream effector of the ER-specific activities of proteins from the Bcl-2 family. In this scenario, Bax and tBid may promote apoptosis, by acting as competitors of the interaction between Bcl-X_L (and possibly Bcl-2) and IP_3R (Fig. 9) (829). This may explain why Bax counteracts the release of ER Ca^{2+} caused by Bcl-2 (101, 558).

Numerous questions concerning the interaction between ER and mitochondria remain unsolved. For instance, it is still not clearly established whether this cross-talk requires microdomains of physical interaction between the two organelles or whether it occurs indirectly only through additional factors. Moreover, the temporal and spatial relationships between Ca^{2+} release and OM permeabilization remain an ongoing conundrum.

Activation of the UPR can cause MMP through a plethora of mechanisms. One is represented by activation of the transcription factor CHOP (C/EBP homologous protein, also known as GADD153, growth arrest- and DNA damage-inducible gene 153) (867). Others range from the p53-dependent transcriptional activation of Puma and Noxa (446) to the accumulation of gangliosides (165). Irrespective of the molecular details, however, it appears that the UPR kills the cells through a mechanism that strictly relies on MMP, since it can be inhibited or retarded by overexpression of Bcl-2-like proteins (557).

C. Lysosomes

Lysosomes are organelles rich in acidic hydrolases, the best characterized of which are the proteases of the cathepsin family. These enzymes are active and stable at low pH, whereas at neutral pH they may be highly active but show variable stability (775). Involvement of cathepsins has been observed in several pathophysiological processes including bone remodeling, hair follicle morphogenesis, antigen presentation, and wound healing (for a

review, see Ref. 775). The expression level of some cathepsins has been identified as an independent negative prognostic marker of breast cancer (727). Rupture of lysosomal membranes leads to the release of cathepsins into the cytosol and eventually to necrosis and/or apoptosis, depending on the amount of proteases released. Cytosolic enzymes, cystatins, exert an endogenous control over this cascade, by acting as reversible inhibitors of cathepsins (for reviews, see Refs. 80, 269).

Lysosomes-initiated apoptosis follows a mitochondrion-dependent pathway and is accompanied by caspase activation (68). Some cathepsins induce cleavage of the protein Bid (137), leading to its proapoptotic activation, interaction with other members of the Bcl-2 family, and MMP (Fig. 9). Interestingly, drug-induced DNA damage also appears to stimulate a lysosomal pathway that ultimately leads to cathepsin release, caspase activation, and MMP (585). Thus compelling evidences accumulate to indicate that lysosomes communicate with mitochondria to activate some forms of apoptotic cell death (for reviews, see Refs. 207, 406). Recently, tumor cell lysosomes containing increased levels of cathepsins have been reported. These organelles represent very attractive targets for the development of selective anticancer strategies (460).

D. Cytosol

Most metabolic pathways take place, as a whole or in part, in the cytosol or at the interface between the cytosol and mitochondria. These include, but are not limited to, glycolysis, gluconeogenesis, lipogenesis, the pentose phosphate pathway, the urea cycle, as well as reactions aimed to maintain the delicate intracellular redox equilibrium. Thus it is not surprising that several intermediate metabolites affect MMP and the mitochondrial control of apoptosis (Fig. 9). A complete compendium of the molecules involved in this subtle interplay goes far beyond the scope of this review. However, selected examples may help the reader to recognize an additional side of the critical role of mitochondria in the control of cell death.

The metabolites sharing direct antiapoptotic effects on the PTPC embrace the following: *1*) ADP and ATP, which act by binding to and inhibiting ANT (53, 798); *2*) creatine and cyclocreatine, through the modulation of creatine kinase (183); *3*) glucose, which favors the antiapoptotic interaction between HKII and VDAC (478), exerts HK-mediated antioxidant effects (161), and promotes Bad inactivation via glucokinase (in hepatocytes) (159); *4*) NADH and NADPH, which contribute to reduce the oxidative burden of cells and have direct effects on VDAC and ANT, respectively (896); and *5*) nonoxidized glutathione, an indispensable cofactor for the enzymatic reduction of protein disulfides (which have been proposed as a PTPC opening mechanism, when involving ANT; see sect. v*B*) (197, 896).

On the other hand, metabolic intermediates may induce MMP. For instance, glucose-6-phosphate promotes VDAC opening via a HKI-dependent mechanism (25). Also glucose, at high concentrations, may have proapoptotic effects due to the local generation of ROS (181). Finally, ROS as well as metabolites with pro-oxidant properties (e.g., NO, lipid aldehydes) promote MMP at different levels, presumably through effects on mitochondrial lipids as well as mitochondrial proteins including ANT (796, 799). Yet another example of proapoptotic mediators that are elicited by multiple lethal signal transduction and damage pathways are cations. In particular, Ca^{2+} appears as a quintessential inducer of MMP, through the PTP. Ca^{2+} is also involved in the signaling of ER stress to mitochondria (see sect. vii*B*) and plays a prominent role in pathological cell death.

Several signaling pathways executed in the cytosol influence the mitochondrion and regulate the mitochondrial phase of apoptosis. This applies to the ubiquitin/proteasome system as well as to several kinase-dependent pathways. These systems are discussed hereafter to some extent.

The ubiquitin/proteasome complex is responsible for the turnover of the vast majority of intracellular proteins and indirectly contributes to the control of proliferation and apoptosis. Protein degradation is a tightly regulated multistep process that requires *1*) the recognition of the protein to be eliminated, *2*) its tagging by means of several ubiquitin molecules (polyubiquitination), and *3*) its degradation by the 26S proteasome. Several Bcl-2 family members are substrates of the ubiquitin/proteasome degradation machinery. The induction of apoptosis by proteasome inhibitors results from the accumulation of a variety of proteins such as p53, p27, Bad, or Bax, which lead to the release of Cyt *c* and the activation of a Bcl-2-inhibitable mitochondrial apoptosis pathway in a variety of cells, including thymocytes (158, 303), cancer cell lines (626), and neurons (296). In myeloma cells, proteasome inhibitors (e.g., MG-132, lactacystin, and bortezomib) trigger the accumulation of Noxa, which in turn may contribute to MMP (626). These findings do not explain the relative specificity displayed toward cancer cells by clinically used proteasome inhibitors (such as bortezomib). However, they illustrate how the regulation of protein degradation can impinge on the control of MMP.

1. The phosphatidylinositol-3-kinase pathway

Phosphoinositide-3 protein kinase (also known as phosphatidylinositol-3-kinase, PI-3K) plays a role in signaling pathways implicated in cellular processes as diverse as proliferation, motility, tissue (neo)vascularize-

tion, carcinogenesis, and as recently discovered, apoptosis (84, 224). Signals from cell surface receptors may be transduced to the intracellular environment via the production of lipid second messengers including phosphatidylinositol 3,4,5-trisphosphate (PIP_3) by the type I PI-3K p110/p85. In turn, PIP_3 activates the kinase Akt/protein kinase B by promoting its recruitment to the plasma membrane and its phosphorylation by the PIP_3-dependent protein kinase 1 (PDK-1) (84). Akt activation then leads to the phosphorylation of a number of proteins involved in cell survival and apoptosis inhibition (Fig. 9). For instance, the phosphorylation of the inhibitory subunit of NFκB (IκB) by Akt results in the activation of the well-documented NFκB survival pathway (579). Moreover, Akt-dependent phosphorylation of caspase-9 blocks the induction of apoptosis (90). Phosphorylation implicates also proteins that affect directly MMP. One example is Bad, which translocates from the cytosol to mitochondria, where it binds to and inhibits Bcl-2 and Bcl-X_L, in a fashion modulated by its phosphorylation state (for reviews, see Refs. 109, 832). Bad phosphorylated on serine-112 or -136 by antiapoptotic kinases is sequestered by proteins of the 14–3-3 family and maintained in an inactive cytosolic localization (162). Moreover, phosphorylation of serine-136 (which is located closely to the BH3 domain of Bad, between amino acids 143 and 166) blocks the interaction between Bad and Bcl-X_L (374). When Akt phosphorylates Bad on serine-136, it hence prevents the proapoptotic interaction between Bad and Bcl-X_L through a dual mechanisms (598). Activation of Akt inhibits MMP through additional mechanisms (Fig. 9). One example is given by the Akt-mediated inhibition of GSK-3β, which in its active (dephosphorylated) form is able to phosphorylate the antiapoptotic Bcl-2-like protein Mcl-1, thus targeting it for ubiquitination and destruction by the proteasome (506). Moreover, Akt may inhibit apoptosis by promoting the binding of HKII to mitochondria, which in turn would prevent Bax from binding to VDAC and favoring MMP (597).

2. *Apoptosis signal-regulating kinase/mitogen-activated protein kinase*

Among the numerous proteins that translocate to the OM, protein kinases belonging to the apoptosis signal-regulating kinase (ASK)/mitogen-activated protein kinase (MAPK) cascade may play a central role in MMP regulation. For instance, the c-Jun NH_2-terminal kinases (JNKs) subfamily of the MAPK are considered as essential signaling molecules in neurodegenerative processes of the mammalian brain (297). Upon cellular stress, indeed, several JNKs associate with mitochondria (378, 414). JNKs reportedly inactivate antiapoptotic and activate proapoptotic proteins of the Bcl-2 family such as Bcl-2, Bcl-X_L, Bad, Bim, or Dp5 (687, 861) and may thus influence MMP.

ASK1 is a member of the MAP3K family. ASK1 protein activation is involved in the response to proinflammatory stimuli, ROS, and other types of cellular stress. In turn, ASK1 promotes the activation of the MAP2K-JNK/p38 cascades along a mitochondrion-dependent pathway. ASK1 is localized in both cytoplasm and mitochondria, and it has been involved in two distinct (namely, JNK dependent and independent) apoptotic pathways (885). ASK1 function is controlled by the cellular redox state via the thioredoxin (Trx) system (778). In the cytosol of resting cells, Trx1 binds to ASK1 and inhibits its proapoptotic activity. Similarly, Trx2 is the major inhibitor of the mitochondrial pool of ASK1. Recently, it has been shown that mitochondrion-targeted expression of a constitutively active ASK1 strongly induces apoptosis without JNK activation, Bid cleavage, and Bax translocation (885).

The protein kinase C (PKC) family participates in many cellular processes including cell growth and differentiation. Some newly identified PKC isoforms, e.g., PKC-δ, have been demonstrated to play also an active role in apoptosis induced by several stimuli (166). PKC modulates apoptosis by various mechanisms. For instance, PKC-δ is able to translocate to the mitochondrial compartment, where it triggers the dissipation of $\Delta\Psi_m$ and the release of Cyt *c* (Fig. 9) (479). Moreover, Murriel et al. (537) showed that PKC-δ mediates the accumulation and dephosphorylation of proapoptotic Bad, thereby favoring MMP and apoptosis. In contrast, other PKC isoforms, such as PKC-ϵ and -θ, may inhibit apoptosis through the modulation of proapoptotic Bcl-2 family members (50). For instance, PKC-ϵ activation was found to directly induce the phosphorylation of Bad, thereby preventing its participation in apoptosis. PKC-ϵ has been reported to translocate to mitochondria and to interact with the PTPC, thus inhibiting its proapoptotic activity, via the phosphorylation of VDAC (30).

These examples illustrate the complex cross-talk between kinase cascades and MMP in the regulation of apoptosis.

E. Cytoskeleton

Several cytoskeletal components, including microtubules, microfilaments, and intermediate filaments, have a key role in regulating both cell life and death. Motility, polarity, shape maintenance, as well as the cytoplasmic trafficking of molecules and organelles are indeed determined/modulated by cytoskeleton constituents and linked, more or less directly, to the cell's fate. For instance, adherent cells undergo apoptosis shortly after detachment from the extracellular matrix, a phenomenon known as "anoikis." Anoikis relies on proapoptotic signals emerging from integrins and its deregulation results in anchorage-independent growth, one of the most promi-

nent features of malignant cells (for reviews, see Refs. 262, 636). Another example of the crucial role of the cytoskeleton in determining the cell's fate comes from mitosis. The mitotic spindle, indeed, is constituted by microtubules, and several current anticancer drugs (e.g., vinblastine, paclitaxel) induce apoptosis by selectively targeting microtubules and blocking mitosis at the metaphase/anaphase checkpoint (for a review, see Ref. 353). A detailed analysis of all these processes would be beyond the aim of the present review, so we will limit our discussion to a few examples of the direct connections existing between the cytoskeleton and MMP.

Microtubules have been shown to sequester the BH3-only proteins Bim and Bmf, which interact with the dynein light chains 1 and 2, respectively (164). Bmf may be involved in anoikis. The interaction of the Bim_{EL} isoform with microtubules is regulated by (de)phosphorylation (111). Upon phosphorylation, Bim is freed and becomes able to counteract the antiapoptotic activity of Bcl-2-like proteins (111). Similarly, the protein Tat (transactivator of transcription) from human immunodeficiency virus-1 (HIV-1) induces apoptosis also by binding tubulin, altering microtubular dynamics, and eventually promoting Bim release (110).

Human gelsolin (a Ca^{2+}-dependent actin regulatory protein) has antiapoptotic effects, via the closure of VDAC (416). Also actin itself is involved in the regulation of VDAC, in organisms as distant as yeast and mammals. Apparently, monomeric actin promotes VDAC closure, and reduced actin dynamics (corresponding to the stabilization of actin in its polymeric state) would enhance sensitivity to several apoptotic stimuli (262). Recently, the increased association of β-actin with mitochondria has been proposed as a general apoptotic phenomenon, occurring before Bax translocation. Accordingly, actin may contribute to the initiation of apoptosis by enabling cytosolic proteins to be carried to mitochondria by the cytoskeleton-driven trafficking system (757).

These few examples demonstrate that the cytoskeleton is deeply involved in the modulation of cell death, not only through its well-characterized role in mitosis, but also through more direct interactions with mitochondria.

VIII. CELL DEATH EFFECTORS RELEASED FROM MITOCHONDRIA

Systematic analyses revealed that mitochondria release all soluble proteins contained in IMS through the permeabilized OM (600, 725, 787). Several among these proteins have important proapoptotic functions.

A. Cytochrome *c*

The cytosolic release of Cyt *c* is one of the key events in the mitochondria-dependent apoptotic pathway (450). Using GFP-tagged Cyt *c*, Green and co-workers (256) found that the release of Cyt *c* is almost invariably completed in 5 min and precedes the exposure of phosphatidylserine and the loss of plasma membrane integrity. In apparent contrast to the idea of a rapid, complete Cyt *c* release, however, two pools of Cyt c have been described. A major fraction of Cyt *c* is tightly associated with mitochondrial lipids (prominently cardiolipin), while a minor fraction diffuses freely within the IMS (577). Cardiolipin-bound Cyt *c* may be mobilized by the disruption of electrostatic interactions (that depend on pH and ion strength) and, more importantly, by the oxidation of cardiolipin mediated by ROS (577). Upon MMP-related apoptosis induction, Cyt *c* acts as a cardiolipin oxygenase, thus contributing via cardiolipin oxidation to both its own release and to that of additional proapoptotic factors (359). Upon release, a fraction of Cyt *c* is also targeted to the ER membrane, where it binds to type I IP_3R to amplify Ca^{2+}-dependent MMP-mediated apoptosis (61, 62). As a matter of fact, while elevation of the intracytosolic Ca^{2+} concentration within the physiological range facilitates IP_3-mediated Ca^{2+} release, higher concentrations inhibit the channel function of IP_3Rs. Interestingly, type I and type III IP_3Rs exhibit different thresholds for Ca^{2+}-mediated inhibition (54, 60). However, the Ca^{2+}-dependent inhibition of type I IP_3R is blocked upon its interaction with Cyt *c*, thus resulting in unrestrained Ca^{2+} release from ER stores, mitochondrial Ca^{2+} accumulation, and consequently, increased ROS generation, Ca^{2+}-mediated opening of the PTPC, and apoptosis (61, 62). These mechanisms may explain how a minor release of the mobile fraction of Cyt *c* may induce the rapid release of the entire Cyt *c* pool from mitochondria, via one or multiple positive amplification loops (for a review, see Ref. 242). Figure 10 schematically resumes the amplification loops underlying the biphasic release of Cyt *c*.

Once in the cytoplasm, Cyt *c* promotes the assembly of the so-called apoptosome, a molecular platform for the activation of pro-caspase-9, that includes Cyt *c*, APAF-1, and ATP/dATP. Upon formation of this complex, caspase-9 acquires the ability to trigger the processing and activation of the downstream caspase cascade, which ultimately culminates in apoptotic cell death (Figs. 1 and 2, see also sect. II*A*) (899). Caspases contribute to the dismantling of numerous cellular structures, including mitochondria. Moreover, activated caspases can access the IMS through the permeabilized OM and degrade essential components of the complex I of the respiratory chain, thus stopping the electron flow on IM (Fig. 10) (645).

Due to the obligate function of Cyt *c* in electron transport, which corresponds to the embryonic lethality of KO animals (447), its requirement for apoptosis and caspase activation has been difficult to establish. This drawback has been recently overcome by Mak and colleagues (284), who generated a "knock-in" mouse model expressing a mutant Cyt *c* (KA allele)

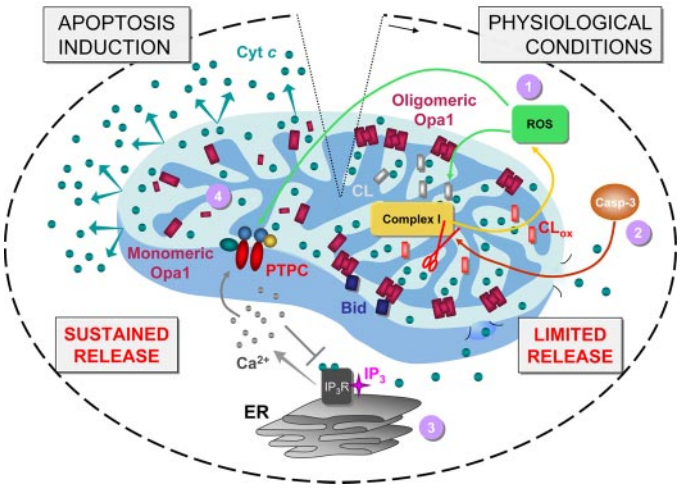


FIG. 10. Amplification loops for Cyt *c* release. *1*) In healthy cells, a major fraction of cytochrome *c* (Cyt *c*) is associated with the mitochondrial IM lipid cardiolipin (CL). This pool of Cyt *c* may be mobilized by the disruption of electrostatic interactions with CL or by the oxidation of CL mediated by reactive oxygen species (ROS) and by the CL-oxygenase activity exhibited by Cyt *c* itself. A limited release of Cyt *c* enhances the generation of ROS at the levels of the oxidative phosphorylation complexes (OXPHOS) I and III, thus favoring CL peroxidation and further Cyt *c* release. For additional details, see section VIII*A* and Ref. 242. *2*) Once in the cytosol, low amounts of Cyt *c* released following a limited mitochondrial membrane permeabilization (MMP) are sufficient to activate part of the caspase-3 (Casp-3) pool. Activated Casp-3, then, can enter the IMS through the partially permeabilized mitochondrial OM and cleave a 75-kDa component of the respiratory complex I. In turn, this provokes the disruption of the respiratory chain followed by an intense generation of ROS, which favor MMP by interacting with the permeability transition pore complex (PTPC) and/or support further Cyt *c* release by oxidizing CL. For more detailed information, see Ref. 242. *3*) At the ER, the second messenger IP_3 binds to its receptor (IP_3R) to modulate Ca^{2+} release. While physiological concentrations of Ca^{2+} enhance the IP_3R channel activity, higher concentrations inhibit the receptor, therefore establishing a negative-feedback regulatory loop. Low amounts of cytosolic Cyt *c* are able to bind to type I IP_3R and remove such Ca^{2+}-dependent inhibition, thus promoting unrestrained release of Ca^{2+} from the ER. In turn, Ca^{2+} favors MMP by direct effects on the PTPC. See sections VII, *B* and *D*, and VIII*A* as well as Ref. 242 for further information. *4*) The mobilization of ICS proteins occurring along with cristae remodeling represents an additional mechanism to account for the biphasic release of Cyt *c* during apoptotis. For additional details about cristae remodeling, see Figure 8 and section VI.

which retains normal electron transfer function but fails to activate APAF-1. Although most KA/KA mice displayed embryonic or perinatal lethality (similarly to the Cyt *c*-deficient models), the few surviving animals exhibited a severe impairment in lymphocyte homeostasis. Moreover, embryonic fibroblasts from the KA/KA mice are resistant to apoptosis induction by several stimuli including staurosporine and irradiation (284), underscoring the physiological importance of Cyt *c* for the activation of the apoptotic machinery.

B. Smac/DIABLO and Omi/HtrA2, Two Inhibitors of IAPs

Second mitochondria-derived activator of caspase (Smac), similarly to its murine homolog (direct IAP binding protein with a low pI, DIABLO), is a mitochondrial protein encoded by the nuclear genome. Smac/DIABLO harbors an NH_2-terminal MLS that is proteolytically removed upon the import into the organelle to yield a mature polypeptide of 23 kDa that resides in the IMS (187, 793). This proteolytic maturation reveals an IAP binding motif (IBM) at the NH_2 terminus of the protein (187). Following MMP, Smac/DIABLO is released from mitochondria and neutralizes endogenous inhibitors of caspases, the IAPs, thus favoring caspase activation (Fig. 2). Smac/DIABLO binds to several IAPs, including XIAP (X-linked IAP), cIAP1, cIAP2, survivin, and Apollon, via their baculoviral inverted repeat (BIR) domains (790). Functional Smac/DIABLO exists as an homodimer, each exposing two IBM motives (100, 840). One Smac/DIABLO dimer binds one XIAP molecule via both IBM, one interacting with BIR2 and the other one with BIR3 (318).

The physiological function of Smac/DIABLO in the IMS is still unknown. DIABLO KO mice have been generated and exhibit no phenotypical alterations (564). Cells isolated from these animals respond normally to apoptotic stimuli such as ultraviolet irradiation, staurosporine, etoposide, and Fas (564). These observations suggest either a minor role for Smac/DIABLO under physiological conditions or the existence of molecules that compensate for its loss. One of these molecules might be Omi/HtrA2.

Similarly to Smac/DIABLO, Omi/HtrA2 is a nuclear-encoded protein possessing an NH_2-terminal MLS that controls its import into the IMS (491, 744). Omi/HtrA2 is proteolytically processed in the IMS from a 49-kDa precursor into a 37-kDa mature form, which presents an IBM at its NH_2 terminus (491, 744). Omi/HtrA2 is a protease whose intramitochondrial targets have not been identified yet (665). Once released into the cytosol, it promotes cell death either by antagonizing IAPs (in a caspase-dependent fashion) and via its proteolytic activity (in a caspase-independent fashion) (665). Thus both Smac/DIABLO and Omi/HtrA2 constitute a means to amplify the caspase cascade activation, by antagonizing the IAPs-mediated inhibitory system (Fig. 2).

The KO of Omi/HtrA2 does not lead to an increased resistance against cell death. Rather, it appears that it enhances the susceptibility of neurons to cell death induction in mice (492). Accordingly, loss-of-function mutations that compromise the serine protease activity of Omi/HtrA2 are found in a fraction of patients with Parkinson's disease (734). Thus, at present, there is no genetic evidence suggesting that Omi/HtrA2 or Smac/DIABLO would contribute to cell death in vivo. It remains to be determined whether the simultaneous KO of both proteins might compromise mitochondrial apoptosis.

C. AIF

Mammalian AIF is a 62-kDa mitochondrial redox-active enzyme capable of oxidizing NAD(P)H in vitro and

exhibiting pro-apoptotic properties (466). These functions of AIF reside in distinct domains of the protein, as demonstrated by the analysis of redox-deficient apoptosis-competent AIF mutants (520). In healthy cells, AIF is confined to the IMS, where it is either present as a soluble monomer or tethered to IM. AIF is required for optimal detoxification of ROS and for the assembly or maintenance of the respiratory chain complex I (780). Accordingly, AIF depletion causes a defect in oxidative phosphorylation and an increase in vulnerability of the cells to oxidative stress (526). The release of AIF from mitochondria is likely to involve two steps, namely, OM permeabilization and proteolytic maturation of AIF, which is required to release AIF from its anchor in IM. The nature of the protease(s) involved in AIF release is not yet established, although either calpains and cathepsins have been shown to be able to mediate this process (526). The mitochondrial import and proapoptotic processing of AIF are illustrated in Figure 11. For a review, the reader may refer to Ref. 526.

Upon apoptosis induction, AIF is released from mitochondria to the cytosol, and it translocates to the nucleus where it mediates chromatin condensation and large-scale DNA fragmentation, through a process that may involve direct binding of AIF to DNA (Figs. 2 and 11) (163, 742). The downregulation of AIF by RNA interference protects differentiated PC12 cells against the neurotoxin 1-methyl-4-phenylpyridinium (MPP^+) (461), Jurkat T lymphoma cells against a combination of γ-irradiation and phytosphingosine (590), or Raji B lymphoma cells against ultraviolet irradiation (873). Microinjection of AIF-neutralizing antibodies can also reduce the neurotoxic effects of *N*-methyl-D-aspartate (NMDA) in primary murine cortical cultures (809), the lethal effects of poly-(ADP-ribose) polymerase 1 (PARP-1) activators in several cellular systems (872), as well as the proapoptotic effects of staurosporine on non-small-cell lung carcinoma cells (237). Mouse embryonic stem (ES) cells lacking AIF due to homologous recombination are resistant against cell death induced by serum deprivation (356) (for a review, see Ref. 526).

Bcl-2 and members of the heat shock protein (HSP) family have been shown to delay or prevent AIF-mediated toxicity, by different means (632, 743). Bcl-2 acts upstream of the mitochondrial release of AIF, whereas HSP70 (i.e., heat shock protein of 70 kDa) prevents its nuclear import (Fig. 2). Moreover, AIF nuclear translocation can be the result of p53 activation, independently from its transcriptional target Bax (149). The mechanism of AIF-mediated chromatin condensation and DNA fragmentation during apoptosis is unclear, but it has been suggested that AIF might bind to DNA (781) and recruit cyclophilin A to cause chromatinolysis (83). Alternatively, AIF might have a concealed nuclease activity. In *Caenorhabditis elegans*, the homolog of AIF (WAH1, i.e., worm

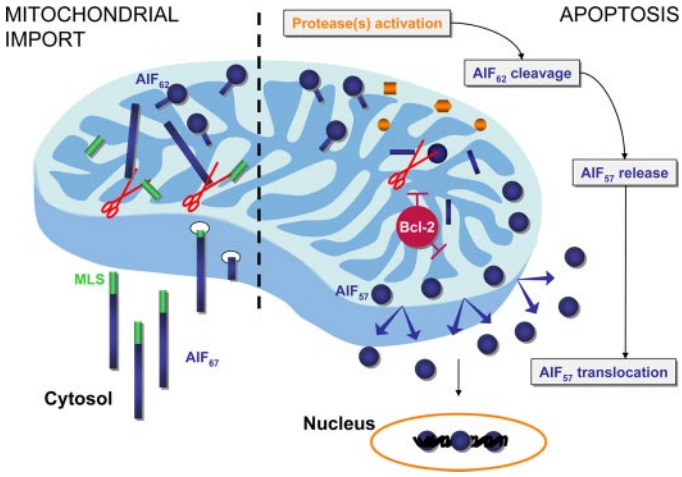


FIG. 11. Subcellular localization of apoptosis-inducing factor (AIF). AIF is synthesized in the cytoplasm as a precursor protein of ~67 kDa (AIF_{67}) that includes a mitochondrial localization sequence (MLS) at the NH_2 terminus. Upon mitochondrial import, MLS is cleaved by a specific peptidase to produce the mature form of 62 kDa (AIF_{62}), which inserts into the IM via an NH_2-terminal transmembrane domain. The rest of the protein forms a globular domain facing the intermembrane space (IMS), where it contributes to the activity of the respiratory chain. The pro-apoptotic release of AIF requires the intervention of a not yet identified inducible protease, which cleaves AIF_{62} to a IMS soluble form of ~57 kDa (AIF_{57}). When OM permeabilization occurs, AIF_{57} is released into the cytosol, then translocates to the nucleus, where it promotes chromatin condensation. Both the proteolytic activation of AIF and its release are regulated by antiapoptotic proteins from the Bcl-2 family. For additional details, see section VIII*C* and Ref. 526.

AIF homolog 1) associates with the homolog of mammalian EndoG (CPS-6, i.e., CED3 protease suppressor 6). This association enhances the nuclease activity of CPS-6 and results in apoptotic DNA degradation (815). In addition, WAH1 and CPS-6 have been shown to recruit nucleases, such as the cell death related nuclease 1 (CRN1) into a nuclear complex (the so-called "degradasome") (593).

The Harlequin (Hq) mouse strain, in which AIF expression is reduced to 10–20% of the normal value due to a retroviral insertion into the first intron of the AIF gene located on chromosome X (AIF^{HQ}), exhibits alterations in cell death control. These mice exhibit neurodegenerative phenomena, including ataxia (due to cerebellar atrophia) and blindness (due to retinal degeneration) (390). This neurodegeneration seems linked to an enhanced apoptotic destruction of neurons (390), as well as to an enhanced susceptibility of neurons to oxidative stress (390). Conversely, in vivo excitotoxicity studies (performed according to the paradigm of kainic acid-induced seizures) revealed that Hq mice have significantly less hippocampal damage than their wt littermates (123). Furthermore, the brain of Hq mice is particularly resistant against ischemia/reperfusion damage (154). These results exemplify that AIF has a dual role in the control of cell death. Generation of cell lines and rodent models in which either of the two AIF functions (lethal or vital) are manipulated separately, for instance, by knock-in ap-

proaches, is required to obtain further insights into the physiological functions of AIF.

D. Endonuclease G

Since the first steps of cell death research, the fragmentation of nuclear DNA has been recognized as a hallmark of apoptosis. It results from the activation of multiple nucleases. One such nuclease is endonuclease G (EndoG), a mitochondrion-specific enzyme that, similarly to AIF, translocates to the nucleus during apoptosis (Fig. 2). Once in the nucleus, EndoG cleaves chromatin DNA into nucleosomal fragments (448). The caspase requirement in the EndoG pathway is still controversial. Some authors demonstrated that the nuclease is able to play its role independently of the caspases, for instance, in response to tBid (788), while others reported the requirement for caspase activation (22, 592). EndoG-deficient mice have been generated by two independent groups, and the resulting phenotype is debated. One study reported the stringent implication of EndoG in early embryogenesis, but these results were likewise based on the adventitious removal of an adjacent gene (884). A more recent paper shows that the EndoG KO has no obvious anatomical or histopathological consequences (331). Thus the physiological role of EndoG remains to be established.

E. Other Mitochondrial Effectors

The above-mentioned factors are not the sole proteins released from mitochondria after MMP, suggesting the existence of a poorly specific efflux mechanism, at least at late stages of the process. For instance, ADK, which catalyzes the (reversible) ATP-mediated phosphorylation of AMP to generate two ADP molecules, normally resides in the IMS and is released into the cytosol during apoptosis. However, its possible active role in cell death has not been elucidated (394). In an attempt to classify the toxic proteins released from mouse liver mitochondria by recombinant tBid, Van Loo et al. (787) performed an analysis by matrix-assisted laser desorption ionization postsource decay (MALDI-PSD) (787) (for a review, see Ref. 665). They found 16 proteins ranging in size from 10 to 123 kDa, including the previously mentioned Cyt *c*, DIABLO, EndoG, Omi, and ADK2. Moreover, they identified a fatty acid-binding protein (FABP1), a polypyrimidine tract-binding (PTB) protein, an RNA-binding protein necessary for efficient translation of internal ribosomal entry site (IRES)-containing mRNAs, an acyl CoA-binding protein (ACBP), an activator of m-calpain and Bid, and several procaspases (namely, procaspase-2, -3, -8, and -9). These results correlate with a previous study conducted on mouse liver mitochondria treated by atractyloside, a PT inducer (600), and confirm that the process of OM permeabilization is not specific for a defined category of proteins. Which among the released proteins actively participates in apoptotic execution is the subject of the continued effort of many investigators.

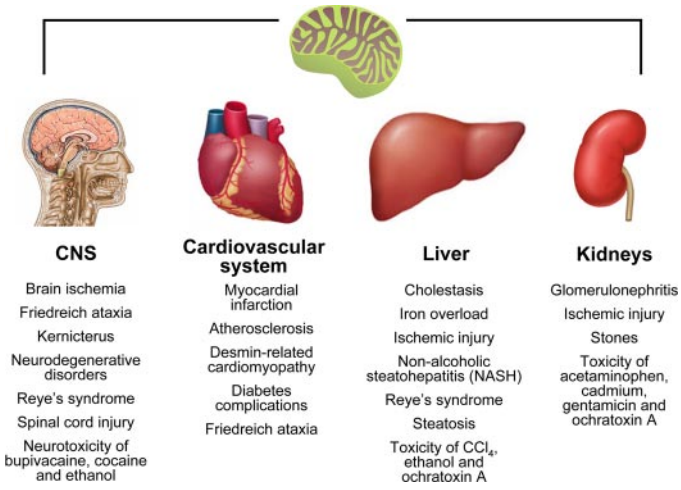


FIG. 12. Examples of the involvement of mitochondrial apoptosis in pathological cell loss. Mitochondrial apoptosis has been implicated in a plethora of acute and chronic human diseases that affect several tissues and organs. The figure reports only a few examples of pathological conditions in which mitochondrial apoptosis plays a prominent role, grouped according to the most affected tissue. Please refer to section IX for further details. CNS, central nervous system; MMP, mitochondrial membrane permeabilization.

IX. MITOCHONDRIAL MEMBRANE PERMEABILIZATION IN MAJOR HUMAN DISEASES

Enhanced or inhibited MMP has been described as a feature of many human diseases such as ischemia/reperfusion, intoxication with xenobiotics, viral infections, or neurodegeneration. These diseases are not restricted to a specific organ or cell type and are favored by altered exogenous conditions (e.g., lack of oxygen, xenobiotic accumulation, pathogen infection) or by mutations affecting endogenous effectors (e.g., huntingtin in Huntington disease). It would be beyond the scope of this review to summarize the vast literature on the pathophysiology of MMP. In the next paragraphs, we simply report some basic notions demonstrating that MMP is important for pathological cell death. Figure 12 reports several examples of human pathologies in which MMP may play an important role. Examples of endogenous and exogenous MMP modulators with a role in prominent human diseases are reported in Tables 4–11.

A. Ischemia/Reperfusion

Apoptotic cell death pathways have been implicated in acute brain injury, including cerebral ischemia/

TABLE 4. *MMP modulators in cardiac ischemia/reperfusion (I/R) injury*

Factors	Target: Mode of Action/Notes	Reference Nos.
	Examples of cardiotoxic endogenous factors promoting MMP (47, 308)	
Accumulation of long-chain fatty acids	PTPC, ANT: Ca^{2+} homeostasis	398, 826
Ca^{2+} overload	PTPC	117, 826
ROS	PTPC	723, 826
	Examples of cardioprotective, MMP-inhibitory factors (47, 308)	
Endogenous factors		
Acetylcholine	HIF-1. Effective in vitro against hypoxia-induced apoptosis	360
Glucose	HIF-1. Effective in vitro against hypoxia-induced apoptosis	481
Insulin	Akt, HK, Effective in vivo in canine and rabbit models of I/R injury	471
L-Carnitine	Caspases, inhibition; ROS generation, antioxidant. Essential cofactor for the β-oxidation of long-chain fatty acids; antioxidant. In vitro, it prevents PT in isolated mitochondria. Effective ex vivo on postischemic recovery of isolated rat hearts and in vivo in multiple models of I/R injury. Effects confirmed in clinical settings	153, 213
NO	PTPC. NO donors are effective in vivo in a mouse model of coronary artery occlusion	808
Ursodeoxycholic acid (UDCA)	PI-3K, PTPC. Effective in vivo in a rat model of coronary artery occlusion	629
Urocortin	HSP90, iPLA2, MAPK, mitoK$_{ATP}$, PKC-ε. Effective in several in vitro, ex vivo, and in vivo models of I/R injury. Upregulated in surviving cells from human heart after I/R injury	424, 678
Exogenous factors		
Amiodarone and derivatives	Unknown: ROS generation(?), Ca^{2+} balance. Effective in vivo in rat models of I/R injury and ex vivo on isolated canine hearts undergoing simulated ischemic conditions	789
Caffeic acid phenyl ester (CAPE)	p38 MAPK, direct effect on the mitochondria. Effective in vivo in a rabbit model of acute myocardial I/R injury	752
Cyclosporin A	CypD. Effective in vitro against hypoxia-induced damage, in vivo in rat and rabbit models of I/R injury, and ex vivo on isolated rat hearts and human atrial tissues undergoing simulated ischemic conditions	19, 291, 701
Diazoxide	MitoK$_{ATP}$. Effective in vitro against oxidative stress-induced apoptosis and in vivo in a rat model of I/R injury	18, 399
Diltiazem	Na^{+}/Ca^{2+} exchange; Ca^{2+} buffering during reperfusion. Effective ex vivo and in vivo in several models of I/R injury	9, 410
2-4-Dinitrophenol (DNP)	OXPHOS, uncoupling. Effective ex vivo on isolated rat hearts undergoing simulated I/R conditions	291, 519
Minocycline	Caspases; Smac/DIABLO; XIAP, transcriptional regulation. Effective in vitro against hypoxia-induced apoptosis and in vivo in models of I/R	679
Nicorandil	MitoK$_{ATP}$. Effective in vitro against oxidative stress-induced apoptosis	7, 539
Sanglifehrin A (SfA)	CypD. Effective ex vivo on isolated rat hearts and human atrial tissues undergoing simulated ischemic conditions	276, 701
SSR180575	PBR. Effective in vitro against oxidative-stress induced $\Delta\psi_m$ dissipation on isolated mitochondria, ex vivo on isolated rat hearts undergoing simulated I/R injury, and in vivo in a rat model of I/R injury	791, 801
TATBH4	VDAC. Effective in vitro on isolated mitochondria and against apoptosis and in vivo in a rat model of I/R damage	572, 714
Trimetazidine	PTPC. Effective in vitro on isolated mitochondria, ex vivo on isolated rat hearts, and in vivo in rat and rabbit models of I/R injury	20, 519
β-Aescin	Unknown. Effective in vivo in a rat model of focal cerebral ischemia (FCI)	314

See text for definitions.

reperfusion damage (for reviews, see Refs. 102, 229). Many studies have indeed revealed an important contribution of mitochondria and have correlated cell death with the release of Cyt *c* after Bax (85) and Smac/DIABLO translocation, enhanced ROS levels, activation of effector caspases-9 and -3 (401), and DNA fragmentation. In the liver, ischemia/reperfusion injury results in apoptotic and necrotic cell death clearly involving the process of mitochondrial PT (438). The underlying molecular mechanisms were extensively studied in primary hepatocytes, in cell lines, as well as in ex vivo and in vivo organs, revealing the occurrence of MMP followed by Cyt *c* release along with reperfusion (302). During ischemia, factors such as intracellular Ca^{2+}, long-chain fatty acids, and ROS accumulate and progressively increase mitochondrial susceptibility to PT. Upon reperfusion, finally, this lethal event takes place. Of note, the exact mechanisms of death (apoptosis versus necrosis) differ in the normal liver compared with the pathological (e.g., steatotic) liver (695), but both may implicate MMP. However, this has not yet been clearly elucidated.

Acute myocardial infarction, cardiac surgery, and chronic heart failure represent additional conditions lead-

TABLE 5. *MMP modulators in acute and chronic intoxication*

Toxin/Antitoxin	Target: Mode of Action/Notes	Reference Nos.
	Examples of exogenous toxins acting via MMP induction	
Metals		
Aluminum (Al^{3+})	ER, proapoptotic transcriptional response(?), VDAC: inhibition of voltage gating	768, 883
Cadmium (Cd^{2+})	PTPC: ROS generation, oxidative injury	449, 706
Chromium (Cr^{4+} and Cr^{6+})	p53, PTPC: ROS generation, oxidative injury	619, 661
Copper (Cu^{2+})	p53, PTPC, OXPHOS complexes: ROS generation, oxidative injury	16, 576
Iron (Fe^{2+})	PTPC: ROS generation, oxidative injury	190, 463
Lead (Pb^{2+})	PTPC: ROS generation, oxidative injury	292
Manganese (Mn^{2+})	PTPC, OXPHOS complex II: ROS generation, oxidative injury	480, 660
Mercury (Hg^{2+})	PTPC: ROS generation, oxidative injury	15, 92
Methylmercury ($MeHg^{+}$)	PTPC: ROS generation, oxidative injury	328, 768
Zinc (Zn^{2+})	Bim (all isoforms): induction, ERKs: activation, PKC: activation, p53, PTPC: ATP and NADH depletion, ROS generation, oxidative injury	485, 576
Others		
Aldehydes	Unknown: oxidative injury(?)	611
Asbestos	p53: upregulation of proapoptotic targets, PTPC: ROS generation, Ca^{2+} homeostasis impairment	583
Bupivicaine	PTPC: oxidative stress. Myotoxic and neurotoxic local anesthetic, unable to promote PT on isolated mitochondria	332
Gentamicin	Unknown, Hrk/DP5 involvement. Ototoxic aminoglycoside, responsible for hearing loss. Induces cyclosporin A- and minocycline-sensitive apoptosis in hair cells	143, 361
	Examples of MMP-inhibitory antitoxins	
Cyclosporin A	CypD. Effective in vivo in salicylate-poisoned rats	285, 369
L-Carnitine	Caspases: inhibition, JNK, ROS generation: antioxidant. In vitro, it prevents PT in isolated mitochondria. Effectively prevents hearing loss and cochlear damage in newborn guinea pigs exposed to gentamicin in utero	361, 538

See text for definitions.

ing to ischemia/reperfusion damage in the heart and involve as well an enhanced cell death via the mitochondrial pathway (for a review, see Ref. 826).

Based on the ever-increasing incidence of ischemia/reperfusion-related pathologies in humans, an intense search for therapeutics has been undertaken during the last years. Interestingly, in the different cells types involved (including but not limited to neurons, hepatocytes, and cardiomyocytes), CsA, an agent targeting the interaction between CypD and ANT within the PTPC (277), can protect cells from MMP and consequent cell death (439, 501). Similarly, the KO of CypD greatly enhances the resistance of neurons and cardiomyocytes against cell death induced by temporal occlusion of the carotid or the coronary arteries, respectively (29, 540, 681). For a list of MMP modulators involved in cardiac ischemia/reperfusion injury, the reader may refer to Table 4.

B. Intoxication

Toxic xenobiotics can affect several mitochondrial processes, such as $\Delta\Psi_m$ maintenance, oxidative phosphorylation, ATP production, and ROS generation. Generally, the alteration of (several of) these functions leads to the uncoupling of mitochondria and the induction of MMP, and eventually results in the cell death. This applies to heavy metals [such as lead, mercury and cadmium (403) as well as arsenite (421)], atractyloside (732), salicylate (772), or acetaminophen (498), all of which target the PTPC (Table 5). Other prominent toxins that inhibit the function of the respiratory chain include MPP^+, rotenone, antimycin A, and paraquat (147; for a review, see Ref. 806). Mitochondrial parameters including $\Delta\Psi_m$, matrix swelling, and enzymatic activities are considered as predictable markers of toxicity and have thus been exploited to set up many automated and miniaturized assays for the development/evaluation of pharmacological agents. For instance, Woolacott and Simpson (839) established a toxicological screen of 100,000 molecules based on the measurement of $\Delta\Psi_m$ by the fluorescent probe JC1 and of the PTPC opening by the calcein release method. Similarly, the group of Lemasters (59) developed a microtiter plate assay that measures PT, mitochondrial swelling, and Ca^{2+} uptake simultaneously. These assays are built on the assumption that MMP would constitute a sort of "master switch" between cell death and cell survival. Drugs that inhibit toxin-induced MMP may be used to fight the acute cell loss induced by intoxications. As an example, again, CsA can prevent the acute hepatorenal toxicity of atractyloside or acetaminophen in vivo, in rodent models (285).

TABLE 6. *MMP modulators in neurodegeneration*

Factors	Target: Mode of Action/Notes	Reference Nos.
	Examples of neurotoxic factors promoting MMP (26, 544, 575, 680)	
Endogenous factors		
Amyloid β-peptide (Aβ)	ABAD, Bcl-2 family members expression, Bim-mediated Smac/DIABLO release, calcineurin- and Akt-mediated Bad mitochondrial translocation, OXPHOS complex IV: inhibition, ER: Ca^{2+} homeostasis impairment, ERAB, NO, p53: transcriptional regulation of proapoptotic targets, PTPC: ROS generation. Involved in the pathogenesis of AD	307, 750, 856
Huntingtin	ATP depletion, Ca^{2+} homeostasis impairment, increased sensitivity to complex II inhibition, ANT: decreased mitochondrial ADP uptake, Omi/HtrA2 and Smac/Diablo: aberrant release, p53: upregulation. Mutated in HD	343, 419, 673
N-methyl(*R*)salsolinol [NM(R)Sa]	PTPC: ROS generation, others(?). Present selectively in monoaminergic neurons, may be relevant in PD pathogenesis. Intrastriatal injection in rats provides a model of PD	494, 543
Phytanic acid	OXPHOS complexes(?) - ROS generation. Involved in the pathogenesis of Refsum disease	639
Presenilins	Akt: downregulation; Bcl-2, Bcl-X_L, and FKBP38: degradation; ER; Omi/HtrA2, proteolytic activity increase; PAR-4: induction; PLC: induction; PSAP; PTPC: Ca^{2+} homeostasis impairment, ROS generation. Involved in AD pathogenesis	618, 749
Tetrahydrobiopterine	OXPHOS complexes I and IV: inhibition, oxidative stress. Present selectively in monoaminergic neurons, may be relevant in PD pathogenesis	132
Unconjugated bilirubin (UCB)	Mitochondrial lipids, PTPC. Involved in the pathogenesis of kernicterus	655, 656
N-butyl-β-carboline-3-carboxylate (BCCB)	Unknown. May be involved in PD	282
Exogenous factors		
3-Nitropropionic acid (3NP)	OXPHOS complex II: inhibition, calpain. Induces striatal lesions in rats (model for HD)	58, 235
6-Hydroxydopamine (6-OHDA)	GSK-3β: PP2A-mediated activation; JNKs: activation, translocation to mitochondria, others: ROS generation, ATP and glutathione depletion. Provides an experimental paradigm of PD	112, 347
Aluminum maltolate (see also "aluminum")	Intracisternal injection in rabbits provides a model for AD	250, 672
Cocaine	Multiple targets	555, 567
Ethanol	PTPC, interruption of neurotrophic supports	456
MPTP/MPP(+)	Bax: NO-dependent posttranscriptional induction, OXPHOS complex 1: inhibition, gene expression dysregulation, superoxide generation. Provides an experimental paradigm of PD.	218, 622
Rotenone	OXPHOS complex 1: inhibition, superoxide generation, Ca^{2+} homeostasis impairment. Provides an experimental paradigm of PD	139, 218
3-(4-Morpholinyl)-sydnonimine (SIN-1) (peroxynitrite generator)	Bax: upregulation, Bcl-2: downregulation, OXPHOS complex 1: nitration, PTPC: lipid peroxidation, ROS generation	702, 853
	Examples of neuroprotective, MMP-inhibitory factors (26, 544, 575, 680)	
Endogenous factors		
Creatine	CK: ATP generation. Effective in vitro against MPP(+)- and 6-OHDA-induced apoptosis and in vivo in multiple models of ALS, HD, and PD	391, 662
Cyclocreatine	CK: ATP generation. Effective in vivo in models of HD and PD	183, 502
Estrogens	Mitochondrial membranes: stabilization of OXPHOS complexes, antioxidant activity. Effective in vitro against 3NP-, Aβ-, and glutamate-induced apoptosis and in vivo in animal models of AD and PD	643, 719
L-Carnitine	Caspases: inhibition; PTPC: antioxidant. Essential cofactor for the β-oxidation of long-chain fatty acids. In vitro, it prevents PT in isolated mitochondria. Effective in vivo in a mouse model of ALS induced by the overexpression of mutated human SOD1 and in a rat model of HD	56, 384
Melatonin	PTPC: ROS generation, Ca^{2+} accumulation. Effective in vitro against 6-OHDA- and oxidative stress-induced apoptosis of astrocytes and neurons	354, 589
Tauroursodeoxycholic acid (TUDCA)	Bax, PI-3K: reduces ROS generation. Effective in vitro against Aβ- or glutamate-induced apoptosis and in vivo in a model of HD	98, 372
Exogenous factors		
CsA	CypD. Effective in vitro against 3NP-, Aβ-, and NM(R)Sal-induced apoptosis and in vivo in a rabbit model of AD, in mouse models of ALS, and in a rat model of HD	250, 373, 385
D609	PTPC: antioxidant, glutathione-like activity, prevents ROS accumulation. Effective in vitro against Aβ-induced apoptosis	739
Decylubiquinone (coenzyme Q10)	PTPC: antioxidant, reduces ROS generation. Effective in vitro against rotenone- and paraquat-induced apoptosis.	191, 527
Diazoxide	MitoK_{ATP}. Effective in vitro against Aβ-induced apoptosis	470, 700
Dibucaine	PTPC, mitochondrial lipids: prevents Bax-mediated MMP but not Bax insertion. Effective in vitro against BH3 peptide-induced apoptosis, proposed for PD therapy	218, 616
Flupirtine	PTPC: antioxidant, reduces ROS generation; increase mitochondrial Ca^{2+} uptake, $\Delta\Psi_m$, and ATP synthesis. Effective in vitro on isolated mitochondria and against Aβ-, glutamate-, or PrP-induced apoptosis and in vivo against methamphetamine-induced striatal damage in rats	244, 683

TABLE 6—*Continued*

Factors	Target: Mode of Action/Notes	Reference Nos.
Fraxetin	PTPC: antioxidant, reduces ROS generation. Effective in vitro against rotenone-induced apoptosis	669
Lithium (Li^{3+})	Extracellular signal-regulated kinases (ERKs): activation, GSK-3β: inhibition, JNK: activation. Effective in vitro against MPP(+)-induced apoptosis and in vivo in models of AD and PD.	125, 868
Minocycline	Caspases, iNOS, others(?): inhibition, Ca^{2+} buffering(?). Effective in vitro against staurosporine (STS)- but not ROS-induced apoptosis, in vivo in models of ALS, HD, PD, and spinal cord injury (SCI)	761, 893
N-methylated β-carbolines (harmaline, harmalol, and harmine)	Antioxidants, ROS scavengers. Effective in vitro against dopamine-induced apoptosis and in vivo in a mouse model of PD	427, 591
Propranolol	PTPC, mitochondrial lipids: prevents Bax-mediated MMP but not Bax insertion. Effective in vitro against BH3 peptide-induced apoptosis, proposed for PD therapy	218, 616
Propargylamines (rasagiline and derivatives)	Bad, Bax: downregulation, Bcl-2, Bcl-w, Bcl-x_L: induction, PBR: displacement from VDAC, PKC: activation and upregulation. Effective in vitro on isolated organelles and against 6-OHDA-, MPTP-, NM(R)Sal-, and SIN-1-induced apoptosis and in vivo in rat models of AD	483, 825
Valproic acid	Bcl-2(?), GSK-3β: inhibition, HSP70: induction. Effective in vitro against rotenone-induced apoptosis	381, 582
UCF101	Omi/HtrA2. Effective in vitro in a model of HD	254

See text for definitions.

C. Neurodegeneration

Mitochondrial dysfunction has been implicated in several different models of both acute and chronic neuronal death (for a review, see Ref. 505). Experimental evidence has accumulated supporting that after an acute stroke or a traumatic injury the death of neurons occurs also via mitochondrial pathways (217, 503). During the phase of reduced blood supply, the ATP, oxygen, and glucose equilibrium would be compromised, leading to cell death. Although apoptosis is not the sole mode of cell death in all brain regions (227), in the tissue immediately surrounding the ischemic region (i.e., the penumbra), the majority of neurons die by apoptosis, exhibiting the typical features of caspase activation, nuclear chromatin condensation, and DNA fragmentation. Interestingly, MMP modulators that inhibit mitochondrial apoptosis (e.g., Bcl-2, Bcl-X_L, CsA) are able to efficiently prevent neuronal cell death following a stroke or a hypoglycemic insult (88, 228) and are active in models of traumatic brain and spinal cord injury as well (548, 670; for a review, see Ref. 738). For instance, CsA-mediated blockade of the PTPC diminishes infarct size in the rat after transient middle cerebral artery occlusion (501).

The pathogenesis of chronic neurodegenerative disorders is likely to involve MMP and apoptosis as well (503). This has been substantiated in both animal models and patients with Alzheimer's, Parkinson's, or Huntington disease (503). These pathologies share enhanced oxidative stress and perturbed cellular energy and ion homeostasis. In Alzheimer's disease (AD), the amyloid β-peptide contributes to the generation of ROS, resulting in increased lipid peroxidation and production of the aldehyde 4-hydroxynonenal, which is a potent activator of apoptosis and MMP via a direct effect on ANT (411, 796). According to some reports, the amyloid β-peptide also exerts a direct permeabilizing effect on mitochondria (657). Intriguingly, recent experiments conducted on mixed astrocyte/neuronal cultures support the idea that the amyloid β-peptide acts preferentially on astrocytes, where it promotes ROS generation and mitochondrial depolarization, yet causes neuronal death, as an indirect consequence of the oxidative stress generated in astrocytes (2). Moreover, the alteration of Ca^{2+} regulation and an ER stress response that activates mitochondrial enzymes and sensitizes mitochondrial membranes to permeabilization (647) have been observed in studies of cultured cells and transgenic mice expressing mutant forms of presenilin-1 (i.e., models of AD) (504).

One of the etiological determinants of Huntington disease (HD) is a mutation in the gene encoding huntingtin. In transgenic mice and cultured neurons, mutated huntingtin can trigger MMP and apoptotic cell death via the impairment of proteasome function and interferences with Ca^{2+} signaling (343, 758). Mutations in frataxin that cause Friedreich's ataxia, another prominent neurodegenerative disease, apparently perturb mitochondrial ion metabolism, leading to enhanced ROS generation and, finally, to MMP and cell death (142, 234). Similarly, some of the mutations that predispose to the development of Parkinson's disease (PD) can affect mitochondrial function. This applies to mutations compromising the ubiquitine ligase function of Parkin as well as to mutations that abolish the protease activity of Omi/HtrA2 (1).

Several mitochondrial toxins induce PD- and HD-like syndromes in rodents, non-human primates, and humans. For example, the complex I inhibitors rotenone (694) and

TABLE 7. *MMP modulators in infectious diseases*

Factor	Target: Mode of Action/Notes	Reference Nos.
	Examples of pathogen-derived factors promoting MMP	
Bacterial toxins		
CagA (*Helicobacter pylori*)	Unknown. Possible involvement of p53 and Bax	415, 510
PorB (*Neisseria gonorrheae*)	VDAC homolog	535
PVL (*Staphylococcus aureus*)	OM lipids: pore-forming protein	245
SipB (*Salmonella enterica*)	Targets mitochondria for autophagy	298
VacA (*Helicobacter pylori*)	Bak, Bax. Possible involvement of Bid and caspase-8	831, 854
Viral proteins		69, 156
2C (AEV)	Unknown. Induced Cyt *c* release and subsequent activation of a caspase-dependent apoptosis pathway	462
Apoptin (CAV)	Nur77/TR3/NGFIB: cytoplasmic translocation, unknown: $\Delta\Psi_m$ dissipation	79, 475
HBx (HBV)	Bcl-X_L, HSP60, OXPHOS complexes, PTPC, VDAC3: mitochondrial aggregation, ROS generation	435, 514
NSs (Bunyavirus)	Unknown, reaper-like protein. Induces Cyt *c* in isolated mitochondria and caspase-dependent apoptosis in mice, in vivo	141
$p13^{11}$ (HTLV-1)	IM lipids	157, 718
p7 (HCV)	Forms amantadine-sensitive ion channels	267
PB1-F2 (Influenza virus)	ANT3, IM lipids, VDAC1	108, 116, 875
Vpr (HIV-1)	ANT, Bax, HAX-1	73, 175, 859
	Examples of pathogen-derived MMP-inhibitory factors	
Bacterial virulence factors		
PorB (*Neisseria meningitides*)	Unknown: direct effect on mitochondria	497
Viral proteins related to Bcl-2		69, 155
BALF1 (EBV)	Bak, Bax, BHRF1	42, 490
BHRF1 (EBV)	Bcl-2 homolog without hydrophobic groove	301, 317
hpvBHRF1 (*Herpesvirus pan*)	BHRF1 (EBV) homolog	313
hpvBHRF1 (*Herpesvirus papio*)	BHRF1 (EBV) homolog	512
KSBcl-2 (HHV-8)	Close structural Bcl-2 homolog	120, 316
Viral proteins unrelated to Bcl-2		69, 155
E1B-19K (Human adenovirus E)	p53 at mitochondria	467
E2 (HCV)	Unknown. Probably related to inhibition of Cyt *c* release from mitochondria	433
F1L (*Vaccinia* virus)	Bak	733, 818
K1 (HHV-8)	Lyn, PI-3K	620
K7 (HHV-8)	Bcl-2, CAML, caspase-3	811
K15 (HHV-8)	HAX-1	703
M11L (*Myxoma* virus)	Bak, PBR	202, 807
NS2 (HCV)	CIDE-B	198
p35 (*Baculovirus*)	iNOS, buffers oxidative insults	630
vMIA (CMV)	ANT, Bax	21, 617

See text for definitions.

MPP^+ induce Parkinsonism (94, 335), and the succinate dehydrogenase inhibitor 3-nitropropionic acid induces HD-like manifestations (12). These toxins presumably act by inducing in neurons oxidative and metabolic alterations that simulate the events occurring in vivo in patients affected by PD and HD.

Thus it appears that chronic neurodegenerative diseases such as AD, HD, and PD may involve mitochondrial dysfunction as an obligate correlate of their pathogenesis. Table 6 reports several examples of endogenous and exogenous factors involved in neurodegenerative phenomena through the modulation of MMP.

D. Viral Infection

Viruses have evolved multiple strategies to modulate apoptosis for their own benefit, including some that act specifically at the mitochondrial level (Table 7). Antiapoptotic viral proteins (e.g., M11L from myxoma virus, F1L from vaccinia virus, and the Bcl-2 homolog BHRF1 from Epstein-Barr virus) contain mitochondrial targeting sequences (MTS) in their COOH terminus that are homologous to tail-anchoring domains. These domains are similar to the COOH-terminal transmembrane domain of some members of the Bcl-2 family and are responsible for inserting the protein into the OM, leaving the NH_2 terminus of the protein facing the cytosol. The antiapoptotic proteins K7 and K15 from avian encephalomyelitis virus (AEV) and vMIA from CMV are capable of binding host-specific apoptosis-modulatory proteins. For the purpose of the present discussion, we only mention a few proapoptotic viral proteins that are relevant for human pathogenesis. For a general overview on viral modulators of mitochondrial apoptosis, the reader may consult recent reviews (69, 330).

TABLE 8. *MMP modulators in liver disease*

Factors	Target: Mode of Action/Notes	Reference Nos.
	Examples of hepatotoxic factors promoting MMP	
Endogenous factors		
Deoxycholic acid (DCA)	Mitochondrial lipids, PTPC. Implicated in the pathogenesis of cholestasis	722
Glycochenodeoxycholic acid (GCDCA)	Mitochondrial lipids, PTPC: ROS generation. Implicated in the pathogenesis of cholestasis	722
Unconjugated bilirubin (UCB)	PTPC: ROS generation. Implicated in the pathogenesis of cholestasis and jaundice	556
Ursodeoxycholic acid (UDCA)	Bcl-2: conformational changes. PTPC: ROS generation. Increases, upon long-term exposure, GCDCA-induced apoptosis in vitro. Implicated in the pathogenesis of cholestasis	97, 779
Exogenous factors		
Acetaminophen	GSK-3β, PTPC: oxidative stress. Toxic for hepatocytes in vitro and in vivo	285, 473
Amiodarone and derivatives	Unknown: ROS generation(?), oxidative injury(?) Promotes the development of nonalcoholic steatohepatitis	230, 370
Atractyloside	ANT. Toxic for hepatocytes in vitro and in vivo	285
Carbon tetrachloride (CCl_4)	PTPC: oxidative stress	841
Ethanol	PTPC: Ca^{2+} increase, ROS generation, glutathione and NADH depletion from acetaldehyde metabolism, ATP synthesis impairment, general oxidative injury. Involvement of Bax and VDAC-dependent pathways. Implicated in acute liver disease and cirrhosis	3, 637
Ochratoxin A	Bcl-X_L(?): downregulation(?), PTPC: ROS generation	23, 306
Salicylates	PTPC: ROS generation. Implicated in Reye's syndrome	38, 439
Valproic acid	PTPC: ROS generation. Implicated in Reye's syndrome	439, 772
	Examples of cytoprotective, MMP-inhibitory factors	
Endogenous factors		
Glutathione	ROS generation: antioxidant. Effective in vitro and in vivo against acetaminophen-induced hepatotoxicity	285
L-Carnitine	Caspases: inhibition, ROS generation: antioxidant. Essential cofactor for the β-oxidation of long-chain fatty acids. In vitro, it prevents PT in isolated mitochondria. Effective in vivo in preventing cisplatin- and ochratoxin A-induced liver injury	24, 105
NO	Caspase-8, PTPC. NO donors are effective in vitro against TNF-α-induced apoptosis of hepatocytes and in vivo against acetaminophen-induced liver failure	216, 383
Tauroursodeoxycholic acid (TUDCA)	Increases glutathione levels, prevents Bax translocation to mitochondria in vivo. Effective against DCA-induced apoptosis in vitro	686
UDCA	PTPC: reduces ROS generation. Effective in vitro against DCA-induced apoptosis and in vivo against fetal liver disease due to obstructive cholestasis during pregnancy	604, 654
Exogenous factors		
Bongkrekic acid	ANT. Effective in vitro against GCDCA-induced apoptosis	860
Cyclosporin A	CypD. Effective in vitro against GCDCA-induced apoptosis	860
Diltiazem	Na^+/Ca^{2+} exchange: Ca^{2+} buffering during reperfusion. Effective in vitro against hypoxia-induced apoptosis and ex vivo in isolated rat livers undergoing simulated I/R injury	150
Dilinoleoylphosphatidylcholine (DLPC)	ROS generation: antioxidant. Effective in vitro against ethanol-induced apoptosis	849
Ebselen	ROS generation: antioxidant. Effective in vitro against GCDCA-induced apoptosis	860
Idebenon	ROS generation: antioxidant. Effective in vitro against GCDCA-induced apoptosis	860
Lycopene	ROS generation: antioxidant. Effective in vitro against ethanol-induced apoptosis	759
Nicorandil	$MitoK_{ATP}$. Effective in vivo against hepatic I/R injury	273
S-15176	PTPC. Effective in vivo against hepatic I/R injury	193, 530
Trifluoperazine	PTPC. Effective in vitro against hypothermia- and metal ion-induced apoptosis	439, 619
Trimetazidine	PTPC. Effective in vitro on isolated mitochondria and in vivo in a rat model of hepatic I/R damage	194, 699
UDCA	PTPC: ROS generation. Effective in vivo in a model of ethanol-induced liver injury	746
α-Tocopherol	ROS generation: antioxidant. Effective in vitro against GCDCA-induced apoptosis	860

See text for definitions.

Viral proapoptotic proteins translocate to mitochondrial membranes and induce MMP, which is often accompanied by mitochondrial swelling and fragmentation. From a structural point of view, all the viral proapoptotic proteins discovered so far contain amphipathic α-helices that are necessary for their proapoptotic effects and seem to have pore-forming properties. Notably, this applies to the viral protein R (Vpr) from HIV-1, the X protein (HBx) from hepatitis B virus (HBV), and PB1-F2 from influenza virus.

1. Vpr from HIV-1

The viral protein R (Vpr) is a small accessory protein encoded by HIV-1 with multiple roles during the infectious cycle. A synthetic peptide corresponding to

TABLE 9. *MMP modulators in renal disease*

Factors	Target: Mode of Action/Notes	Reference Nos.
	Examples of nephrotoxic factors promoting MMP	
Endogenous factors		
Age	Increased mitochondrial apoptosis upon renal I/R injury	625
Oxalate (stone constituent)	iPLA2: activation, PTPC(?): ROS generation, lipid peroxidation	86
Exogenous factors		
Acetaminophen	PTPC: oxidative stress. Toxic for proximal renal tubular cells in vitro and in vivo	285
Atractyloside	ANT: ATP/ADP exchange inhibition, PTPC: opening. Toxic for proximal tubular cells in vitro and in vivo	285
S-(1,2-dichlorovinyl)-L-cysteine (DCVC)	Unknown. Induces Bcl-2-sensitive $\Delta\Psi_m$ dissipation and apoptosis in proximal tubular cells in vitro	118
Gentamicin	Unknown. Toxic for renal cell lines in vitro	698
Mercuric chloride ($HgCl_2$)	PTPC: ROS generation, oxidative injury. Induces acute renal failure due to severe proximal tubule atrophy in rats	729
Ochratoxin A	Bcl-X_L(?): downregulation(?), $\Delta\Psi_m$: increase, HIF-1: upregulation, PTPC: ROS generation	23, 247
	Examples of cytoprotective, MMP-inhibitory factors	
Endogenous factors		
Acidic pH	Apoptosome. Effective in vitro against ATP depletion-induced apoptosis	75
Glutathione	ROS generation: antioxidant. Effective in vitro and in vivo against acetaminophen-induced toxicity	285
L-Carnitine	Caspases: inhibition, ROS generation: antioxidant. Essential cofactor for the β-oxidation of long-chain fatty acids. In vitro, it prevents PT in isolated mitochondria. Effective in vivo in preventing cisplatin-induced and I/R renal injury	105, 260
Exogenous factors		
(−)-Epicatechin 3-*O*-galate	Unknown: increase in antioxidant enzymes. Effective in vitro against 3-(4-morpholinyl)-sydnonimine (SIN-1)-induced apoptosis and in vivo in a rat model of renal damage induced by lipopolysaccharide (LPS) and I/R (peroxynitrite dependent)	865
Azelnidipine	Voltage-dependent Ca^{2+} channels: blocking, Ca^{2+} buffering. Effective in vitro against ATP depletion-induced apoptosis and in vivo in a rat model of renal I/R injury	756
Edarabone	Free radical scavenger. Effective in vitro against cisplatin-induced apoptosis and in vivo in a rat model of cisplatin-induced renal failure	671
Minocycline	Bcl-2: induction. Effective in vitro against hypoxia-, azide-, cisplatin-, and staurosporine (STS)-induced apoptosis and in vivo in models of renal ischemic injury	376, 812
Pifithrin-α	p53. Effective in vivo in a rat model of I/R involving GTP depletion	375
Sanguiin H-6	Unknown: antioxidant(?) Effective in vivo in a rat model of renal damage induced by LPS and I/R (peroxynitrite dependent)	864
Sodium arsenite	HSP70. Effective in vivo in a rat model of renal I/R	855
Trifluoperazine	PTPC. Effective in vitro against hypothermia-induced apoptosis	34, 439
Zinc (Zn^{2+})	Bax(?), caspases(?). Effective in vitro against ATP depletion-induced apoptosis	824

See text for definitions.

the COOH-terminal moiety of Vpr (residues 52–96) induces MMP via a specific interaction with PTPC (339). Vpr52–96 has been demonstrated to interact with ANT to form high-conductance channels in artificial lipid bilayers (338). This channel-forming activity may depend on a protein-to-protein interaction involving an α-helical dodecapeptide domain (residues 71–82) of Vpr, since it is abolished by the addition of a recombinant peptide corresponding to the Vpr binding site of ANT (663). The structural basis of ANT/Vpr channel formation has been recently described (663). However, ANT may not be the sole mitochondrial target of this peptide. Indeed, Vpr had been previously reported to form cation-selective channels in artificial membranes by means of its NH_2-terminal domain (residues 1–40) (610). This effect is ANT independent and, accordingly, the resulting channels exhibit a much lower conductance than pores formed by the cooperation between Vpr and ANT. Bax and Bcl-2 have been shown to modulate the functional and physical Vpr/ANT interaction. While Bcl-2 inhibits this interaction and suppresses channel formation in synthetic membranes, Bax increases the conductance of Vpr/ANT channels (338).

2. *HBx from hepatitis B virus*

HBV X protein (HBx) contributes to the development of hepatitis B virus (HBV)-induced hepatocellular carcinoma (763). HBx controls multiple key cellular processes as diverse as proliferation and apoptosis and exhibits

TABLE 10. *Mitochondrial apoptosis-related genes in cancer*

Gene	Notes	Reference Nos.
	Examples of proapoptotic tumor suppressor genes inactivated in cancer	
AMID	Downregulated in a majority of human tumors	843
ASC	Silenced as a result of aberrant methylation in breast, colorectal, ovarian, and prostate cancers. Restored expression results in enhanced sensitivity to chemotherapy, in vitro	562
Bad	Dysregulated in epidermal dysplastic and neoplastic lesions. Somatic mutations inactivating its BH3 found in a small proportion of colon cancers. In vivo, systemic delivery of a prostate cancer-specific promoter-driven Bad results in the suppression of tumor growth in nude mice	430, 887
Bak	Mutated in gastric and colorectal cancers as well as in uterine cervical carcinoma	667, 816
Bax	Inactivated in >50% of colon and gastric cancers of the microsatellite mutator phenotype; this event contributes to tumor progression by providing a survival advantage. Differentially expressed in CNS cancers during tumor progression and differentiation. In vivo, systemic delivery of a prostate cancer-specific promoter-driven Bax results in the suppression of tumor growth in nude mice	329, 532, 887
Bid	Inactivating mutations reported in few cases of gastric cancers. The frameshift mutant inhibits other apoptotic pathways in a dominant-negative fashion. May be downregulated by HIF-1-dependent and independent pathways in hypoxic zones of solid tumors	200, 429
Bik/Blk/Nbk	Lost in clear-cell renal cell carcinoma (RCC). Loss-of-heterozygosity (LOH) results rarely from mutations or more frequently from deletions; DNA methylation mediates silencing. In vivo, systemic delivery of different Bik-expressing constructs results in the inhibition of pancreatic and breast tumor growth in mice	453, 735
Bim	Behaves as a tumor suppressor in epithelial solid tumors and confers resistance to paclitaxel, in vivo and in vitro	451, 754
Bnip3/Nip3	Silenced by aberrant methylation in gastric, colorectal, and pancreatic cancers. Lost at late stages of pancreatic cancers; its loss contributes to resistance to therapy and worsened prognosis. In non-small cell lung carcinoma (NSCLC) its expression represents a major independent factor for overall survival. Upregulated by an HIF-1-dependent pathway in perinecrotic region of tumors	199, 536, 565
Bnip3L/Nix	Involved in EGFR-related sensitivity to therapy of breast cancer cells and in PTEN-dependent apoptosis of various cancer cell lines, in vitro. Unlikely to be implicated in LOH in ovarian and breast cancers	418, 635
Caspase-8	Frequently inactivated by aberrant methylation or by other mechanisms in pediatric and neuroendocrine lung tumors, but not in NSCLC	289, 717
Ferredoxin reductase	Intriguingly overexpressed in colorectal cancers. Several single nucleotide polymorphisms (SNPs) described with no apparent relationship with protein expression and tumor development	871
GADD45α	Rarely mutated but frequently silenced upon epigenetic mechanisms in breast cancer. In pancreatic cancer, expression correlates with lower survival rate, but is lost in a substantial percentage of the cases. Combined expression with thymidine phosphorylase may predict the clinical outcome after neoadjuvant chemotherapy in gastric cancer	545, 814
Hrk/DP5	Epigenetically inactivated by aberrant methylation in a subset of colorectal and gastric cancers. Restoration of expression results in increased sensitivity to apoptosis	559
IGFBP3	Downregulated in squamous cell carcinoma complicating recessive dystrophic epidermolysis bullosa. Genetic polymorphisms in both the coding sequence and promoter are associated with increased risk of breast, colorectal, and prostate cancer. May be silenced by methylation of p53-binding sites in the promoter	280, 482
LKB1	Mutations are responsible of familial and nonfamilial Peutz-Jeghers syndrome. Allelic losses, but not mutations, are common in sporadic breast and colon cancers. Epigenetically inactivated in sporadic colorectal cancer. Low expression is a negative prognostic factor in breast carcinoma	704, 863
Maspin	Expression dysregulated in several cancers as a result of epigenetic control mechanisms or p53 inactivation. Expression levels correlate with malignancy grade, vascularization, invasiveness, and clinical features, in either a direct or indirect fashion, according to the tumors. Proposed as a marker for the detection of residual disease in breast cancer patients. In vivo, gene therapy approaches have been effective in mice models of breast and prostate cancer	511, 736, 819
Noxa	Dysregulation of uncertain clinical and pathological value occurs in colorectal cancers. One somatic mutation, with no functional consequences, has been reported in a transitional cell carcinoma of the urinary bladder	345, 434
p53	p53. Inactivated as a result of mutations or functional events in ~50% of human malignancies	532, 724
p53AIP1	Adenovirus-mediated gene transfer suppresses tumor growth, in vivo, independently of p53 status	866
p66Shc	Involved in the development of bronchopulmonary dysplasia	432
Proline oxidase	Expression reduced or absent, as a result of p53-dependent mechanisms, in a substantial proportion of renal carcinomas	507
Puma	Affected by LOH in a considerable percentage of head/neck and lung cancers. No directly inactivating mutations have been described so far. Dysregulated only in a few cases of sporadic colorectal cancer; it may have a minor role in the pathogenesis of this disease	311, 344

TABLE 10—*Continued*

Gene	Notes	Reference Nos.
Smac/DIABLO	Downregulated or lost in RCC. Its loss correlates with a worse prognosis	524
	Examples of antiapoptotic oncogenes overexpressed of functionally hyperactivated in cancer	
A1/Bfl-1	Overexpressed in several surgically resected cancer tissue specimens, but not in the corresponding established cell lines. May be preferentially expressed in infiltrating inflammatory cells and play only a contributory role in tumorigenesis	357, 587
ANT2	Overexpressed in oncocytoma and urothelial renal tumors, as well as in highly proliferative cells	206, 253, 707
Bcl-2	Overexpressed in several human malignancies. Overexpression correlates with therapy resistance, aggressive clinical course, and poor survival	103, 388
Bcl-X_L	Overexpressed in several human cancers. In breast and colorectal tumors, overexpression is associated with high tumor grades and nodal metastases	57, 569
Bcl-w	Overexpressed in a relevant proportion of infiltrative gastric adenocarcinomas and in colorectal cancers	389, 428
CK	Downregulated by epigenetic mechanisms in oral squamous cell carcinoma. Downregulation inversely correlates with tumor differentiation. Aberrant expression reported also for other humans malignancies, including lung, breast, and colon cancers. Proposed, with no definitive validations, as a circulating tumor-associated marker	571, 774
HKII	Overexpressed in several cancers. Interesting link between the well-known highly glycolytic phenotype of malignant cells and their apoptosis dysregulation. Its promoter has been proposed as a tumor-specific promoter for cancer gene therapy. [^{18}F]fluoro-2-deoxy-D-glucose positron emission tomography (^{18}F]FDG-PET) imaging relies on HK increased activity, in association with increased glucose transport by tumors	309, 721
HIF-1	Overexpressed or functionally hyperactivated in RCC and other tumors	33, 696
HSP60	Overexpressed in colorectal, prostate, and ovarian cancers. In ovarian carcinomas, overexpression is not the result of gene amplification and correlates with worse survival	144, 529
HSP70	Overexpressed in several malignancies, among which pancreatic, colorectal, gastric, and bladder cancer. In some instances, but not all, overexpression correlates with tumor grade and poor prognosis	334, 362
HSP90	Expressed in several malignancies, among which primary and metastatic intracranial tumors, urinary bladder, and breast cancers. Its chaperon activity towards several oncoprotein is a convenient therapeutic target	89, 547
Mcl-1	Overexpressed in multiple human cancers. Overexpression generally correlates with high proliferation, high-grade morphology, and poor prognosis	133, 379
MUC1	Overexpressed in a large range of human cancers of epithelial and hematological origin. Cellular expression levels correlate with aggressiveness, tumor progression, and poor prognosis. Circulating levels of MUC1, anti-MUC1 antibodies, or immune complexes have been widely used as a tumor progression marker or to discriminate between neoplastic and inflammatory diseases	32, 255
Parkin	Frequently affected by LOH and altered expression in NSCLC, breast, and ovarian cancers	177, 609
PBR	Overexpressed in breast, colorectal, and prostate cancers. Its expression is associated with tumor progression and aggressiveness. May have a prognostic value in specific patients groups	472

See text for definitions.

cellular effects including transcriptional activation, disruption of p53 activity, DNA repair, stimulation of kinase signaling pathways converging on mitogenic Raf, Ras, and MAPKs (624, 764). HBx is also a potent apoptosis inducer, whose effects may be neutralized by Bcl-2 or not (689, 764). HBx has been shown to localize to mitochondria, to promote their aggregation at the nuclear periphery, and to dissipate $\Delta\Psi_m$ (628). A putative transmembrane region (residues 54–70) may facilitate HBx mitochondrial targeting, perhaps aided by two α-helical domains (residues 75–88 and 109–131) (319). Reportedly, HBx interacts with VDAC3 (628), via its COOH-terminal domain (817). Whether this interaction contributes to the cytopathic effect of HBx and hepatic carcinogenesis, however, remains to be established.

3. Influenza virus PB1-F2

The influenza A virus encodes a conserved protein of 87 amino acids, i.e., PB1-F2, which is capable of inducing cell death. PB1-F2 has unusual properties compared with other influenza virus proteins, including a peculiar mode of translation, its absence from some animal isolates of the virus, variable expression levels in infected individuals, proteasome-dependent degradation, and mitochondrial localization (116). PB1-F2 can sensitize cells to apoptotic stimuli such as TNF-α, as proved by increased caspase-3 activation in PB1-F2-expressing cells (875). Moreover, when added to purified mouse liver mitochondria, PB1-F2 triggers Cyt *c* release and $\Delta\Psi_m$ loss and enhances tBid-induced mitochondrial permeabilization. Taken together, these data

TABLE 11. *MMP modulators in cancer*

Modulator	Target: Mode of Action/Notes	Reference Nos.
	Examples of MMP facilitators with an established/possible role in cancer therapy (238)	
17-Llylaminogeldanamycin (17-AAG)	HSP90. Completed phase I trials against acute leukemias and advanced refractory cancers. Ongoing phase II trials against hormone refractory prostate cancer and other tumors	294, 547
ABT-737	Bcl-2. Antitumor activity in vitro against cancer cell lines and primary patient-derived cells and in vivo against small cell lung cancer xenografted in nude mice	570
Antimycin A	Bcl-2, Bcl-X_L. Particularly toxic for Bcl-X_L overexpressing cancer cells, in vitro	484, 776
Arsenite	ANT. Established treatment of promyelocytic leukemia, multiple myeloma, and other hematological malignancies	43, 249, 421
Bad-DTTR	Mimics endogenous Bad. Toxic for glioma cell lines in vitro	324
BaxBH3Ant	Mimics endogenous Bax. Toxic for Bcl-2 overexpressing cells, in vitro	797
Bcl-X_L antisense oligonucleotides	Bcl-X_L. Effective in vitro in the chemosensitization of mesothelioma cell lines	310
Betulinic acid	Unknown. Induces PT in isolated mitochondria and apoptosis in vitro in several tumor cell lines	232, 233
BH3 inhibitors (BH3Is)	Bcl-2, Bcl-X_L. Induces PT in isolated mitochondria and apoptosis in vitro in several tumor cell lines	210, 649
CD437	ANT. Synthetic retinoid; it induces apoptosis in vitro in several types of cancer cells, via retinoic acid receptor (RAR)-independent pathways	63, 371, 489
Cladribine	Unknown. Purine analogs, it induces apoptosis also by activating the mitochondrial pathway. Therapy of leukemia and lymphoproliferative disorders	246, 393
Clodronate	ANT. Therapy for bone metastases from primary prostate and breast cancers	140, 515
Etoposide	Unknown. DNA damaging agent, it induces MMP directly, at high doses. Established therapy of several cancers	336, 588, 651
F16	Mitochondrial membranes. Effective in vitro against multiple tumor cell lines	204, 205
Fludarabine	Unknown. Purine analogs, it induces apoptosis also by activating the mitochondrial pathway. Therapy of leukemias and lymphoproliferative disorders	246, 393
FTY720	Akt: dephosphorylation. PTPC(?). Immunosuppressant, induces PT on isolated mitochondria and apoptosis in several cancer cell lines in vitro; inhibits in vivo growth of androgen-independent prostate cancer	135, 858
GSAO	ANT. Angiogenesis inhibitor in vitro and in vivo in a mouse model of solid tumor development	185
HA14-1	Bcl-2, Bcl-X_L. Effective in vitro against multiple tumor cell lines	283, 720
hGM-CSF-Bad	Chimeric protein that mimics endogenous Bad	11
$(KLAKKLAK)_2$ peptide	IM lipids. Effective in vivo in prostate cancer-prone transgenic mice	14, 195
Lonidamine	ANT. Phase II trials for glioblastoma and ovarian cancer	43, 578
MKT-077	Mitochondrial membranes, mtDNA. Effective in vitro against carcinoma cell lines and in vivo against human tumors xenografts transplanted in nude mice.	124, 525
Oblimersen sodium	Bcl-2. Antisense oligonucleotide. Phase I, II, and III trials against several tumors	103, 769
Paclitaxel	Established therapy (alone or in combined regimens) of several cancers	380, 857
PK11195	PBR, others: ROS generation. Chemosensitization. Reverses Bcl-2-mediated resistance and facilitates apoptosis induction in vitro in several tumor cell lines and in vivo in nude mice xenografted with human small cell lung cancers	169, 258, 304
Resveratrol	PKC-α, PKC-δ: inhibition, PTPC(?). Chemoprevention	6, 900
SAHBs	Bcl-2, Bcl-X_L: Effective in vitro and in vivo against human leukemia xenografts in mice	805
Thiazolidenediones	Bcl-2, Bcl-X_L: inhibition of Bak binding, independently of PPARγ activation. Effective in vitro against PPARγ-expressing and PPARγ-deficient cancer cell lines	705
	Examples of MMP inhibitors involved in carcinogenesis	
2-Acetylaminofluorene (AAF)	Bcl-2, PTPC. Increases in vivo resistance of hepatocytes to LPS-induced apoptosis	392
Nicotine	Bad: phosphorylation-dependent interaction with 14-3-3, Bax: phosphorylation-dependent inactivation	349, 845
NNK	Bcl-2, c-Myc: ERKs- and PKC-α-dependent phosphorylation	350

GSAO, 4-(*N*-(*S*-glutathionylacetyl)amino)phenylarsenoxide; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone.

suggest that the proapoptotic action of PB1-F2 relies on MMP. Indeed, two PTPC members (i.e., ANT3 and VDAC1) have been identified as interactors of the viral protein using glutathione-*S*-transferase pulldown coupled to mass spectrometry analyses (875). Inhibitors of the PTPC (such as CsA and BA) suppress PB1-F2-induced MMP, confirming a functional cooperation between PTPC and PB1-F2 (875).

E. Cancer

Impaired MMP may lead to the invalidation of the apoptotic response that is found in cancer (178, 281). Several independent mechanisms may cause MMP resistance. On theoretical grounds, these include the following: *1*) alterations (e.g., upregulation, repression) of gene expression, resulting from genetic (e.g., amplification) or

epigenetic (e.g., aberrant methylation) events; *2*) loss-of-function mutations; or *3*) defects in the posttranslational regulation of activity resulting from intracellular localization/trafficking (e.g., inhibition of Bax translocation to mitochondria). All these aberrations may concern structural PTPC proteins as well as MMP regulators. To date, most of the above-mentioned mechanisms have been already reported, either in patients involved in clinical studies, in animal models, or in cell cultures. Examples of MMP-related genes involved in the pathogenesis of cancer are provided in Table 10. Table 11 reports exogenous factors affecting MMP that may be employed in cancer therapy (MMP inducers/facilitators) or that promote carcinogenesis (MMP inhibitors).

Cancer-associated alterations in the expression level of PTPC components have been described for ANT (206), HK (640, 693), the peripheral-type benzodiazepine receptor (PBR) (472), and VDAC (715). PTPC proteins may be overexpressed in various tumors and cancer cell lines (707). The overexpression of the HKII isoform reportedly leads to an enhanced interaction between HKII and VDAC, which in turn limits the translocation of Bax to mitochondria and hence Bax-mediated MMP (652). The overexpression of PTPC components may affect multiple isoforms (e.g., VDAC1, -2, and -3) (715) or a single one, which is the case for ANT (253, 707). ANT2, but neither ANT1 nor ANT3, is overexpressed in a growth-dependent manner by highly proliferating tissues (253) and by fibroblasts transfected with the oncogene *c-myc* (707). For ANT and VDAC, isoform specificity has been correlated directly with apoptotic functions. Indeed, ANT1 and VDAC1 (40, 874) exhibit proapoptotic activity, whereas ANT2 and VDAC2 have antiapoptotic effects (40, 121). VDAC2 may exert this function by the sequestration of the proapoptotic protein Bak (121). However, the exact mechanism through which ANT2 may inhibit MMP and promote carcinogenesis has not been elucidated yet.

The upregulation of Bcl-2 (and of other antiapoptotic members of the Bc-2 family) and/or the downregulation of Bax have been reported in several clinical studies of cancer patients and, notably, in a high proportion of hematopoietic and lymphoid neoplasms (243, 388). Obviously, these changes may be directly related to MMP regulation. Similarly, it is tempting to speculate that loss-of-function mutations of p53 (or other mechanisms accounting for its functional inactivation) may reduce the capacity of p53 to mediate MMP, either at the nuclear (transcriptional) and at the mitochondrial (nontranscriptional) levels (131, 724). Other possible mechanisms through which the cancer cell can inactivate MMP include the local overexpression of MMP-inhibitory proteins (such as Bcl-2 homologs and unrelated proteins as the mucin MUC1) (641) or altered signal transduction pathways leading to the inhibition of MMP (for instance, by constitutive activation of Akt), just to mention a few examples.

X. PHARMACOLOGICAL MANIPULATION OF MITOCHONDRIAL PERMEABILIZATION

A cornucopia of human pathologies, including several for which no efficient therapy is currently available, exhibit impaired apoptosis. The description of the multiple signaling pathways leading to apoptosis and the discovery of crucial checkpoints (e.g., caspase activation, mitochondrial Bax translocation, MMP) have identified the therapeutic control of MMP as one of the most promising strategies to treat apoptosis-linked diseases (638). Many genetic strategies to target mitochondrial proteins are currently developed, but their enumeration is well beyond the scope of this review. We limit our discussion to the pharmacological manipulation of MMP.

A. BH3 Mimetics

Bcl-2 is the prototype of antiapoptotic proteins. It stabilizes mitochondrial membranes and inhibits cell death via multiple and complex processes. According to a recent review (441), Bcl-2 antagonists can trigger MMP through a variety of mechanisms, namely, *1*) by increasing the bioavailability of BH3-only proteins (e.g., Bid, Bim, and Puma) (119, 122), *2*) by disrupting MMP-inhibitory protein-to-protein interactions with Bax and Bak (533, 608), and *3*) by disrupting interactions between Bcl-2 and PTPC constituents, including VDAC (713) and ANT (495). According to additional models, Bcl-2 antagonists might promote caspase activation (145, 315, 623) and mitochondrial Ca^{2+} accumulation, thus indirectly favoring MMP (412).

Compounds such as tetrocarcin A, a secondary metabolite derived from *Actinomyces spp.*, and antimycin A, an antibacterial/antitumoral agent, were identified indirectly as Bcl-2 antagonists in a screening procedure involving Fas-triggered apoptosis (542) and in a respiration-based cell assay (776), respectively. Antimycin A was shown to bind to Bcl-2 in competition with a peptide corresponding to the BH3 domain of Bak, and to directly induce swelling and $\Delta\Psi_m$ loss in isolated mitochondria overexpressing Bcl-X_L (776). Over the last decade, structure-based computer screens have been exploited to identify natural or synthetic Bcl-2 or Bcl-X_L antagonists (172, 813). Subsequent NMR analyses have revealed that such inhibitors target the BH3-binding pocket of Bcl-2 or Bcl-X_L, block the BH3-mediated heterodimerization between Bcl-2 family members in vitro and in vivo, and induce apoptosis. This pioneering work corroborated the notion that BH3-dependent heterodimerization is required for

the stabilization of mitochondrial membranes and cellular homeostasis (172).

Also, some natural compounds isolated from green tea are able to bind to Bcl-X_L. These polyphenols (i.e., gossypol and purpurogallin) are able to displace a synthetic BH3 domain from Bcl-X_L and Bcl-2 at submicromolar concentrations (387, 440). Gossypol efficiently promotes apoptosis in several malignant cell lines, including prostate, head, and neck cancer cells (39, 847), and it has been reported to reverse cisplatin resistance mediated by wt p53 and Bcl-X_L overexpression in vitro (39). Moreover, gossypol directly induces Cyt *c* release on mitochondria isolated from Bcl-2 overexpressing cells (568), suggesting that this compound, already in phase I/II clinical trials, may be a promising agent to treat malignancies that are resistant to conventional therapies. Other recent highlights in the field include the development of ABT-737, a small molecule which occupies the BH3 binding domains of Bcl-X_L and Bcl-2 (570), and that of synthetic BH3 peptides that have been stabilized and rendered cell-permeable by hydrocarbon stapling (805). These reagents may be employed either to sensitize tumor cells to conventional chemotherapy or as single agents, since they are able to kill a specific panel of human tumor cells xenotransplanted into immunodeficient mice.

B. Mitochondriotoxic Compounds for Cancer Therapy

Shortly after the discovery that MMP is frequently impaired in cancer, mitochondria have become an attractive target to induce apoptosis and to overcome resistance to chemotherapy (74, 168, 170, 264, 265). Currently, more than 20 mitochondrion-targeted compounds have been reported to induce apoptosis selectively in malignant cell lines, and some of these are already being used in phase II/III clinical trials or validated in vitro in preclinical settings (72, 238). These compounds can be classified according to their chemical nature into three main groups: peptide derivatives, small molecules, and cationic lipophilic agents.

Peptides derived from Vpr and ANT (176, 337), as well as synthetic peptides such as $(KLAKKLAK)_2$ (195), demonstrated the ability to kill cancer cells, both in vitro and in mouse models, by triggering MMP. The activity of these peptides is usually accompanied by the complete set of MMP hallmarks, including Cyt *c* and AIF release, matrix swelling, and increased ROS generation. Their specific effects on mitochondria can be demonstrated by their capacity to induce MMP also when added to the purified organelles.

Among the small molecules, arsenite (421), lonidamine (633), and the synthetic retinoid CD437 {6-[3-(1-adamantyl)-4-hydroxyphenyl]-2-naphtalene carboxylic acid} (489) induce the death of cancer cell lines via direct effect on mitochondria (43). All these compounds are able to permeabilize proteoliposomes containing a reconstituted form of the PTPC or ANT alone, suggesting that ANT might represent their actual target (43). Endogenous metabolites including butyrate and short-chain fatty acids (295, 341), resveratrol (767), and betulinic acid (233), also exert antitumoral activity via a direct effect on mitochondria.

Lipophilic cations can cross cellular membranes and accumulate in mitochondria driven by the negative $\Delta\Psi_m$. Since $\Delta\Psi_m$ is often higher in malignant cells (115), lipophilic cations may selectively accumulate in their mitochondria, sparing the organelles of normal cells. The same concept supports the use of lipophilic ^{99m}Tc-complexes used for tumor imaging. Several lipophilic cations have intrinsic mitochondriotoxic properties and exert proapoptotic effects. For instance, the pyridinium derivative F16 inhibits growth of human breast cancer cell lines (204). Another example is provided by the rhodocyanine MKT-077, whose anticarcinoma activity has been associated with an effect on mitochondrial membranes and mtDNA (124, 525). Furthermore, lipophilic cations may be employed as specific carriers, to selectively deliver toxins to mitochondria of cancer cells (203). Finally, a promising class of photoactivatable antitumor agents, such as verteporfin (44) and merocyanine dyes (606), is being developed for mitochondrion-targeted chemotherapy.

C. Inhibitors of the Permeability Transition Pore

Agents that stabilize mitochondrial membranes may be useful for the therapeutic inhibition of cell death. Here, we present some agents capable of preventing PTP opening that are already used in clinical or preclinical trials.

The quintessential PTP inhibitor is CsA. This drug specifically targets CypD, presumably inhibiting its interaction with IM (and ANT). CsA acts at submicromolar concentrations, when added to isolated mitochondria. This has led to the widespread use of this molecule as a selective PTP inhibitor (48, 277). Nonetheless, mitochondria isolated from different tissues do not exhibit the same sensibility to CsA activity (127). CsA is also a potent inhibitor of cell death in vivo, notably in models of ischemia/reperfusion injury of several tissues, including liver (676), brain and central nervous system (184, 670), and myocardium (728). Taken together, these results demonstrate the protective role and the possible benefits that PTP inhibition may bring about in several human diseases. One major drawback about the therapeutic use of CsA is the fact that it provides only a transient, and hence incomplete, PTP inhibition. The future will tell whether other CypD ligands, preferentially not exerting immunosuppressive side effects (through the inhibition of calcineurin), may achieve therapeutic responses in the clinics.

A few studies revealed that some drugs that exert cytoprotective effects in vivo may act as PTP inhibitors. One such molecule is rasagiline, which is an established drug for the treatment of PD. Rasagiline prevents apoptosis via multiple intracellular processes including the induction of survival genes and the suppression of proapoptotic genes (483, 825, 869). In addition, rasagiline can mediate direct PTP inhibition, as demonstrated in cellula and in isolated mitochondria (8). Whether this effect is truly responsible for the neuroprotective effect of rasagiline, however, remains to be proven. Similarly, it has been shown that heterocyclic compounds such as promethazine (currently used as an antihistamine and neuroleptic agent) can prevent PTP opening in vitro (in isolated mitochondria), and exert neuroprotective effects in vivo, according to the results of clinical studies (731). However, the exact cause-effect relationship between the alleged PTP-inhibitory and cytoprotective effects have not been established.

Recently, MitoQ, an ubiquinol antioxidant coupled to a mitochondrion-targeting lipophilic cation, has been shown to efficiently protect rats from mitochondrial damage, cell death, and cardiac dysfunction upon ischemia/reperfusion injury (4). The same effects were not observed with untargeted antioxidants, suggesting the importance of the mitochondrial localization of the drug for its therapeutic potential.

These examples suggest that it might be possible to design small molecule inhibitors of pathogenic cell death with a selective action exerted at the mitochondrial level.

D. Mitochondrial ATP-Sensitive K^+ Channel Modulators

While OM is freely permeable to ions, ion fluxes across the IM are tightly regulated by several transporters, each characterized by specific structural and functional properties. These systems include, but are not limited to, specific channels, antiporters, and pumps transporting Ca^{2+}, H^+, K^+, and Cl^- (for reviews, see Refs. 18, 55, 240). In many models of cell death, MMP is modulated by mitochondrial ions fluxes. It is commonly accepted that, above a certain threshold or in combination with increased ROS, Ca^{2+} accumulation in the mitochondrial compartment induces per se PT and Cyt *c* release (323, 355, 580). Notably, this applies also to neuronal and cardiac models of cell death (126, 837, 838).

Mitochondrial ATP-sensitive K^+ channels (mitoK_{ATP}) have been implicated in apoptosis since their discovery, more than 14 years ago (18). The molecular nature of mitoK_{ATP} channels is not yet clearly defined. Intriguingly, it appears that a polyprotein complex that includes ANT may build up this channel (17).

MitoK_{ATP} function can be modulated by pharmacological agents such as diazoxide or RP66471 (openers) and the antidiabetic sulfonylurea glibenclamide (blocker). Opening of the mitoK_{ATP} and activation of PKC have been implicated in cardioprotective mechanisms during ischemic preconditioning (IPC) of ex vivo rat hearts (777). IPC, the most potent method for reducing ischemia/reperfusion injury of the heart, is mediated by transient opening of mitoK_{ATP}, perhaps linked to a transient dissipation of the $\Delta\Psi_m$, which in turn may prevent mitochondrial Ca^{2+} overload (291, 333). IPC consists of exposing the heart to brief ischemic episodes before prolonged ischemia, and its protective effect is completely inhibited by mitoK_{ATP} blockers (468). MitoK_{ATP} openers such as diazoxide confer cardioprotection in correlation with an increase of flavoprotein oxidation, which is a reliable indicator of mitoK_{ATP} activity. Moreover, diazoxide effects are abolished by the use of the selective mitoK_{ATP} blocker 5-hydroxydecanoate. Altogether, these results suggest that the activation of mitoK_{ATP} is the trigger and mediator of IPC (777). Specific modulators of mitochondrial ion channels might be taken advantage of for therapeutic neuro- or cardioprotection.

XI. CONCLUSIONS

This review has described a few aspects in an area of research, mitochondrial cell death, that has literally exploded during recent years, producing thousands of publications per year. Several major rules emerge.

1) It appears that many different signals can induce (and inhibit) MMP, linking distinct types of cellular stress and damage to mitochondria. This highlights the capacity of mitochondria to function as general cell death sensors and to integrate many separate lethal signals.

2) MMP is not just induced (or inhibited) by one single class of molecules. Rather, there appear to be several alternative modes of MMP, mediated by distinct classes of proteins and modulators, which cooperate in a wide array of partially overlapping yet distinct processes. This introduces some sort of redundancy into the system that regulates cell death, thus avoiding that simple mutations would lead to complete cell death inhibition, an event that would be intrinsically oncogenic.

3) Once MMP has trespassed a critical threshold, its consequences are able to stimulate further permeabilization of adjacent and distant mitochondria, thus resulting in rapid self-amplifying phenomenon, which occurs prominently in an all-or-nothing fashion.

4) When MMP has occurred, it leads to cell death rapidly and efficiently, through a variety of independent and redundant mechanisms. These include not only caspase activation but also the release of caspase-independent death effectors, as well as irreversible metabolic changes.

5) To protect cells from death, it is hence important to prevent MMP or the upstream events leading to MMP.

In contrast, there is no way to avoid the cellular demise by inhibiting the postmitochondrial phase of apoptosis, which indeed comprises biochemical changes occurring after the "point of no return" has been trespassed (post mortem events). This is of the utmost importance for the design of neuro- or cardioprotective therapies.

6) Pathological MMP contributes to the unwarranted loss of postmitotic cells in the brain and in the heart. Agents that target specific mitochondrial ion channels or proteins that contribute to MMP may be useful for the therapeutic inhibition of acute cell death.

7) Cancer cells are often relatively resistant to MMP induction, and the therapeutic induction of MMP may constitute a therapeutic goal in anticancer chemotherapy. The inhibition of MMP suppressive proteins (such as Bcl-2-like proteins) can sensitize tumor cells to apoptosis induction.

These few rules illustrate that mitochondrial cell death control has far-reaching implications not only in the field of molecular biology but also for biomedical science and practice, at the levels of physiology, pathology, and pharmacology.

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G. Kroemer and L. Galluzzi are at the INSERM Unit "Apoptosis, Cancer and Immunity," Institut Gustave Roussy and Université Paris Sud/Paris 11, Villejuif, France. C. Brenner is at CNRS UMR 8159, Universite de Versailles/St. Quentin, Versailles, France.

Address for reprint requests and other correspondence: G. Kroemer, INSERM Unit "Apoptosis, Cancer and Immunity," 39 avenue Camille Desmoulins, 94085 Villejuif, France (e-mail: kroemer@igr.fr).

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