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Cell pathology

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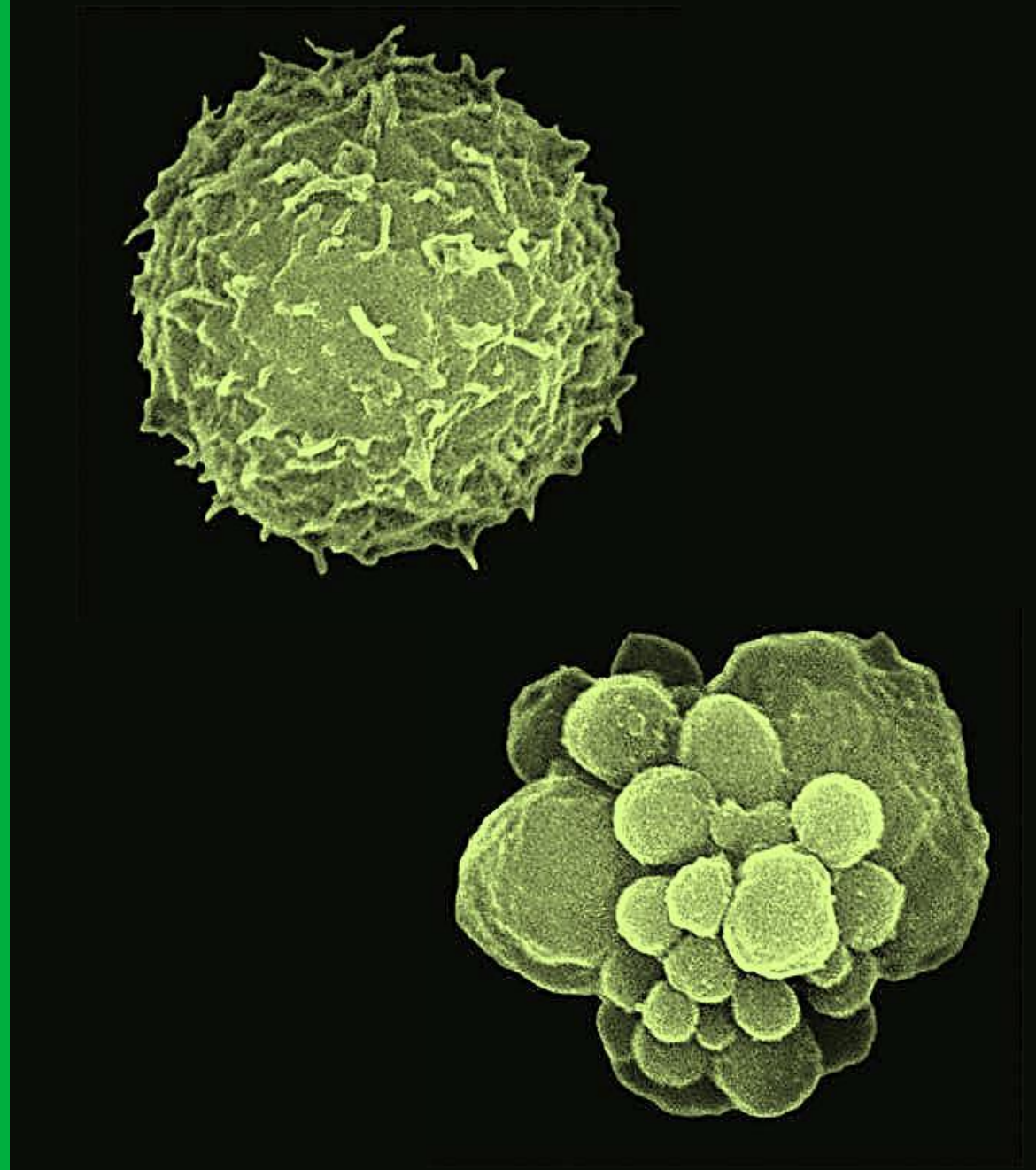
Department of Experimental Biology



Outline

- Cellular responses to stress conditions
  - Physical stress (temperature, radiation)
  - Chemical stress (xenobiotics)
  - Biological stress (intracellular parasites)
- Cell death
  - Necrosis
  - Necroptosis
  - Apoptosis
  - Autophagic cell death
  - Ferroptosis

Cellular responses to stress conditions

Stress factors

Non-specific stress factors

- Significant **increase of temperature**, **heavy metals**, **aldehydes** → denaturation of proteins

Specific (targeted) stress conditions

- **Radiation of a specific wavelength** → absorption by target molecules or specific response at the cellular level
- **Specific inhibitors/activators** (antibiotics, toxins etc.) → target specific process in the cell

Cellular stress response

- **Programmed adaptive processes of the cell**
- Aimed to **protect** against the damaging consequences of the stress factors and **restore homeostasis**
- Various stress-signaling pathways → **changes in the gene expression** → upregulation of **stress (heat shock) proteins** and other genes required to restore the balance

- **Prolonged activation of stress-signaling** induces expression of proteins involved in activation of **cell death**

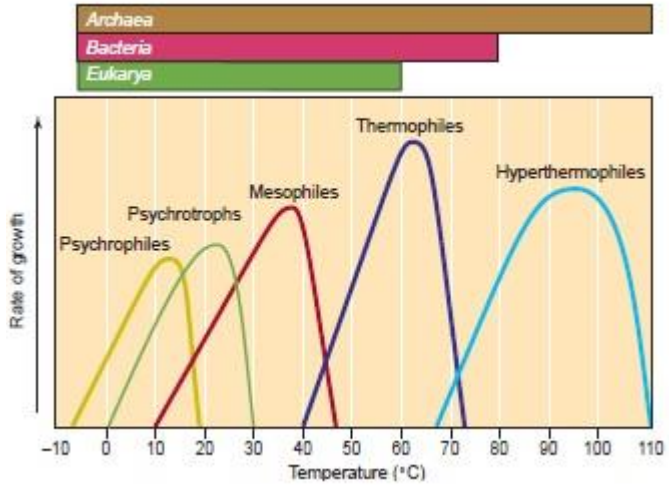
Physical stress

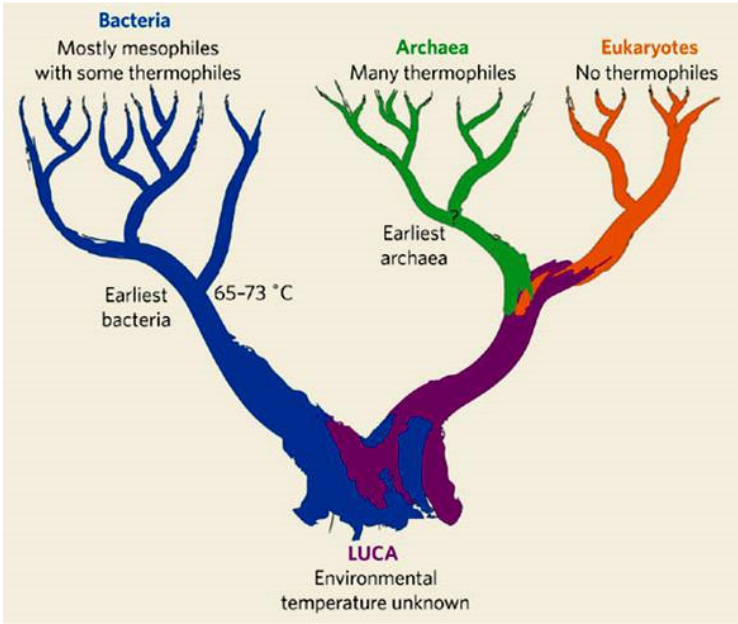
Heat stress

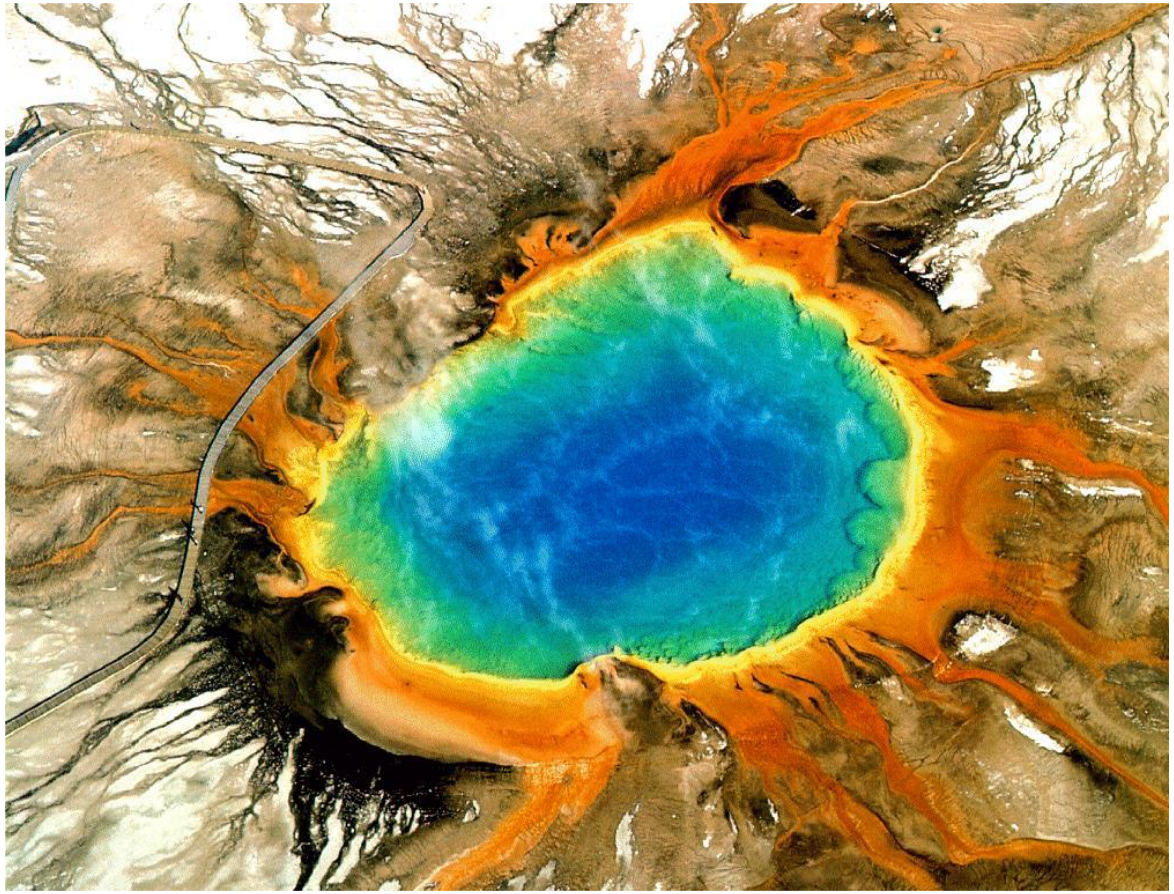
- Irreversible damage of cells under **heat shock** – 40-50°C
- Changes in the **tertiary structure of proteins** → defects in their function
  - Disrupted coordination of metabolic pathways (optimal temperature for enzymes)
  - Disorganization of biomemebranes
  - Disrupted cytoskeleton (F-actin stabilization and depolymerization of microtubules)
- **Heat shock proteins**
  - Upregulated in response to various stressors (not only increased temperature)
  - Evolutionarily conserved **molecular chaperones**
  - **Refolding of misfolded proteins:** restore correct conformation or target proteins for degradation (cochaperones with ubiquitin ligase activity)

Hyperthermophilic bacteria

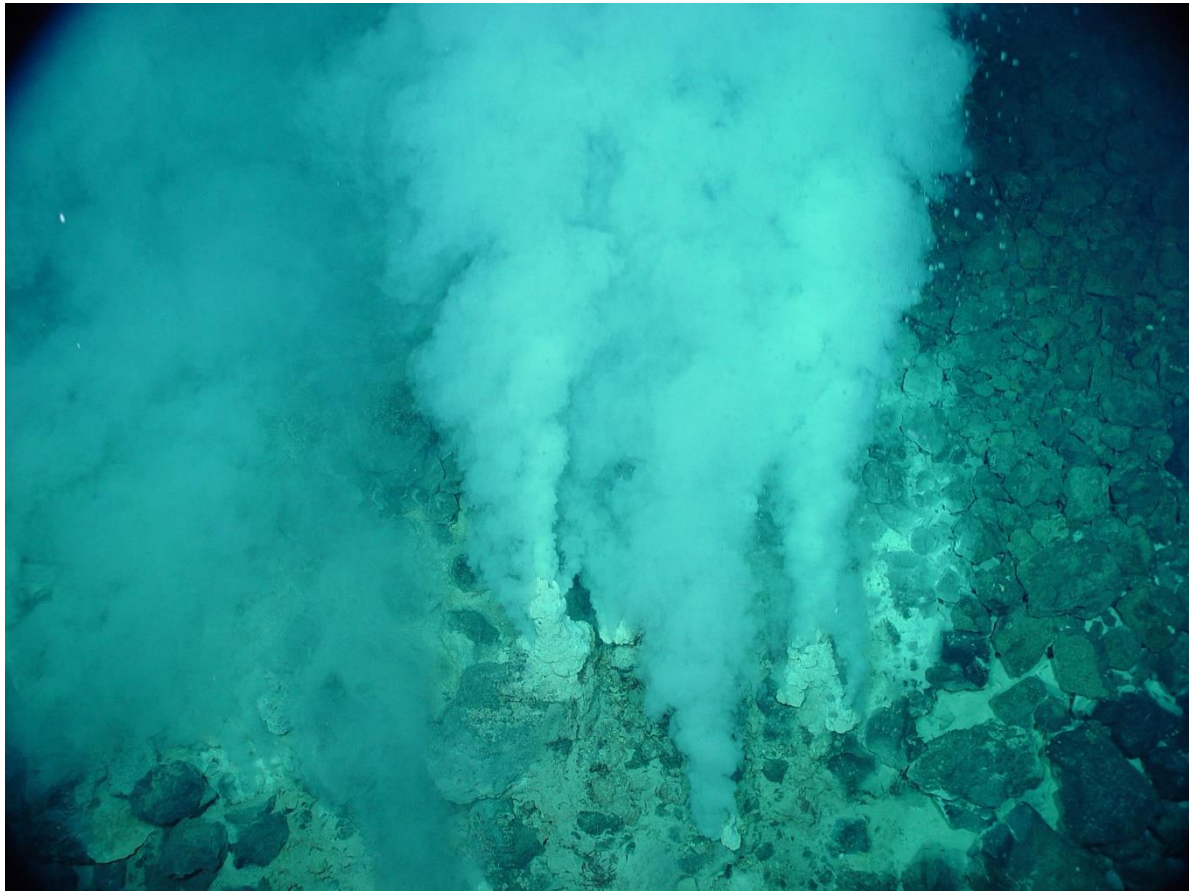
- Tolerate extremely high temperatures
- Optimal temperature ~90°C
- **Common in domain Archea**
- Thermostable enzymes (proteins)
  - Isolation of commercially useful enzymes (e.g., polymerases): fast reactions, hot start reactions etc.







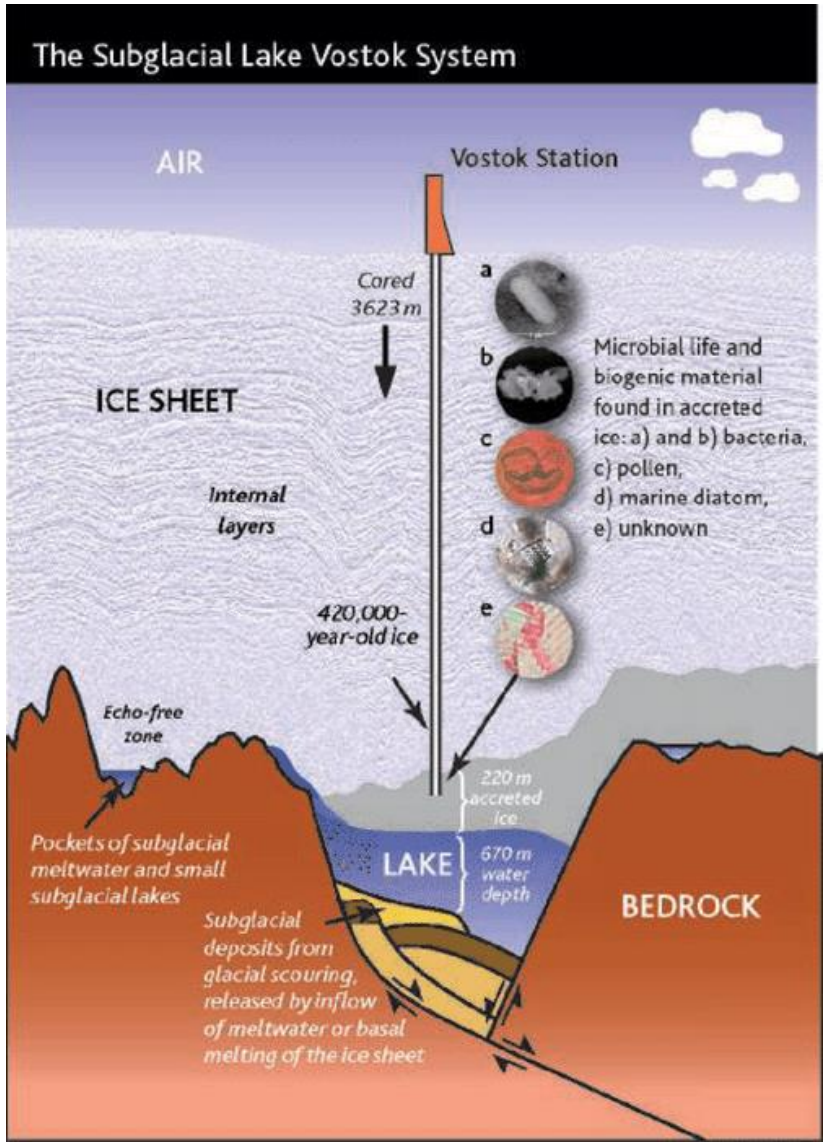
Hot springs (e.g., Grand Prismatic Spring)

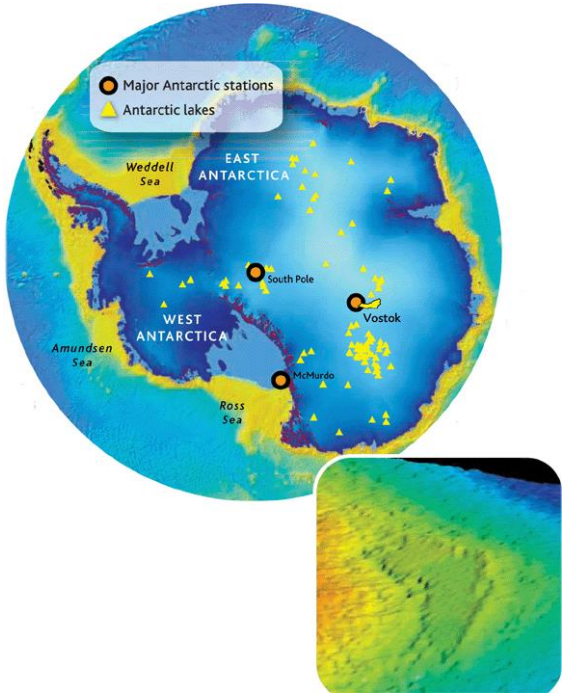


Deep-sea hydrothermal vents

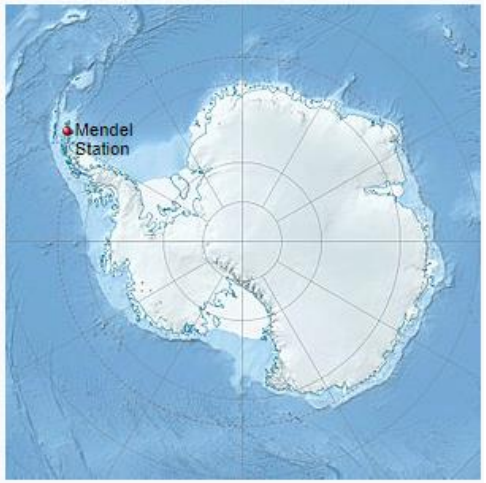
Cold stress

- Irreversible damage in temperatures around 0°C
- Mechanical damage of biomembranes/organelles caused by ice crystals, desiccation of the cell, vitrification (glass-like form; prevents biologically relevant movement of molecules)
  - Animal cells are highly prone to this type of stress
- Mechanisms of cell resistance
  - **Reduced water content:** seeds, spores
  - Different **composition of lipids in membranes** (lower melting point), specific **antifreezing proteins** (prevent ice nucleation and growth), **cold-active enzymes:** psychrofilic bacteria, algae, fungi, insects





Pseudomonas gregormendelii



Electromagnetic radiation: Visible light

- **Weakly absorbed by the cytoplasm**
- Generally effective only when strong intensities / laser beams applied
- Presence of pigments increases the effects

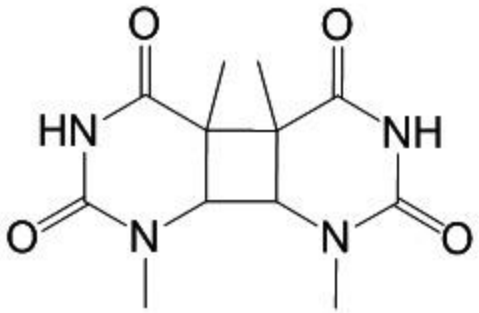
Photosensitizers

- **Molecules increasing sensitivity of cells to light**
- Absorb light → activation of photosensitizer → **oxidative stress**
- Eosin, fluorescein, acridine, chlorophyll, porfyrins…

Electromagnetic radiation: Ultraviolet light

- **Effects correlate with the energy (shorter wavelength):**
  UVC (200-280 nm) > UVB (280-315 nm) > UVA (315-400 nm)

- **Direct effect:** UVC induces **cyclobutan pyrimidine dimers** and other pyrimidine dimer photoproducts

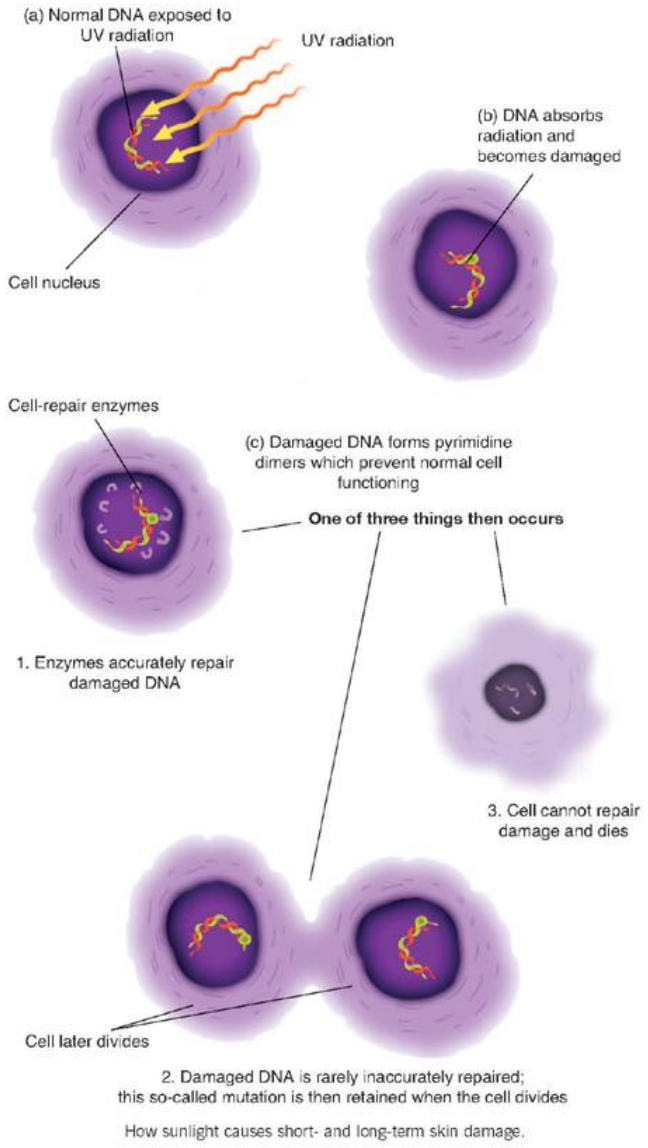


- **Indirect effects:** production of **reactive oxygen species (ROS)** → oxidative damage (DNA, proteins, lipids) of cell structures

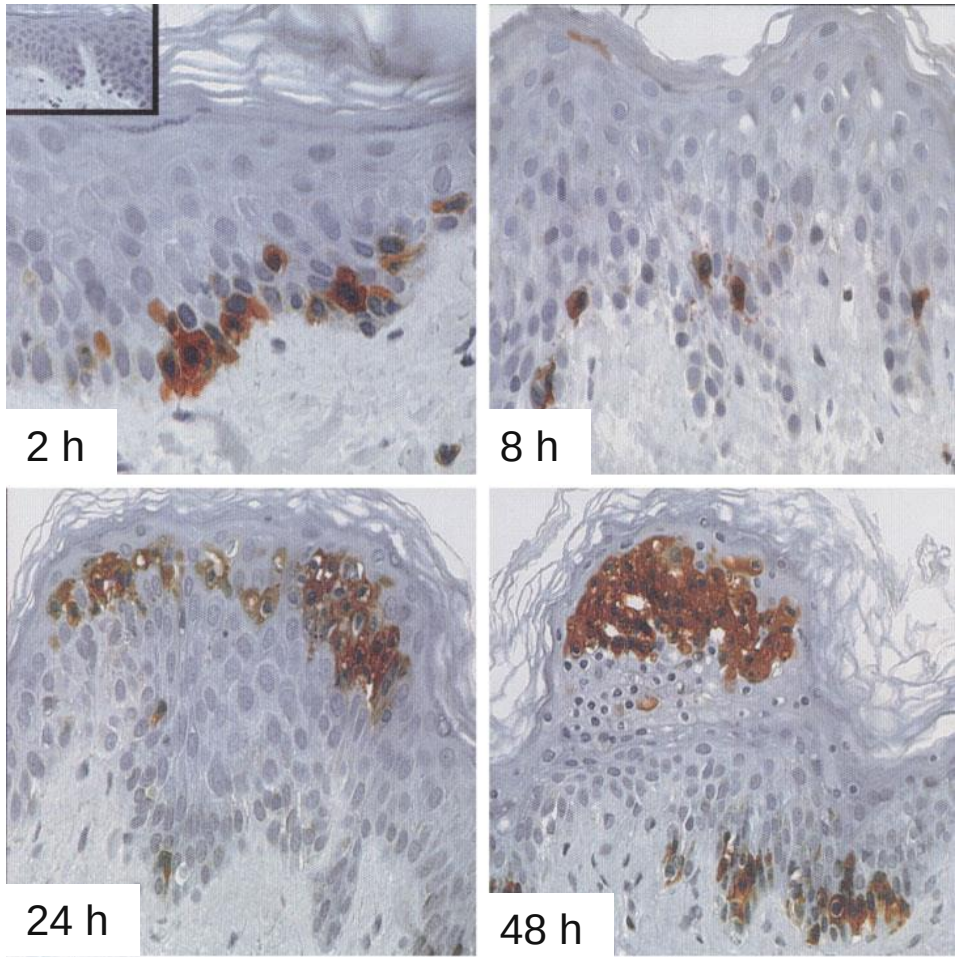
Short-term and long-term effects

- Induction of apoptosis → photoaging

- Mutations → e.g., skin cancer



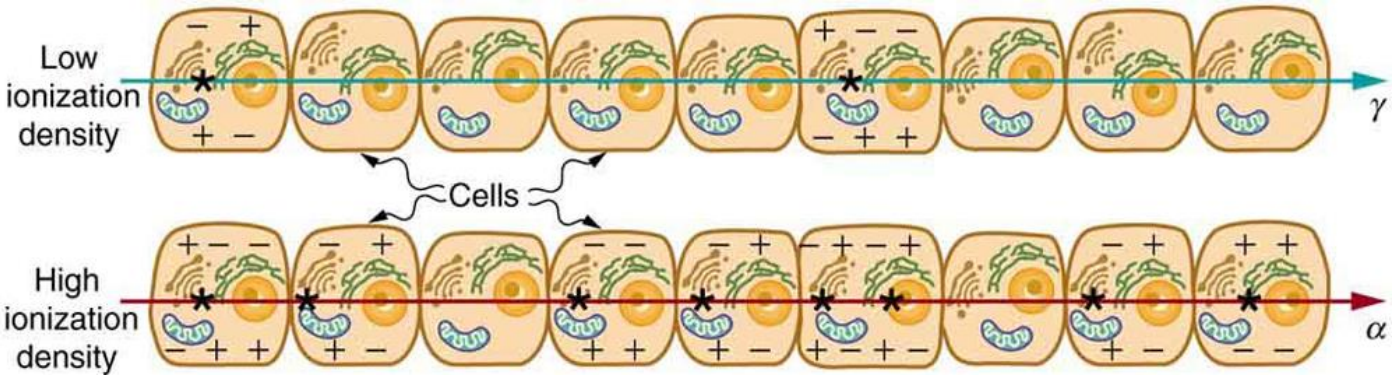
How sunlight causes short- and long-term skin damage.



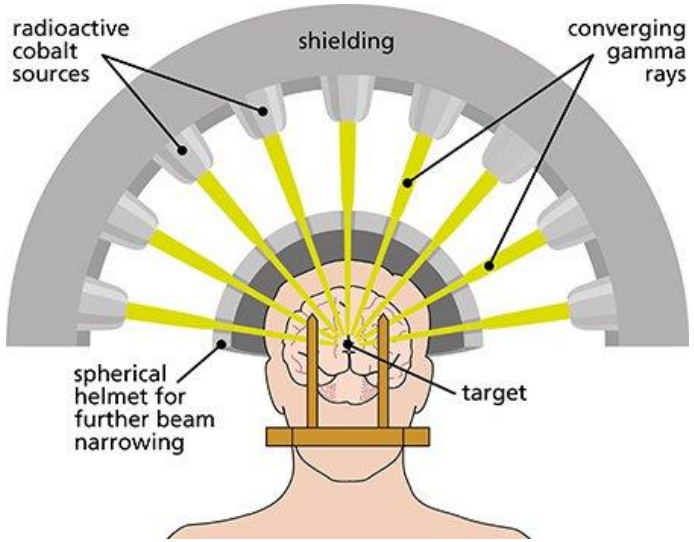
Apoptotic cells (cleaved caspase 3) in UV-irradiated (100 mJ/cm^2) epidermis

Electromagnetic radiation: Ionizing radiation

- **Gamma rays, X-rays**, (high energy UV light)
- Higher frequency (γ > X-rays) = lower ionization density
  → less damage

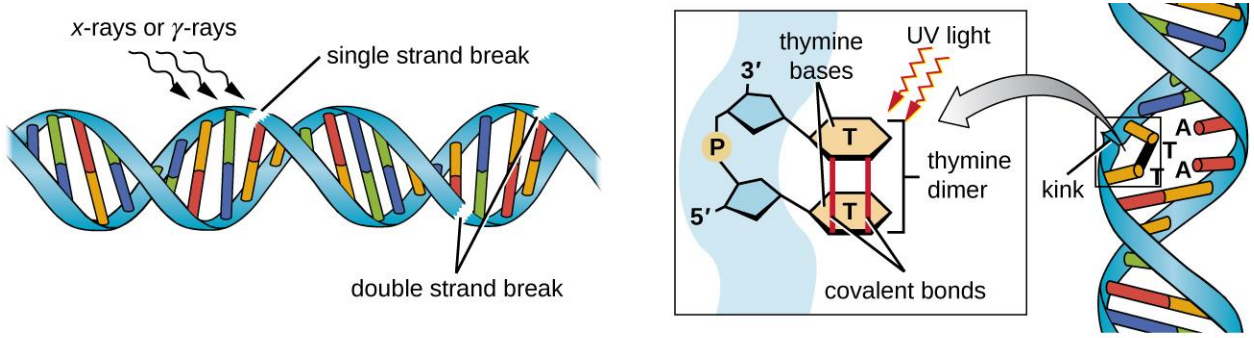


Gamma knife



Electromagnetic radiation: Ionizing radiation

- **Direct effects: DNA breaks**
- **Indirect effects:**
  ROS production



(a) Ionizing radiation

(b) Non-ionizing radiation

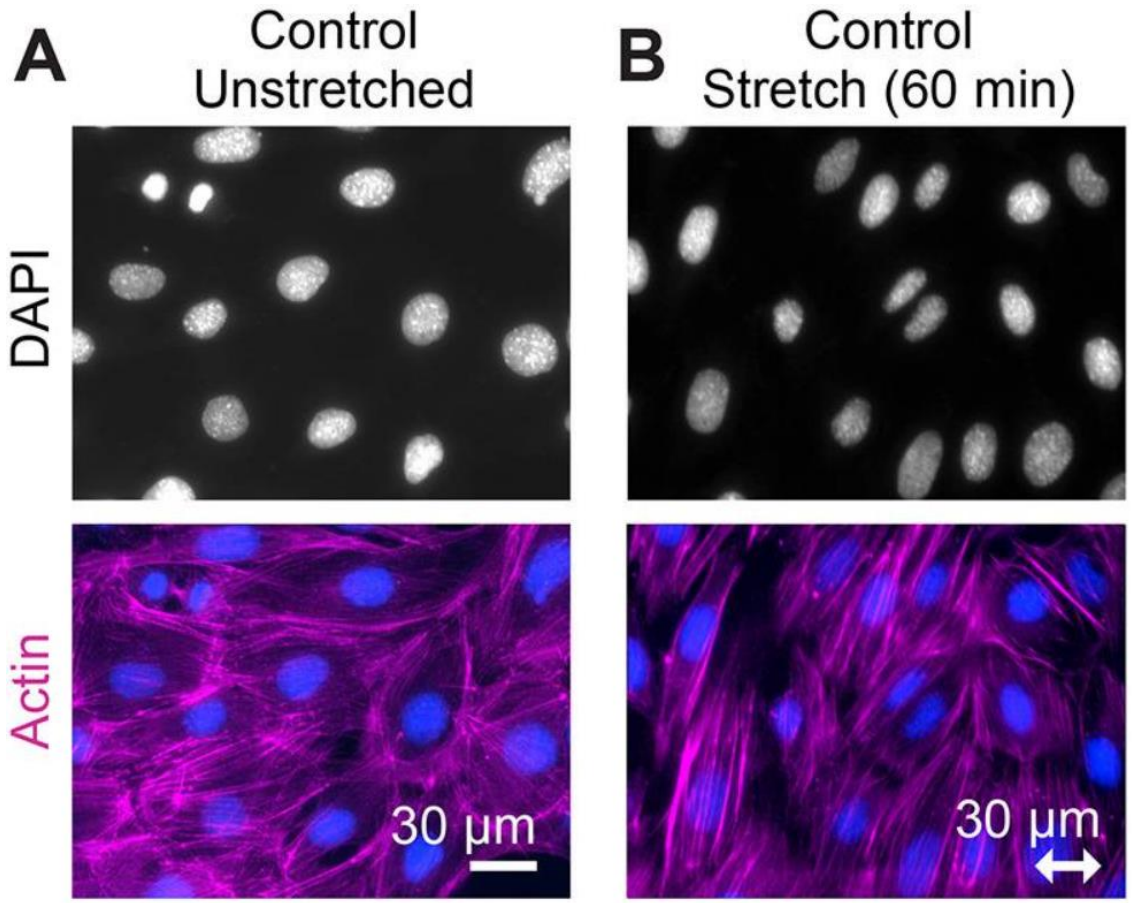
Radiosensitivity

- Cells of higher organisms
- Cells (species) with high DNA content, gametes
- Rapidly proliferating cells (bone marrow, lymph nodes, germ cells, epithelial cells, embryonal cells…)

Mechanical stress

- Cells with the cell wall are highly resistant
- **Intermediary filaments in animal cells** crucial for protection from mechanical stress (tissue integrity)
- Mechanical forces (tension, compression…) may cause critical damage of membranes
- **Actin filaments** reorganization
  - Transmission of the mechanical stress – signaling
  - Compensate local mechanical stress (micromanipulation studies)
  - Recovery of membrane after perforation (e.g., after microinjection)

Actin remodeling after mechanical stress induced by stretching the cell culture surface



Intracytoplasmic sperm injection

Chemical stress (xenobiotics)

Xenobiotics

- Chemical substances not naturally occurring in the cell (organism)
- **Often toxic** – accumulation, interaction with target molecules
- Specific and non-specific effects

Classification of xenobiotics

- Chemical composition (heavy metals, acids, alkaloids…)
- Origin (chemical toxins, biological toxins)
- Mechanism of action (DNA damage, cytoskeleton defects, inhibition of protein synthesis, inhibition of respiratory chain…)

Specific inhibitors: Synthesis of biopolymers

- Crosslinking of DNA: **mitomycin C**
- Nucleotide synthesis inhibitors: **azaserine, C-mercaptopurine**
- Blockage of RNA polymerase movement: **actinomycin D**
- Binding to RNA polymerase: **α-amanitin, ethionin, lomofungin**
- Peptidyl transferase inhibition: **cycloheximide**
- Blocking AA-tRNA binding: **tetracycline**
- Blocking mRNA translocation: **chloramphenicol**
- Polypeptide release from ribosome: **puromycin**
- Release of ribosomes from ER: **aflatoxins**

Specific inhibitors: Membrane function

- Changes in phospholipids → formation of micelles: **phospholipases**
- Interactions with cholesterol → membrane break down: **saponins (digitonin), nystatin, amphotericin**
- Increasing ion permeability: **valinomycin, gramicidin A**
- Blocking sodium-potassium ion pump (N^+/K^+ ATPase): **ouabain**

Specific inhibitors: Energetic metabolism

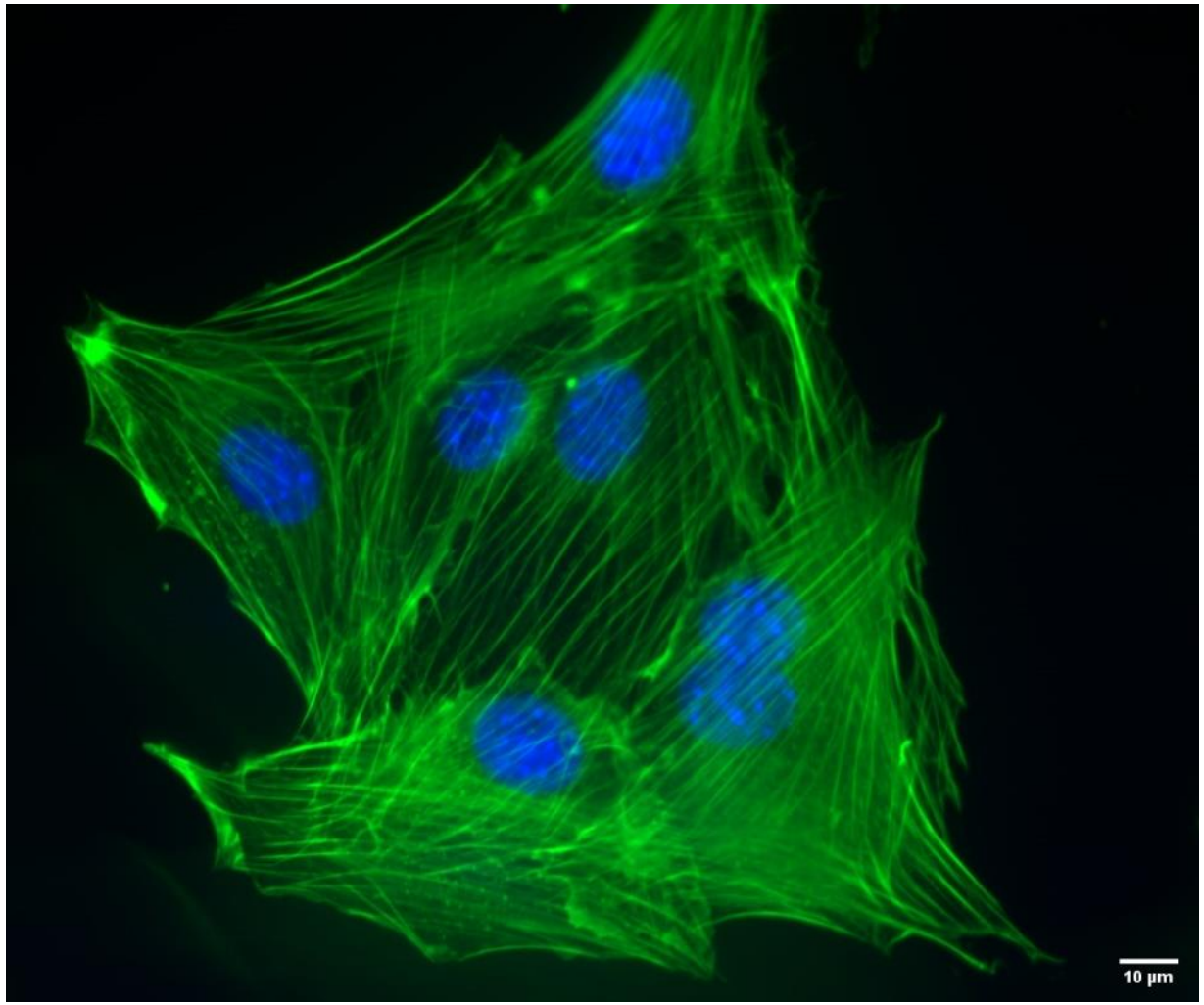
- Uncoupling oxidative phosphorylation from ATP synthesis in mitochondria (allowing protons to bypass ATP synthase): **benzimidazoles, 2,4-dinitrophenol**
- Blocking electron transport chain complexes: **cyanides**, **metformin/phenformin**
- Inhibition of dehydrogenases: **urethane, disulfiram, barbiturates**

Specific inhibitors: Cytoskeleton dynamics

- Microtubule polymerization inhibition: **colchicine, vinca alkaloids (vincristine, vinblastine)**
- Microtubule depolymerization inhibition: **taxanes, paclitaxel**
- Inhibition of actin filament polymerization: **cytochalasins, latrunculins**
- Inhibition of actin filament depolymerization: **phalloidin, jasplakinolide**

Phalloidin

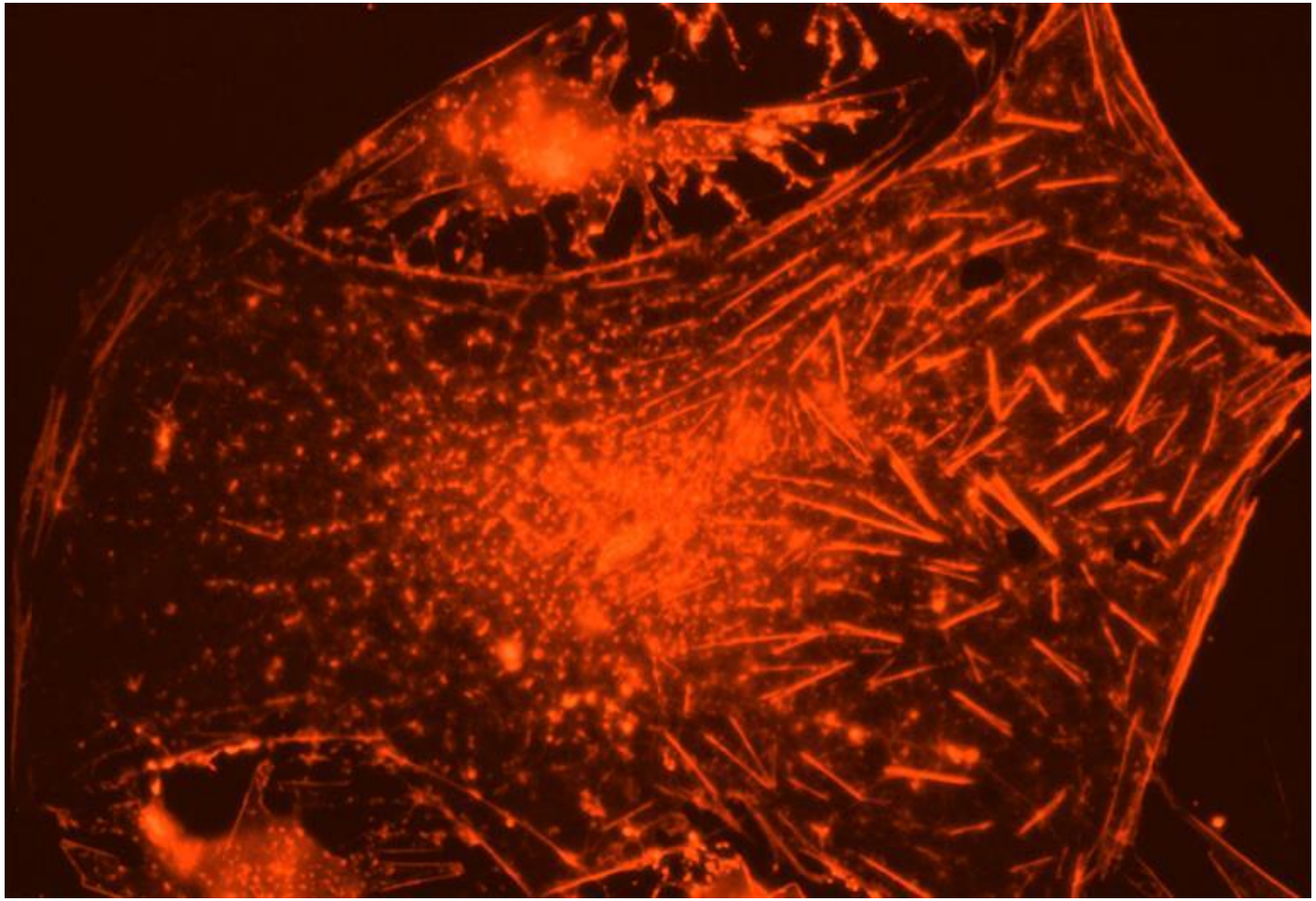
- Mouse fibroblasts



F-actin (Phalloidin), DNA

Cytochalasin B

- Human skin fibroblasts



F-actin

Biological stress factors

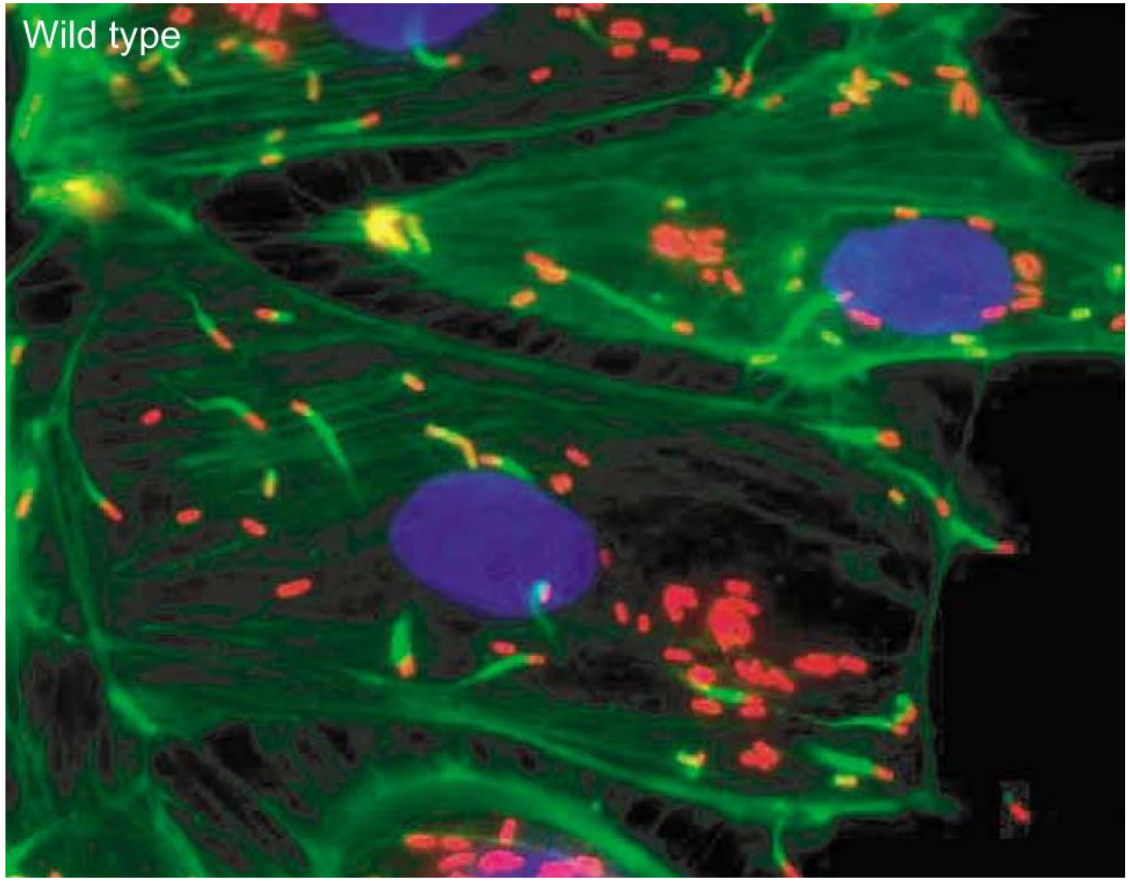
Intracellular parasitism

- Viruses (cell lysis or integration into the genome)
- *Mycoplasma* – lack cell wall
- *Rickettsia*, *Chlamydia, Listeria monocytogenes*
- *Plasmodium malariae*, *Toxoplasma gondii*

Changes of the infected cells

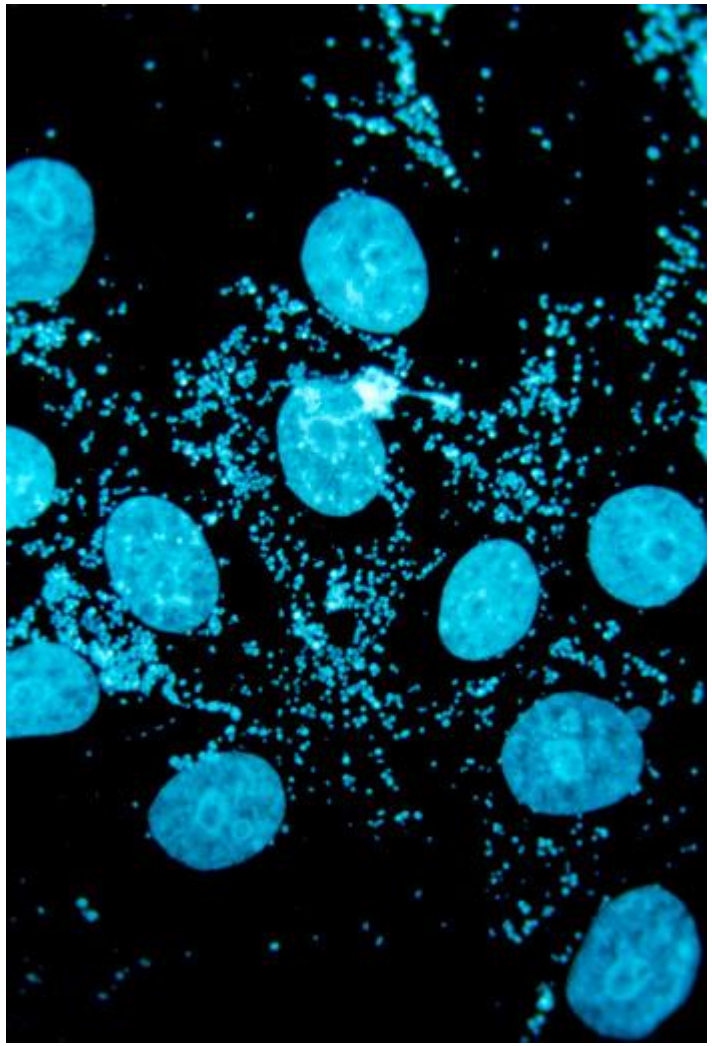
- Metabolism (exploit protein synthesis apparatus; affect growth rate)
- Cell morphology (cytoskeleton, plasma membrane)
- Behavior of the infected cell, whole organism
- **Modulation of apoptosis** (pro- & anti-apoptotic effects, stress signaling)

– *Listeria monocytogenes*



F-actin, *Listeria*, DNA

– *Mycoplasma hyorhinis*



DNA (nuclei and mycoplasma DNA)

Cell death

Types of cell death

- **Necrosis** = catastrophic cell death caused by non-specific stress factors and/or extreme damage

- **Necroptosis** = programmed form of necrosis; regulated by specific factors
- **Apoptosis = programmed cell death**
- **Autophagic cell death**
- **Ferroptosis** = iron-dependent programmed cell death

Cell death: Necrosis

Induction of necrosis

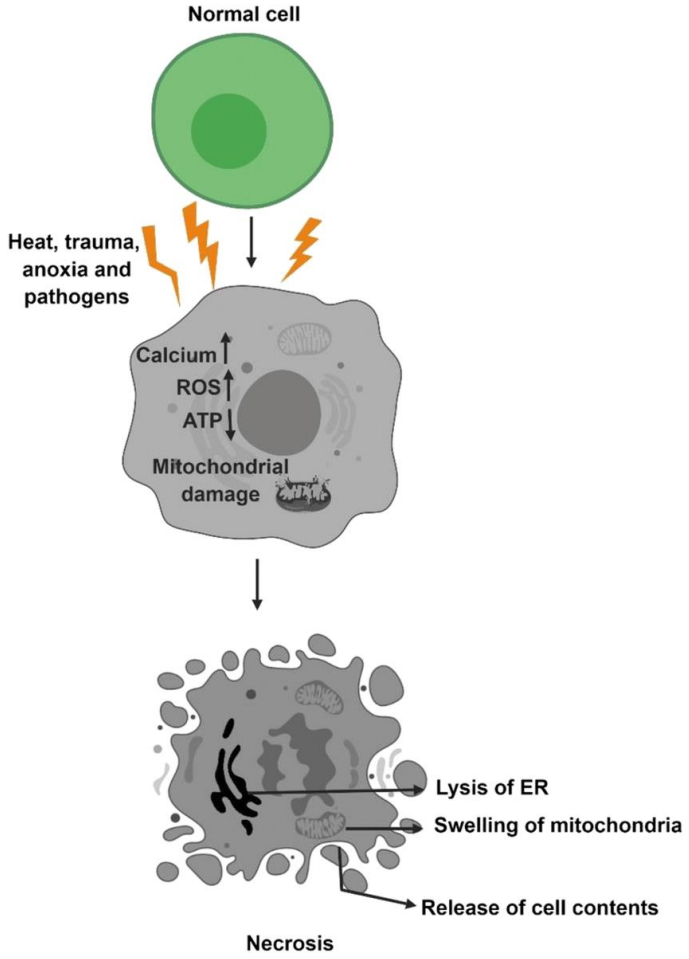
- **Rapid and extensive damage** – mechanisms of programmed cell death cannot be activated

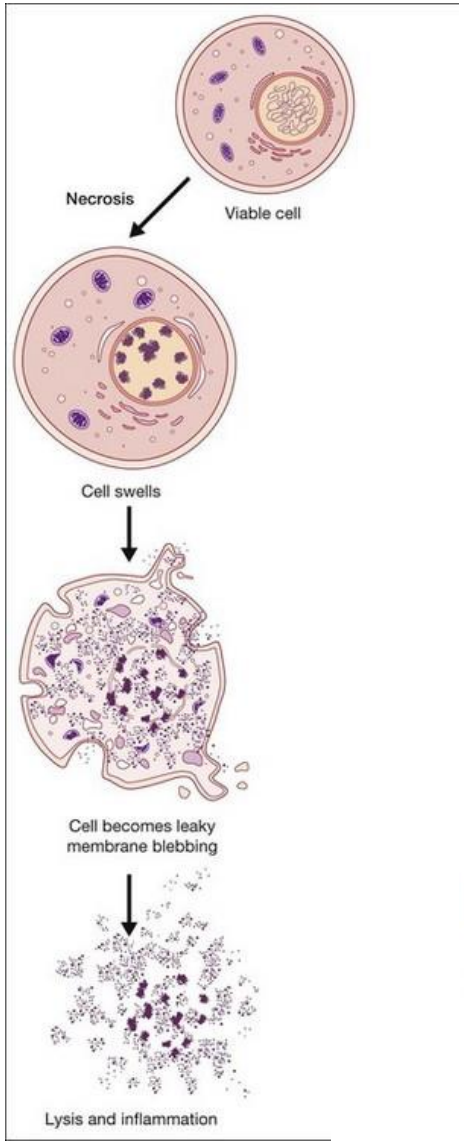
- **Effects of extreme non-specific stress factors**
- Changes in concentration of ions, in pH...
- Depletion of energy sources
- Extremely high or low temperatures
- Mechanical trauma – damaging cells / tissues

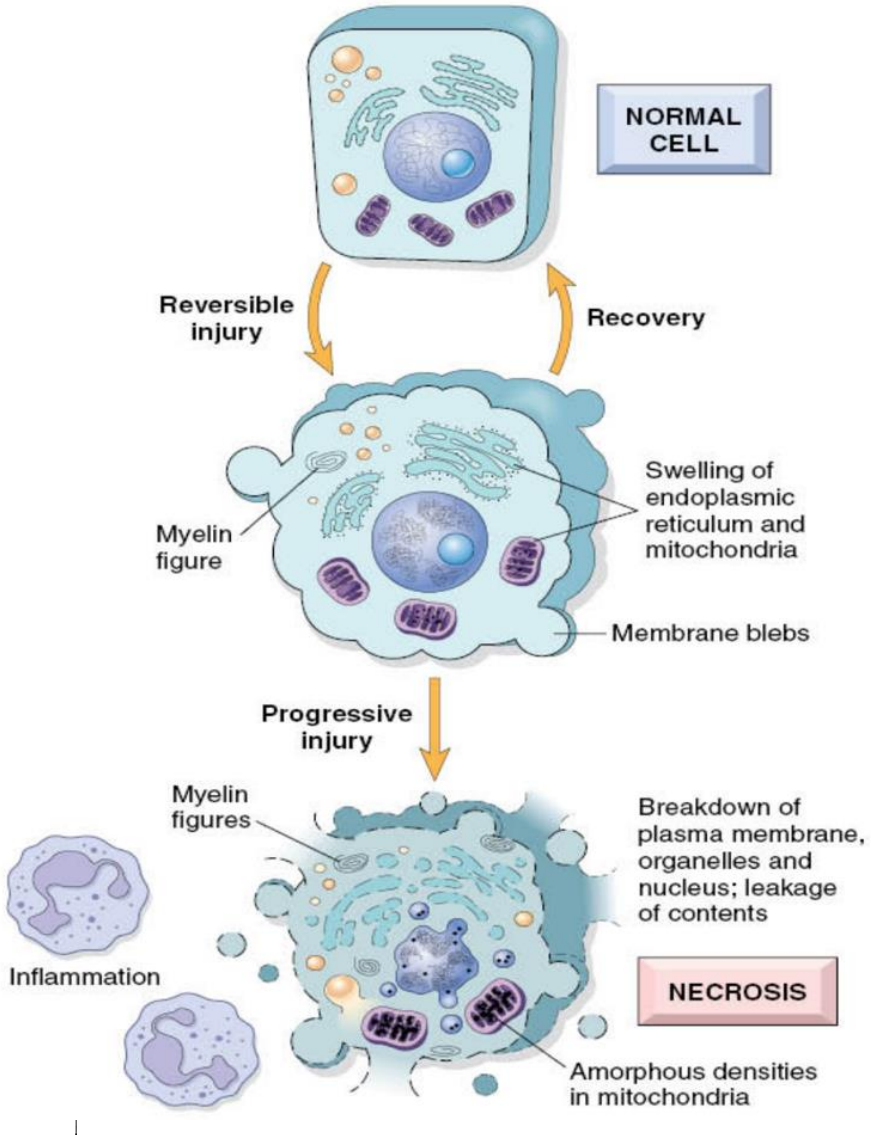
Progression and hallmarks of necrosis

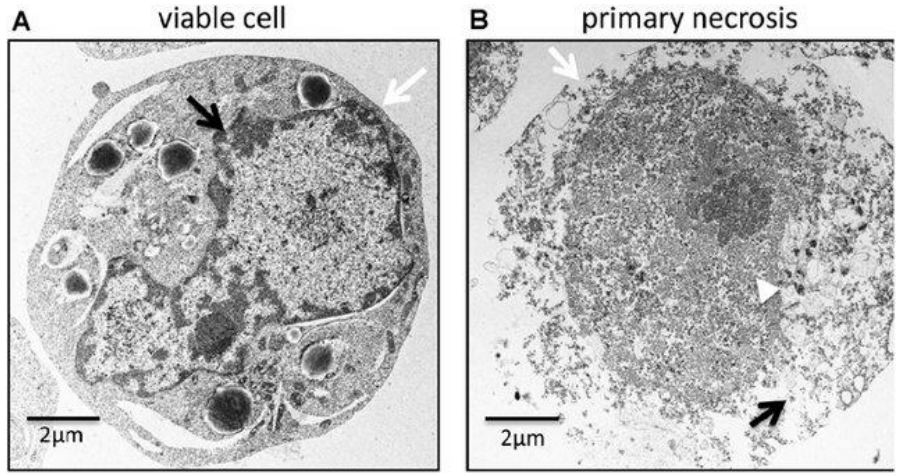
- Overloading of mitochondria with Ca^{2+}
- Loss of mitochondrial membrane potential: ↓ATP
- Generation of ROS – mitochondrial damage
- **Swelling and rupture of mitochondria**
- **Swelling of the cell and lysis**
- **Release of cell contents → inflammation**

- At the tissue level: formation of a necrotic lesion → invasion of macrophages → inflammation

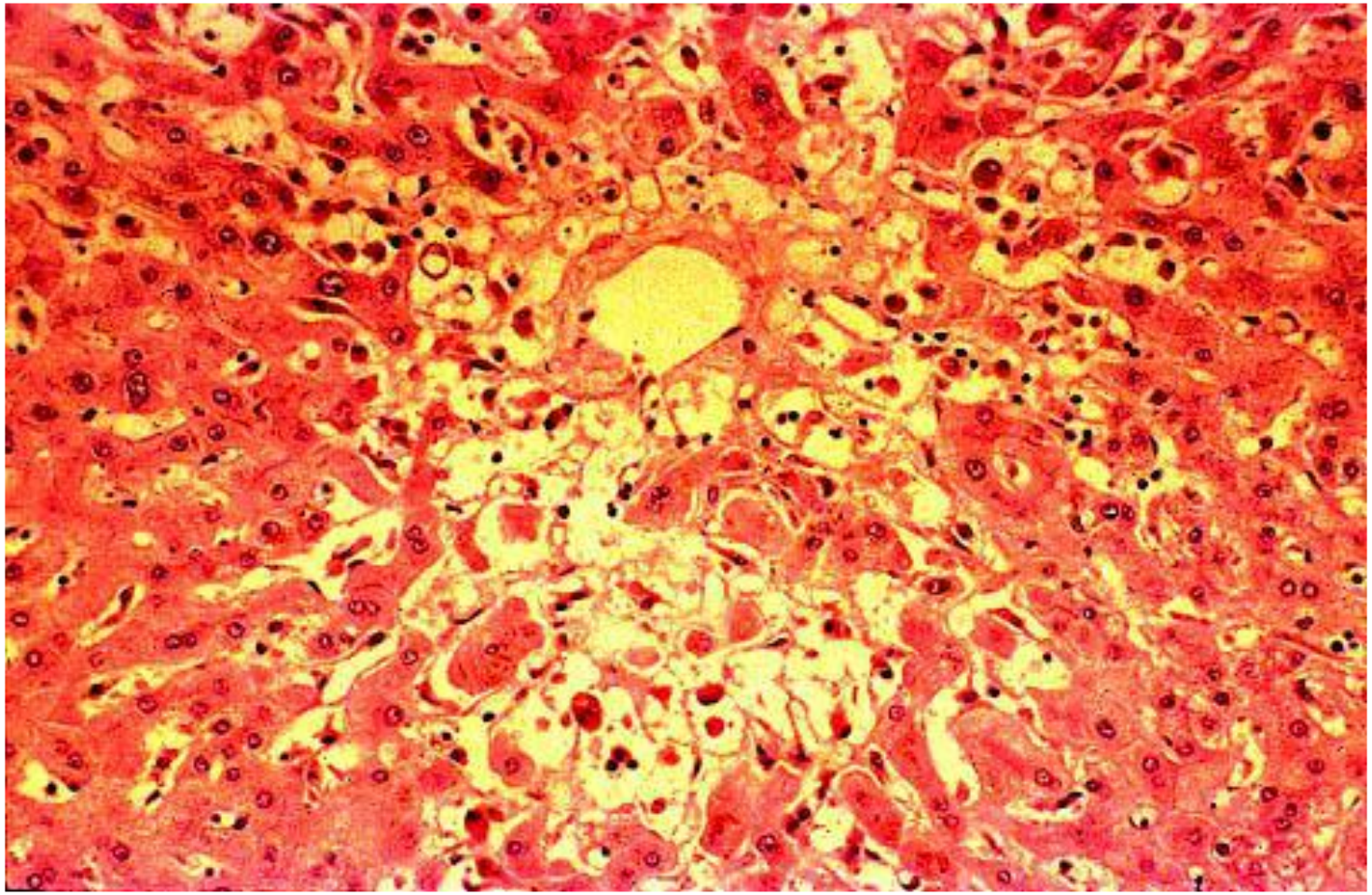



Necrosis
Viable cell
Cell swells
Cell becomes leaky
membrane blebbing
Lysis and inflammation


NORMAL CELL
Reversible injury
Recovery
Swelling of endoplasmic reticulum and mitochondria
Myelin figure
Membrane blebs
Progressive injury
Myelin figures
Breakdown of plasma membrane, organelles and nucleus; leakage of contents
Inflammation
NECROSIS
Amorphous densities in mitochondria


A
viable cell
B
primary necrosis
2µm
2µm

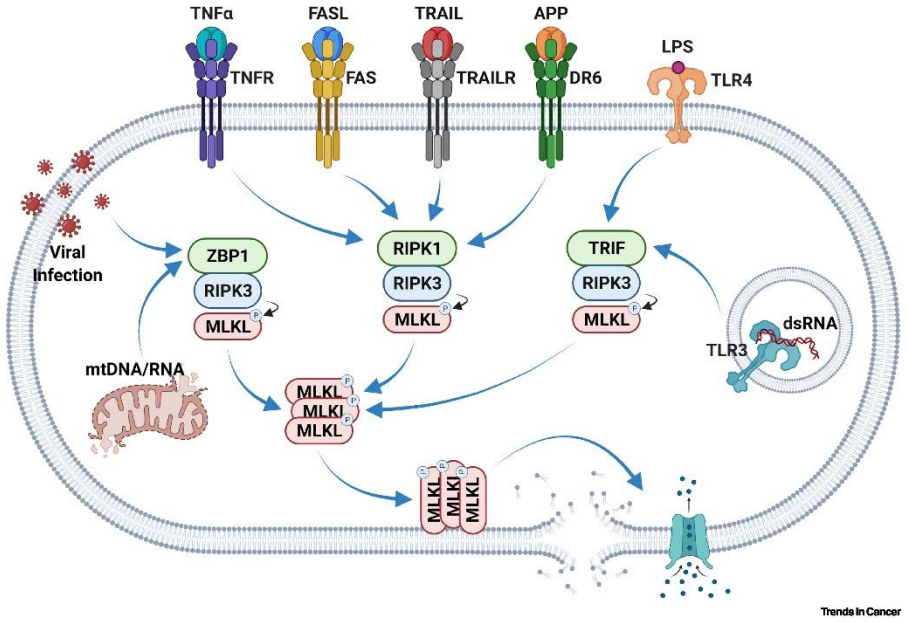
- Necrotic lesion in animal tissue



Cell death: Necroptosis

Necroptosis

- Regulated cell death with **features of apoptosis and necrosis**
- Triggered by similar stimuli as extrinsic apoptotic pathway
- **Specific proteins** (RIPK3, MLKL etc.) **shift extrinsic apoptosis to necrosis mode of cell death**



- **Endpoint: same as necrosis**
- **Immunogenic: favored in defense against certain pathogens**

Cell death: Apoptosis

Br. J. Cancer (1972) **26**, 239

APOPTOSIS: A BASIC BIOLOGICAL PHENOMENON WITH WIDE-RANGING IMPLICATIONS IN TISSUE KINETICS

J. F. R. KERR*, A. H. WYLLIE AND A. R. CURRIE†

From the Department of Pathology, University of Aberdeen

Received for publication April 1972

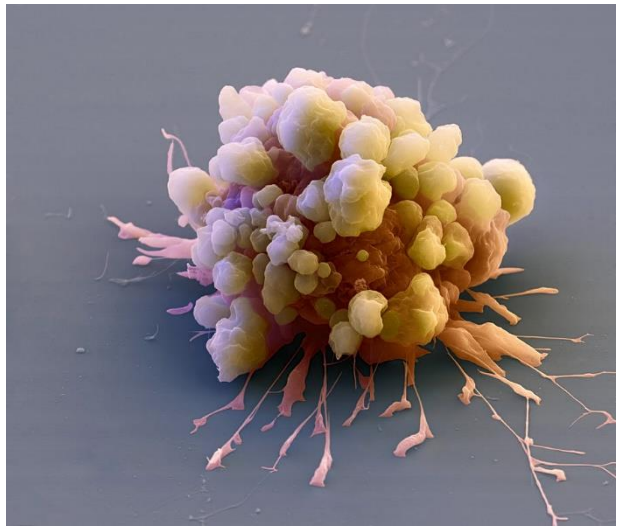
Summary.—The term apoptosis is proposed for a hitherto little recognized mechanism of controlled cell deletion, which appears to play a complementary but opposite role to mitosis in the regulation of animal cell populations. Its morphological features suggest that it is an active, inherently programmed phenomenon, and it has been shown that it can be initiated or inhibited by a variety of environmental stimuli, both physiological and pathological.

The structural changes take place in two discrete stages. The first comprises nuclear and cytoplasmic condensation and breaking up of the cell into a number of membrane-bound, ultrastructurally well-preserved fragments. In the second stage these apoptotic bodies are shed from epithelial-lined surfaces or are taken up by other cells, where they undergo a series of changes resembling *in vitro* autolysis within phagosomes, and are rapidly degraded by lysosomal enzymes derived from the ingesting cells.

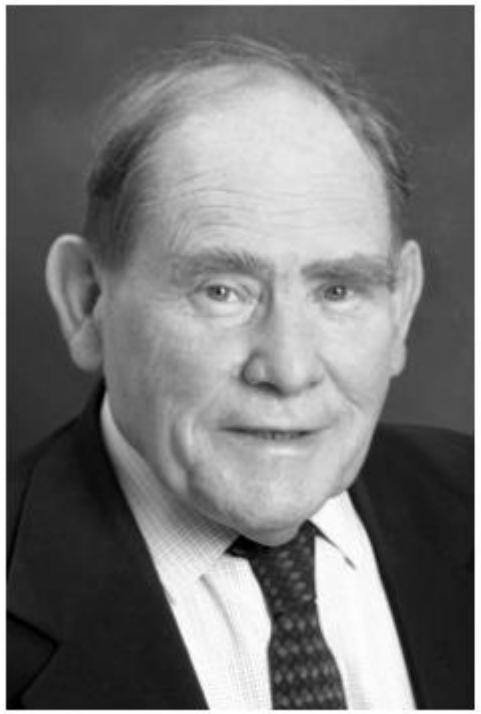
Apoptosis seems to be involved in cell turnover in many healthy adult tissues and is responsible for focal elimination of cells during normal embryonic development. It occurs spontaneously in untreated malignant neoplasms, and participates in at least some types of therapeutically induced tumour regression. It is implicated in both physiological involution and atrophy of various tissues and organs. It can also be triggered by noxious agents, both in the embryo and adult animal.

Apoptosis

- 1972: Kerr, Wyllie and Currie coined the term **ἀπόπτωσις:**
  dropping/falling off

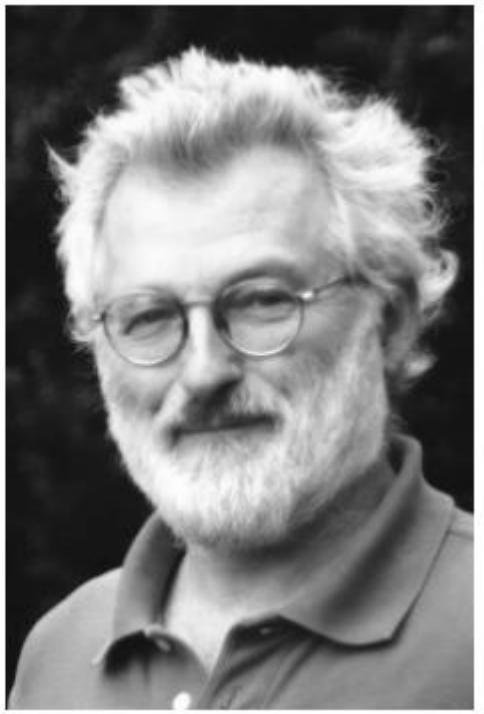


2002 Nobel Prize in Physiology or Medicine



Sydney Brenner

H. Robert Horvitz

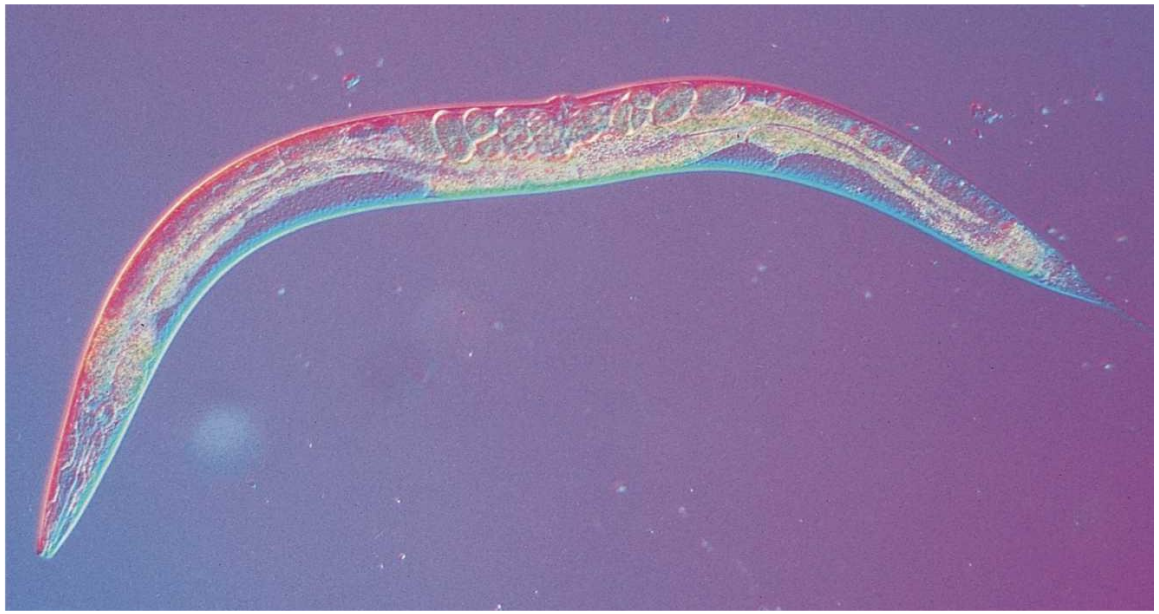


John E. Sulston

– for their discoveries concerning genetic regulation of organ development and programmed cell death

Caenorhabditis elegans

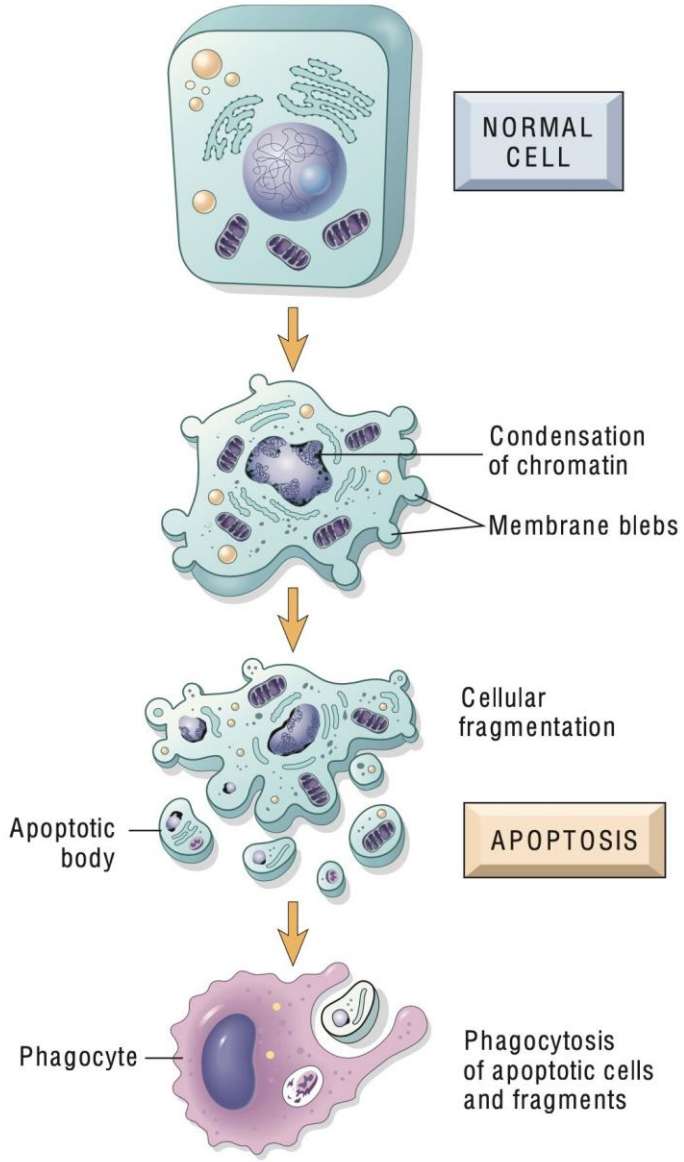
- Hermaphrodite adult: 959 somatic cells
- 131 cells eliminated by apoptosis during development: predictability, easy to observe
- **Genes involved in regulation of apoptosis – 14 Ced genes:**

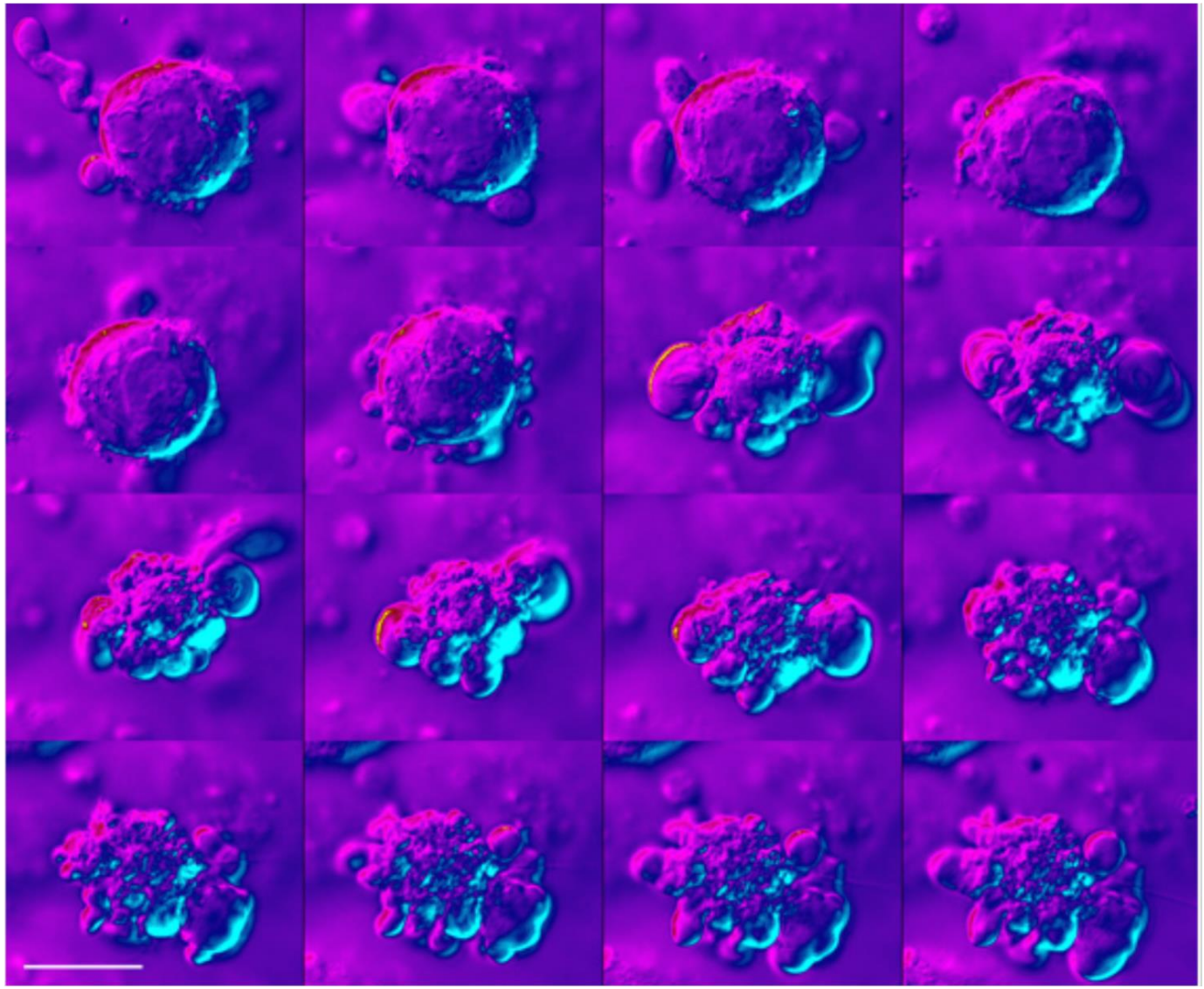


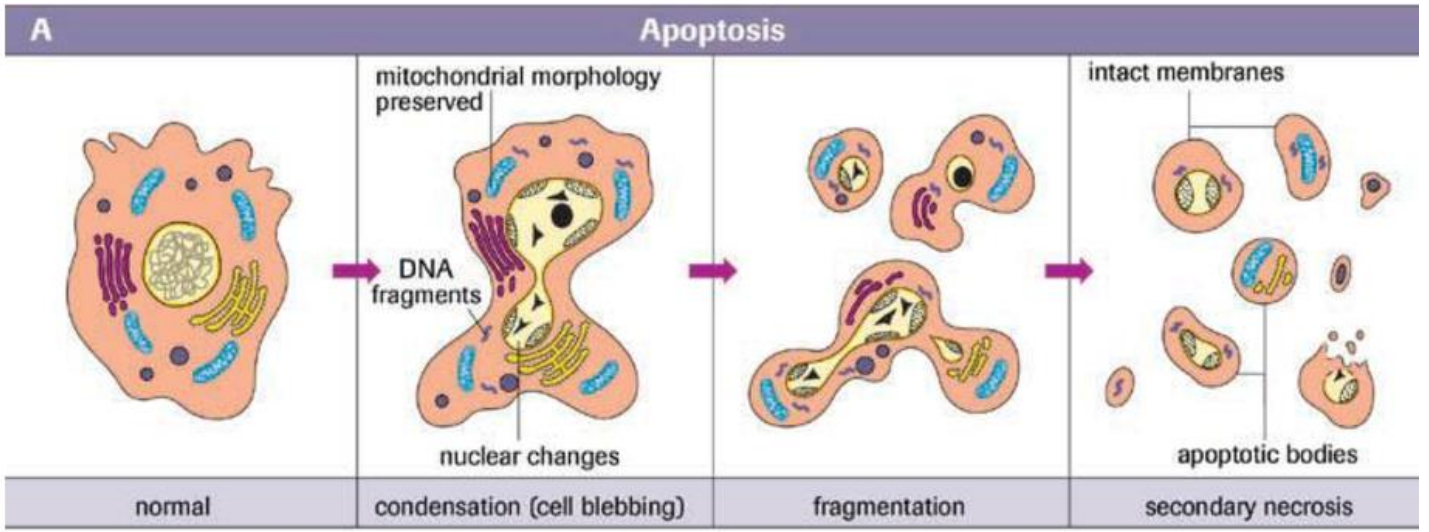
- Ced-3, Ced-4 – induction of apoptosis
- Ced-9 – anti-apoptotic role

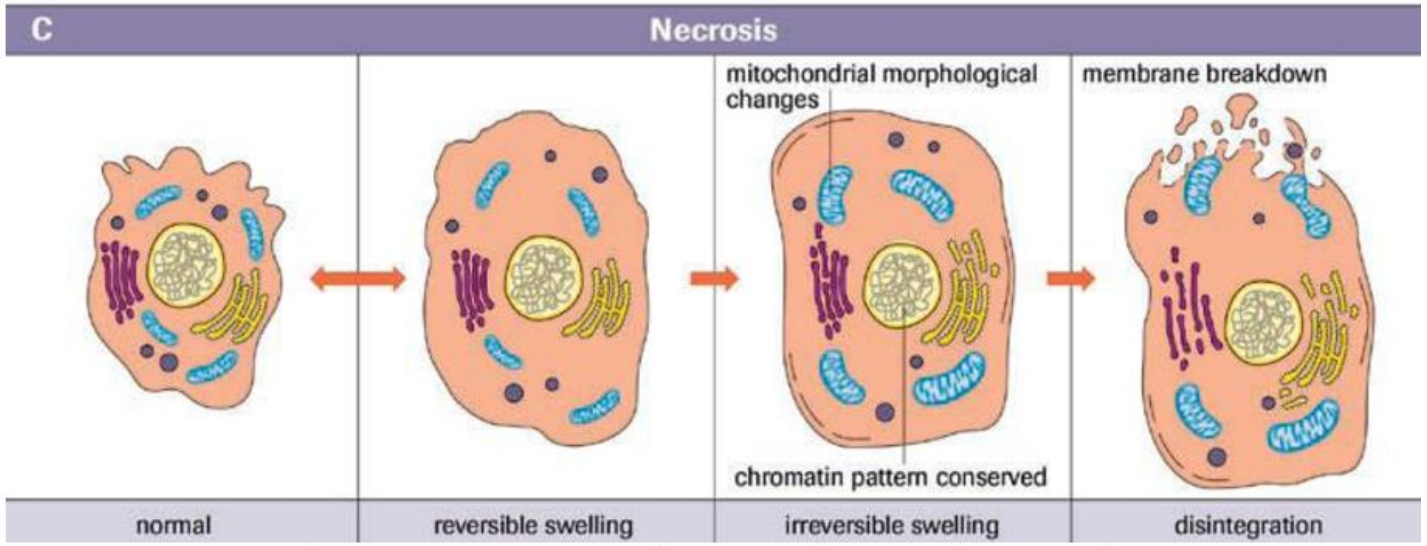
Hallmarks of apoptosis

- Chromatin condensation
- Nuclear fragmentation
- Plasma membrane integrity retained
- Cellular fragmentation into apoptotic bodies






A
Apoptosis
mitochondrial morphology preserved
DNA fragments
nuclear changes
intact membranes
apoptotic bodies
normal
condensation (cell blebbing)
fragmentation
secondary necrosis

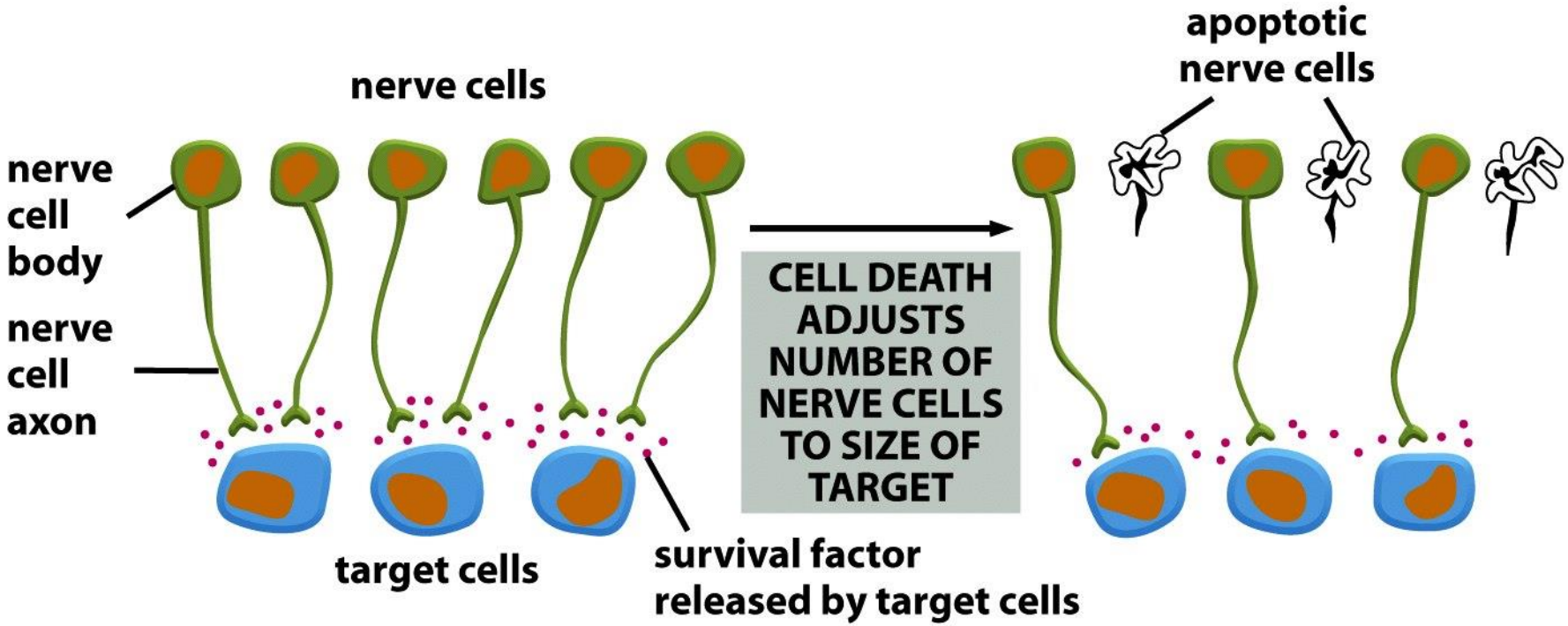

C
Necrosis
mitochondrial morphological changes
chromatin pattern conserved
membrane breakdown
normal
reversible swelling
irreversible swelling
disintegration

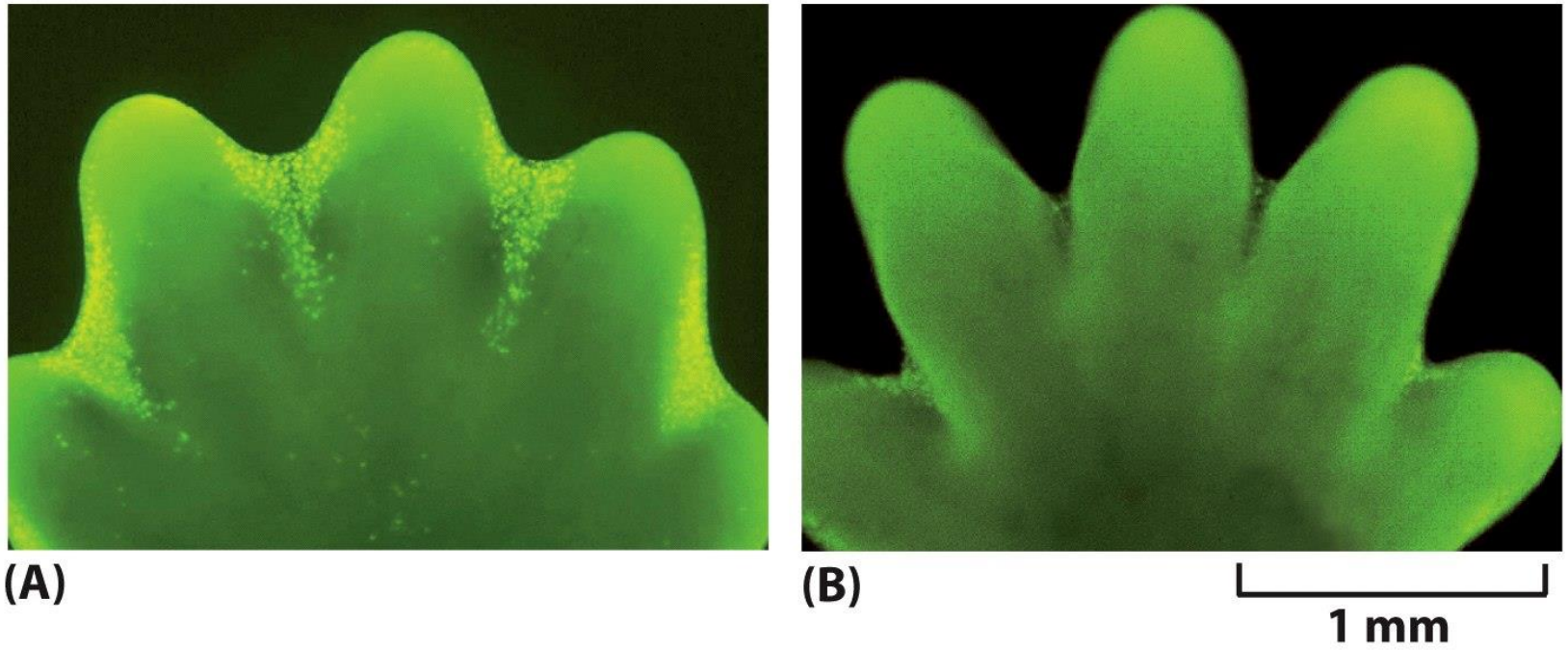
The role of apoptosis

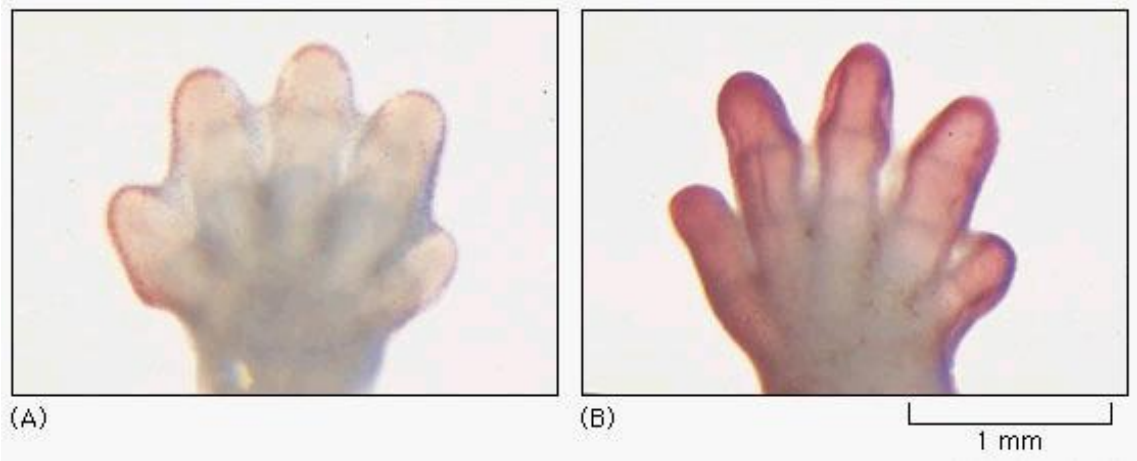
- **Regulated elimination of unwanted cells**

1. **Indispensable for proper development of multicellular organisms**

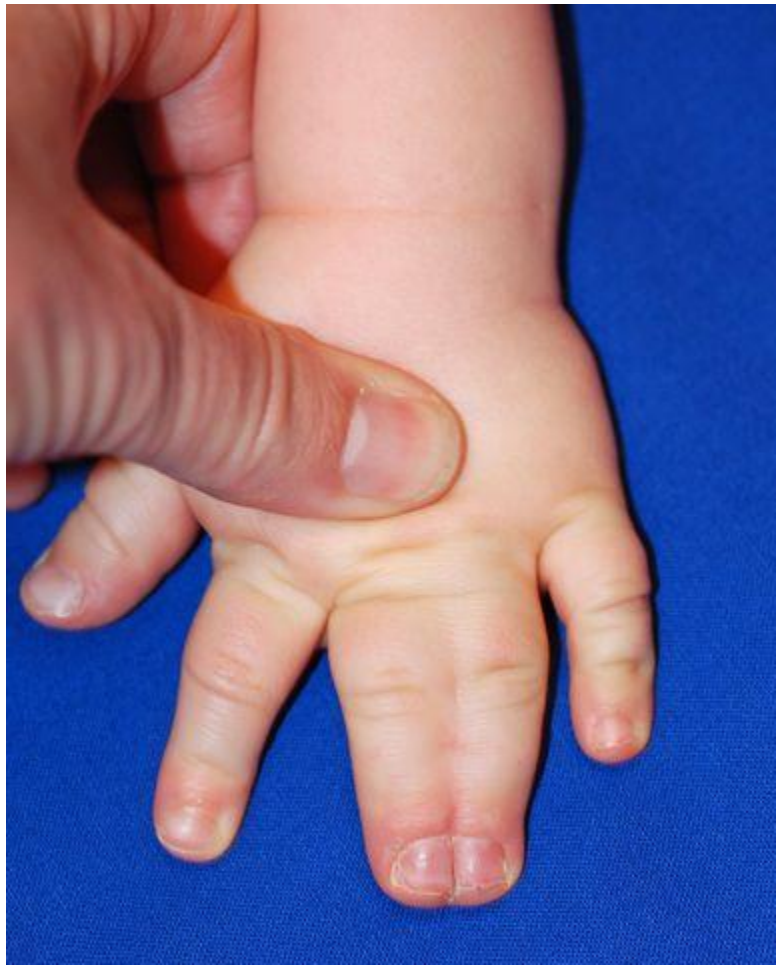
- Elimination of tissues between digits during embryogenesis: sculpting hands/paws
- Resorption of the tail during tadpole metamorphosis into a frog
- Adjusting the number of developing nerve cells to the number of target cells

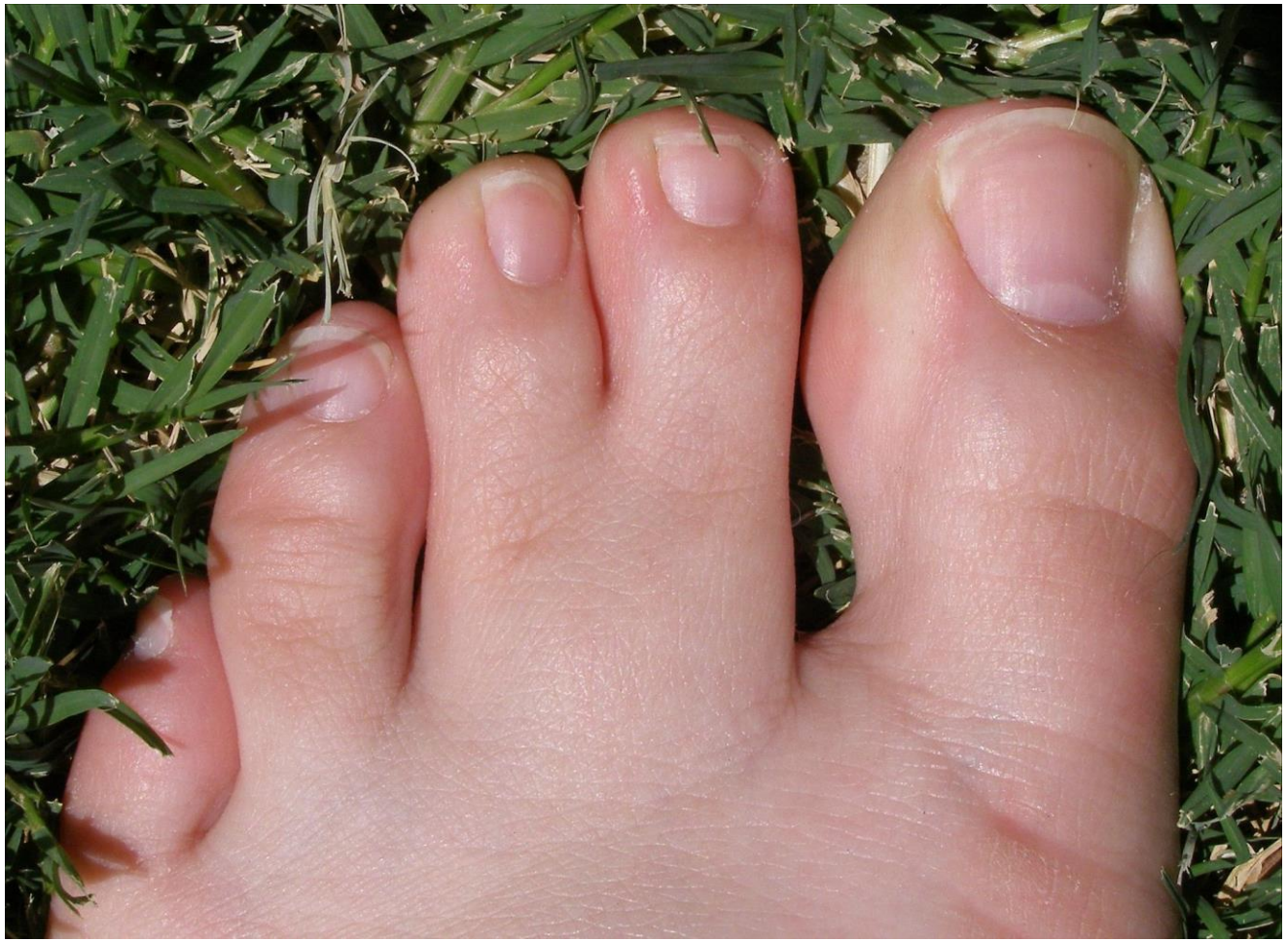

nerve cells
apoptotic nerve cells
nerve cell body
nerve cell axon
CELL DEATH ADJUSTS NUMBER OF NERVE CELLS TO SIZE OF TARGET
target cells
survival factor released by target cells


(A)
(B)
1 mm


(A)
(B)
1 mm

Syndactyly: defects in apoptosis



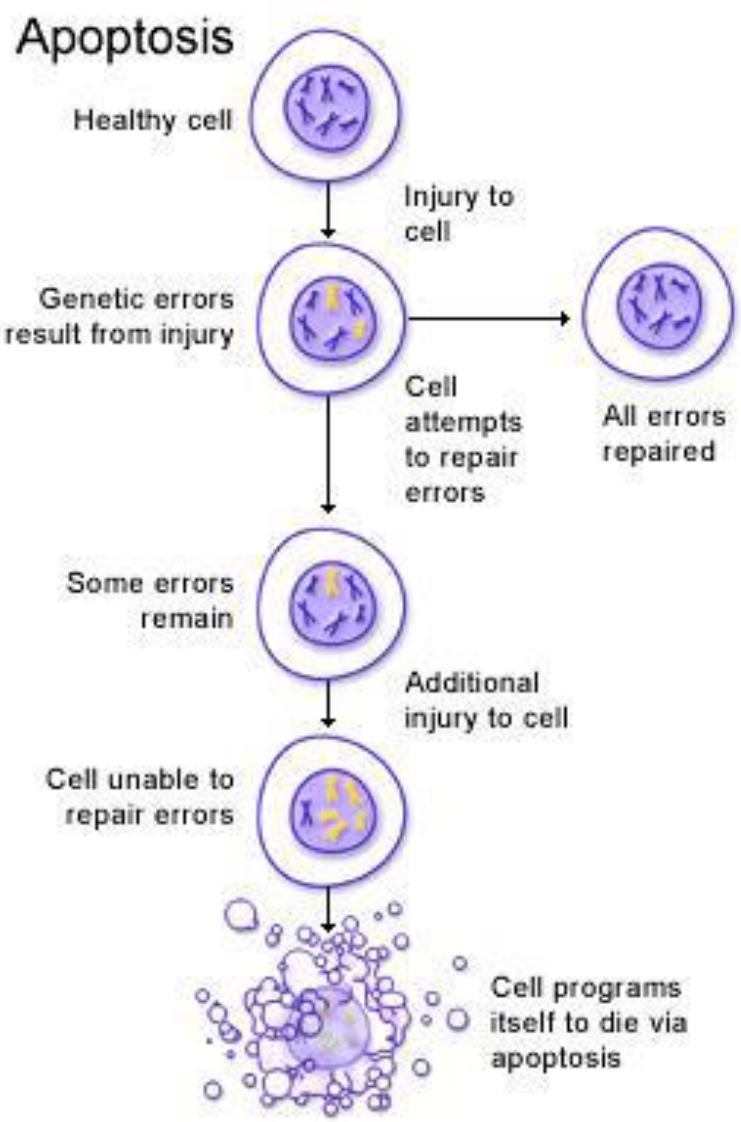


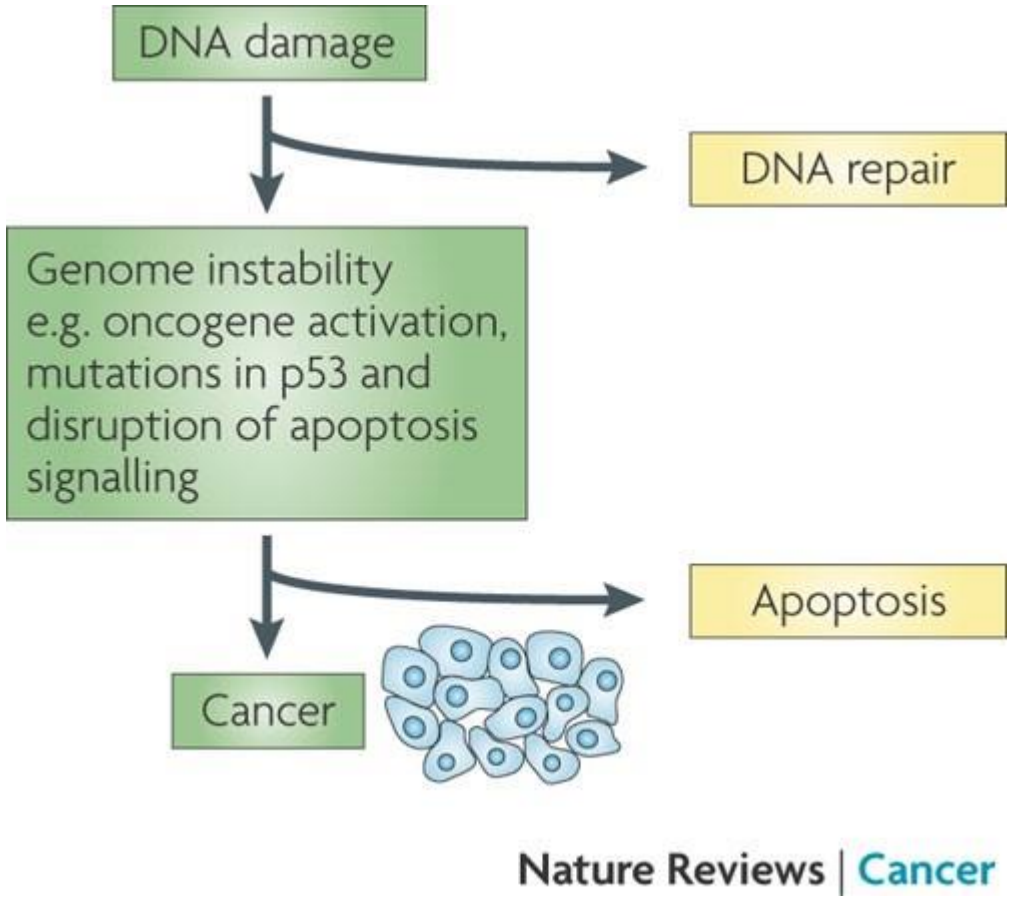
The role of apoptosis

- **Regulated elimination of unwanted cells**

2. Quality-control mechanism for eliminating abnormal, misplaced, defective cells dangerous for the organism integrity

- Cells infected with viruses (parasitic bacteria can inhibit apoptosis)
- Effector cells of the immune system after the immune response
- Cells with damaged DNA (checkpoint kinases → p53 downstream targets: DNA repair or induction of apoptosis) vs. cellular senescence
- Precancerous cells and transformed cells

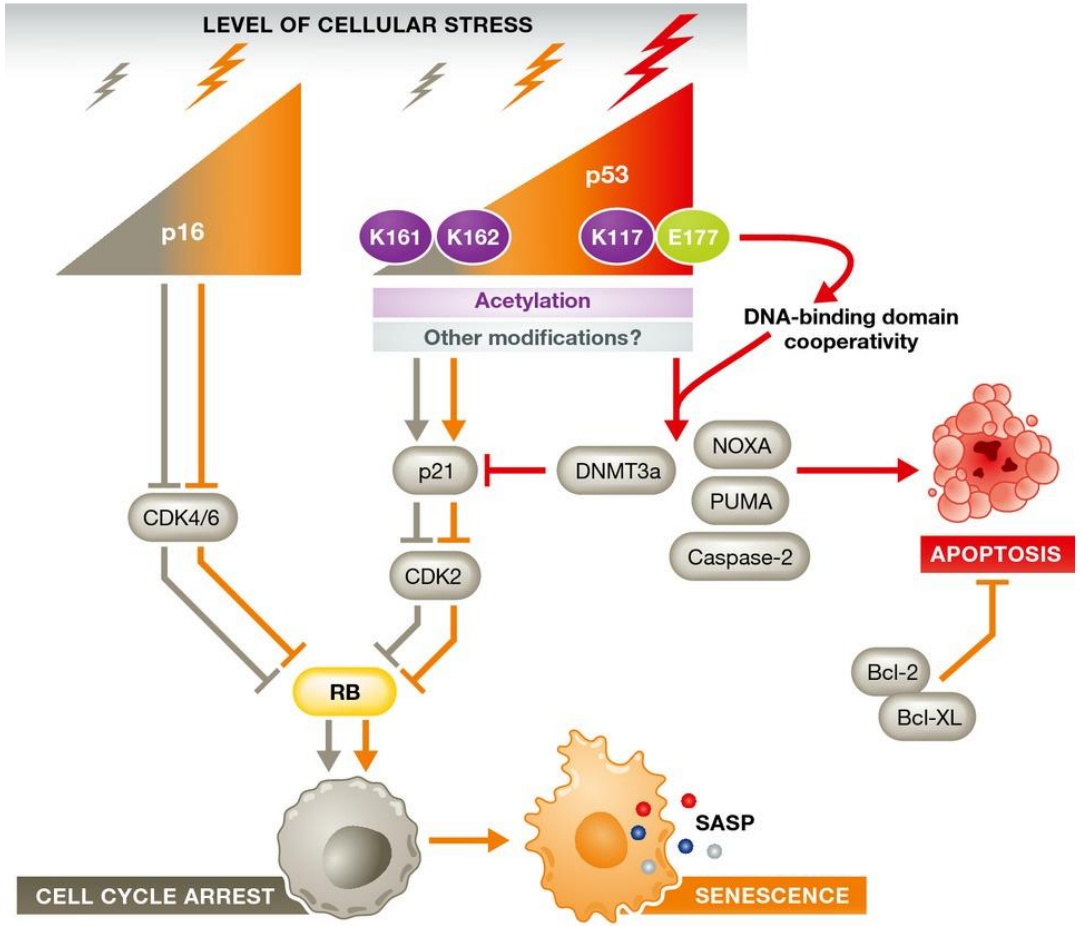

Apoptosis
Healthy cell
Injury to cell
Genetic errors result from injury
Cell attempts to repair errors
All errors repaired
Some errors remain
Additional injury to cell
Cell unable to repair errors
Cell programs itself to die via apoptosis


DNA damage
DNA repair
Genome instability e.g. oncogene activation, mutations in p53 and disruption of apoptosis signalling
Apoptosis
Cancer
Nature Reviews | Cancer

The level of cellular stress matters

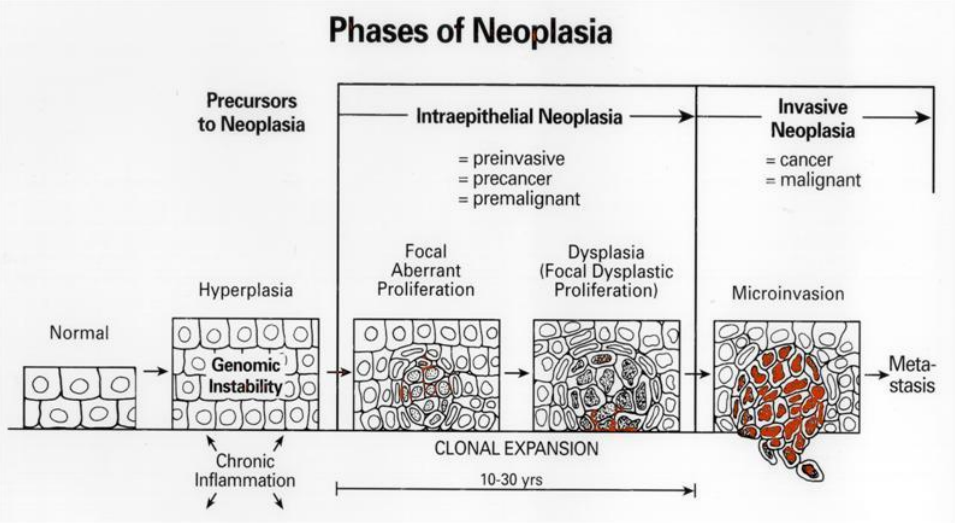
- Nature and severity of the stress dictates whether a cell becomes senescent or undergoes apoptosis

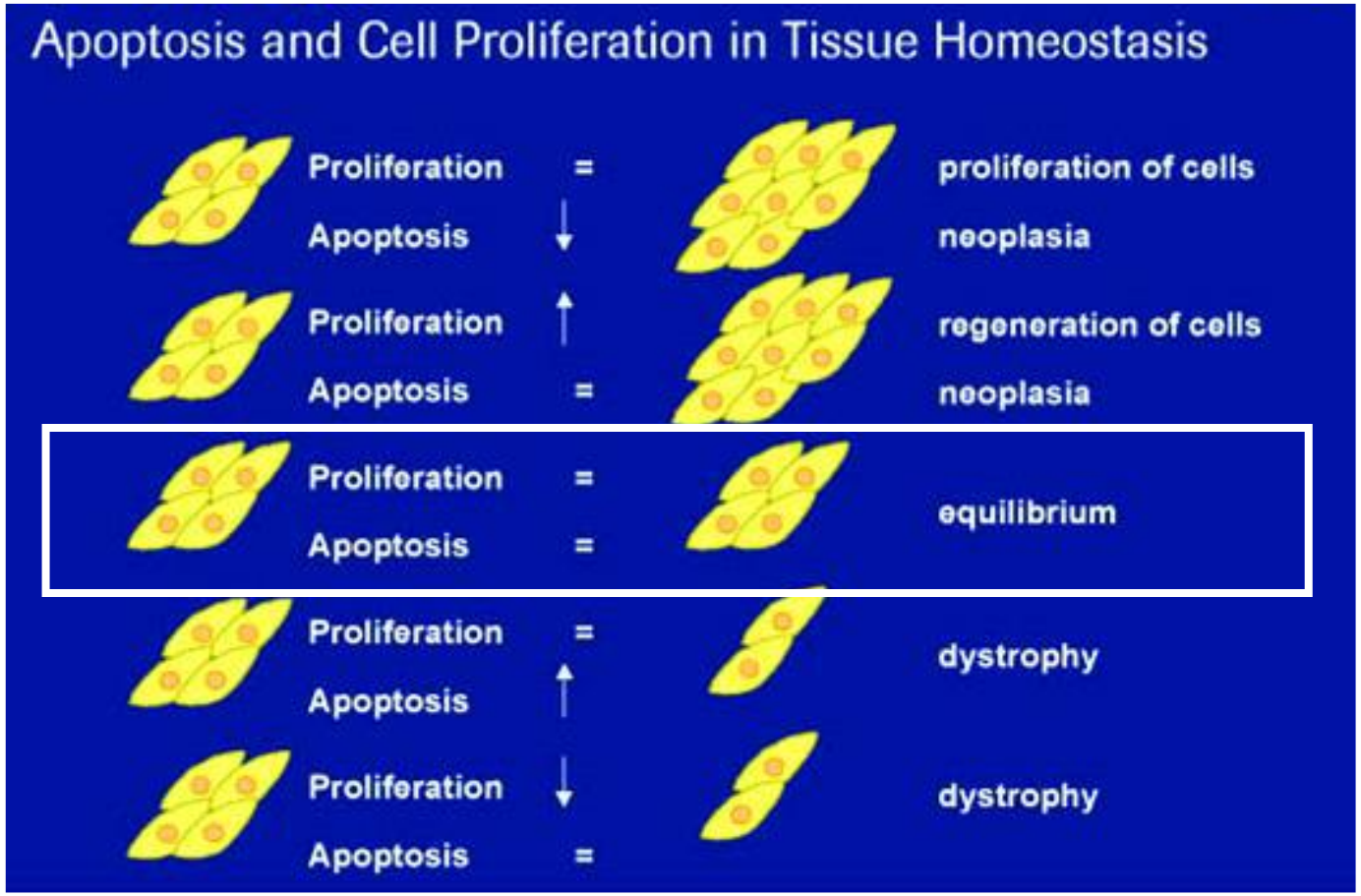
- Senescent cells
  - Prolonged and generally irreversible cell cycle arrest – induced by less sever damage
  - Active prosurvival pathways = enhanced resistance to apoptosis



Tissue homeostasis – apoptosis vs. proliferation

- Failure of apoptosis → development of neoplasms (benign → malignant)





Induction of apoptosis

Withdrawal of antiapoptotic (survival) stimuli

- Growth factors – various cell types including neurons
- Interleukin 2 (IL-2), IL-3 – lymphocytes, hematopoietic stem cells

Receiving apoptotic stimuli

- **Internal signals**
  - Prolonged or severe stress: upregulation of ROS-damaged molecules, DNA damage, ER stress, viral infection, amino acid starvation, glucose deprivation…
- **External signals**
  - **Death ligands** binding to **death receptors**

Phases of apoptosis

Initiation phase = induction of apoptosis

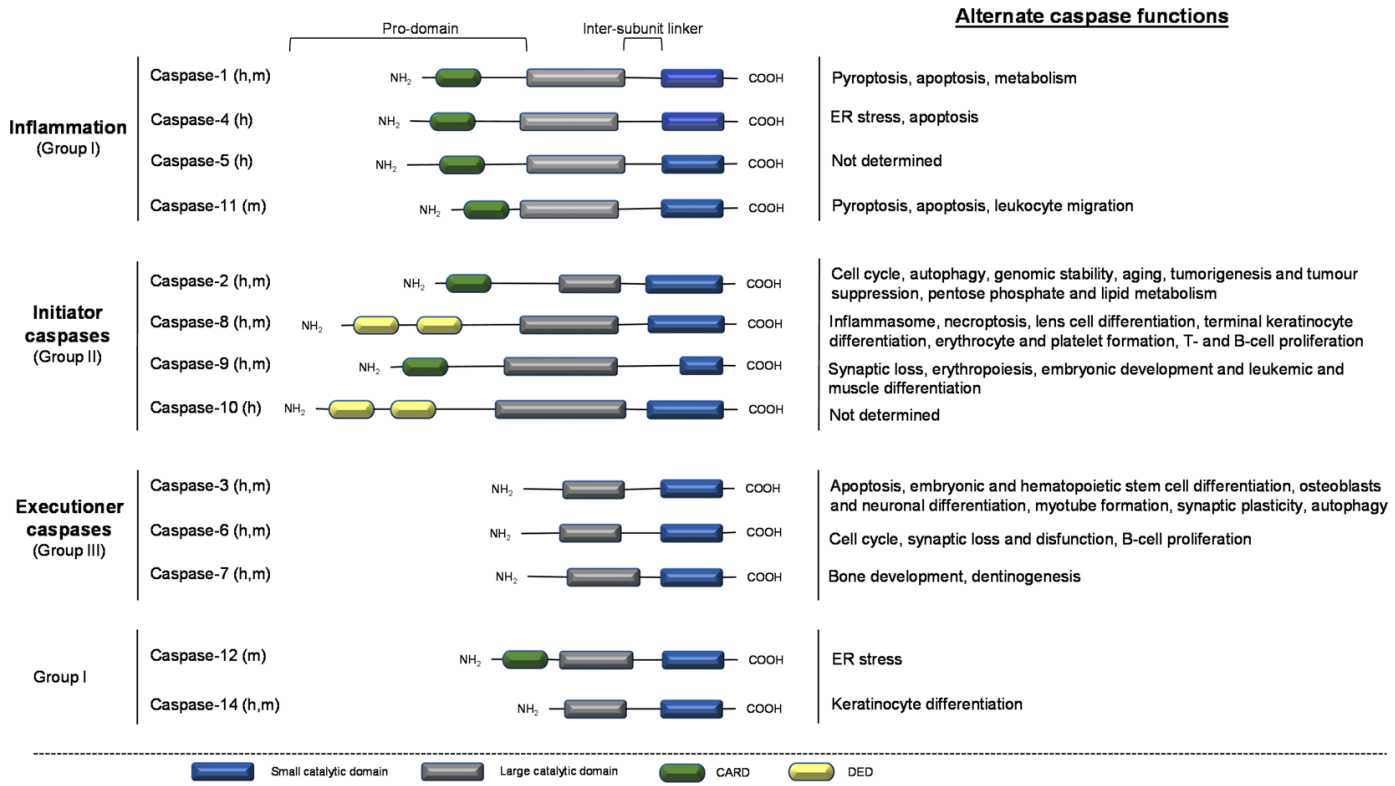
- **Intrinsic pathway**: mitochondrial outer membrane permeabilization & release of cytochrome c
- **Extrinsic pathway**: activation of death receptors
- Activation of **initiator caspases**

Execution phase

- Activation of **executioner caspases**
- Cell shrinkage, plasma membrane blebbing
- Changes in the plasma membrane composition
- Chromatin condensation, degradation and fragmentation
- Proteolytic cleavage of intracellular proteins
- Fragmentation into apoptotic bodies (followed by phagocytosis)

Caspases – proteolytic cleavage

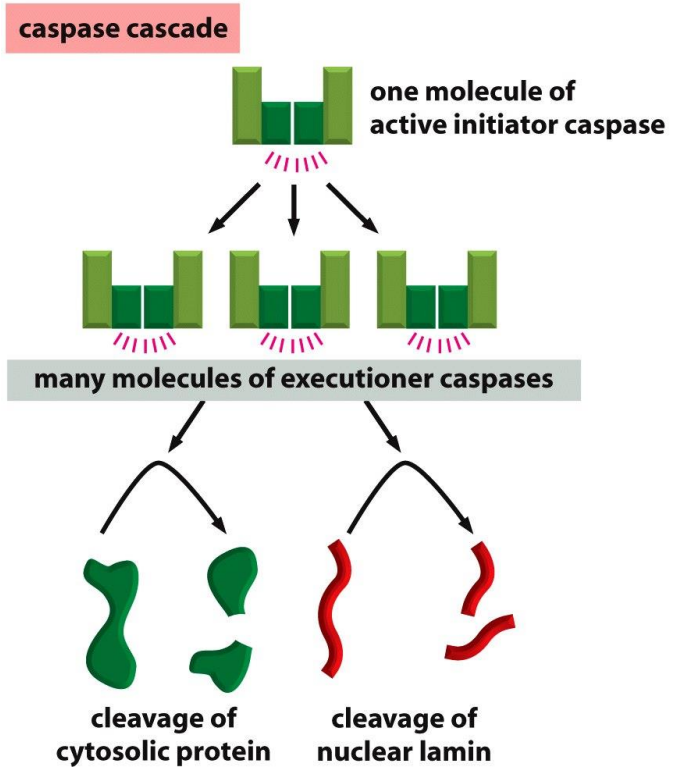
- **C**ysteine-**asp**artic protea**ses: cleave proteins at the carboxy group of aspartic acid residue**
- **13 human caspases:**
- **Initiator** (2, **8, 9**, 10)
- **Executioner** (**3**, 6, 7)
- Synthesized as inactive zymogens (**pro-caspases**)
- Activated by cleavage



Proteolytic cleavage

Caspases

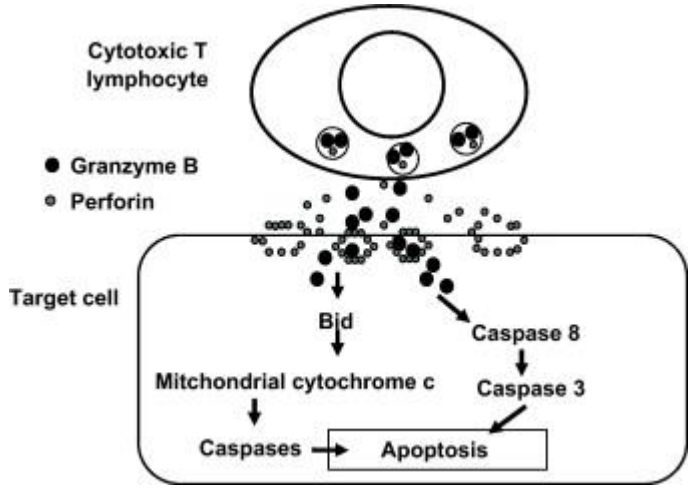
- Cleavage activated by apoptotic stimuli (intrinsic or extrinsic)
- **Initiator pro-caspases dimerization** after binding to specific protein complexes → **autocatalytic cleavage of the pro-domain → active caspases**
- **Executioner pro-caspases cleaved by initiator caspases = caspase cascade**



Proteolytic cleavage

Caspases might be activated by other proteases:

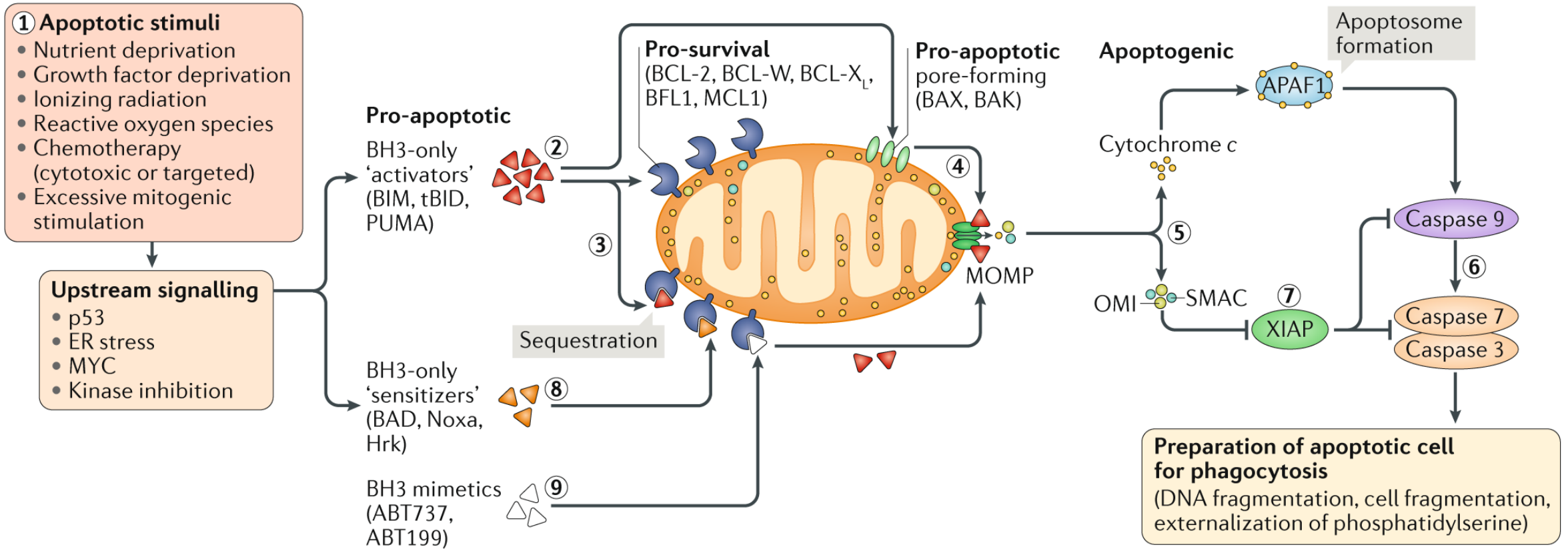
- **Granzyme B** – produced by cytotoxic T cells and NK cells
- **Cathepsins** – released from ER; direct (cleavage) and indirect activation of caspases; positive feedback loop
- **Calpains** – activated by Ca^{2+} (e.g., ER stress)

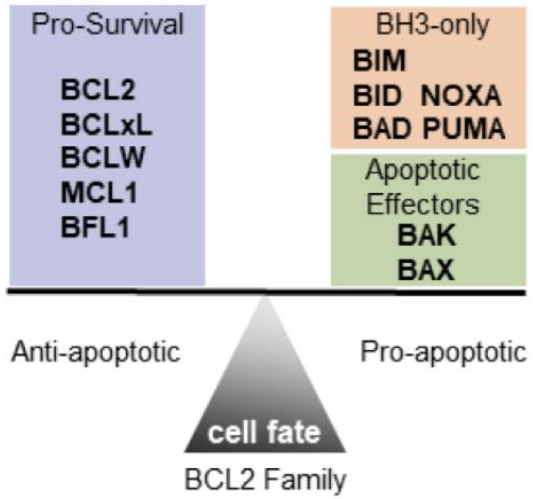


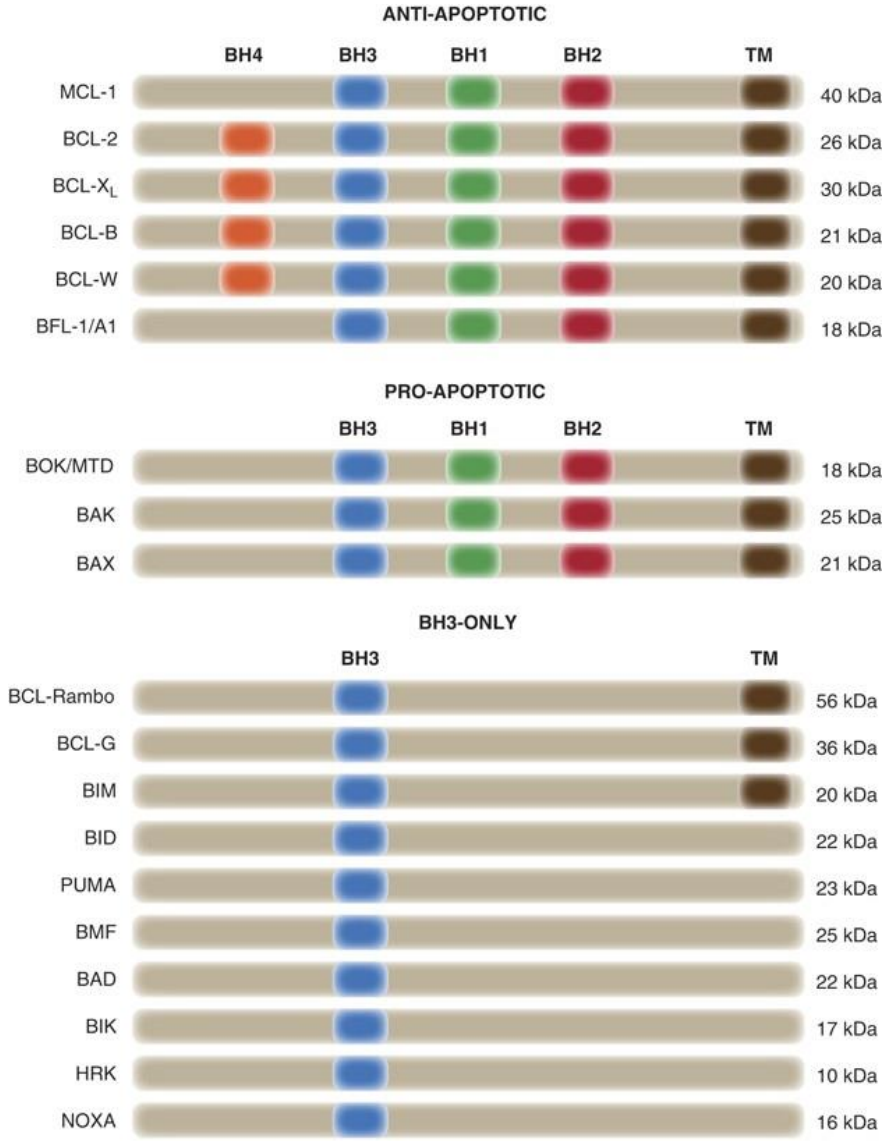
- All these protases also target (activate) other proapoptotic proteins & facilitate proteolytic cleavage

Intrinsic (mitochondrial) apoptotic pathway

– Balance of anti-apoptotic and pro-apoptotic BCL-2 proteins




Pro-Survival
BCL2
BCLxL
BCLW
MCL1
BFL1
BH3-only
BIM
BID NOXA
BAD PUMA
Apoptotic Effectors
BAK
BAX
Anti-apoptotic
Pro-apoptotic
cell fate
BCL2 Family


ANTI-APOPTOTIC
BH4
BH3
BH1
BH2
TM
MCL-1 40 kDa
BCL-2 26 kDa
BCL-XL 30 kDa
BCL-B 21 kDa
BCL-W 20 kDa
BFL-1/A1 18 kDa
PRO-APOPTOTIC
BH3
BH1
BH2
TM
BOK/MTD 18 kDa
BAK 25 kDa
BAX 21 kDa
BH3-ONLY
BH3
TM
BCL-Rambo 56 kDa
BCL-G 36 kDa
BIM 20 kDa
BID 22 kDa
PUMA 23 kDa
BMF 25 kDa
BAD 22 kDa
BIK 17 kDa
HRK 10 kDa
NOXA 16 kDa

Intrinsic (mitochondrial) apoptotic pathway

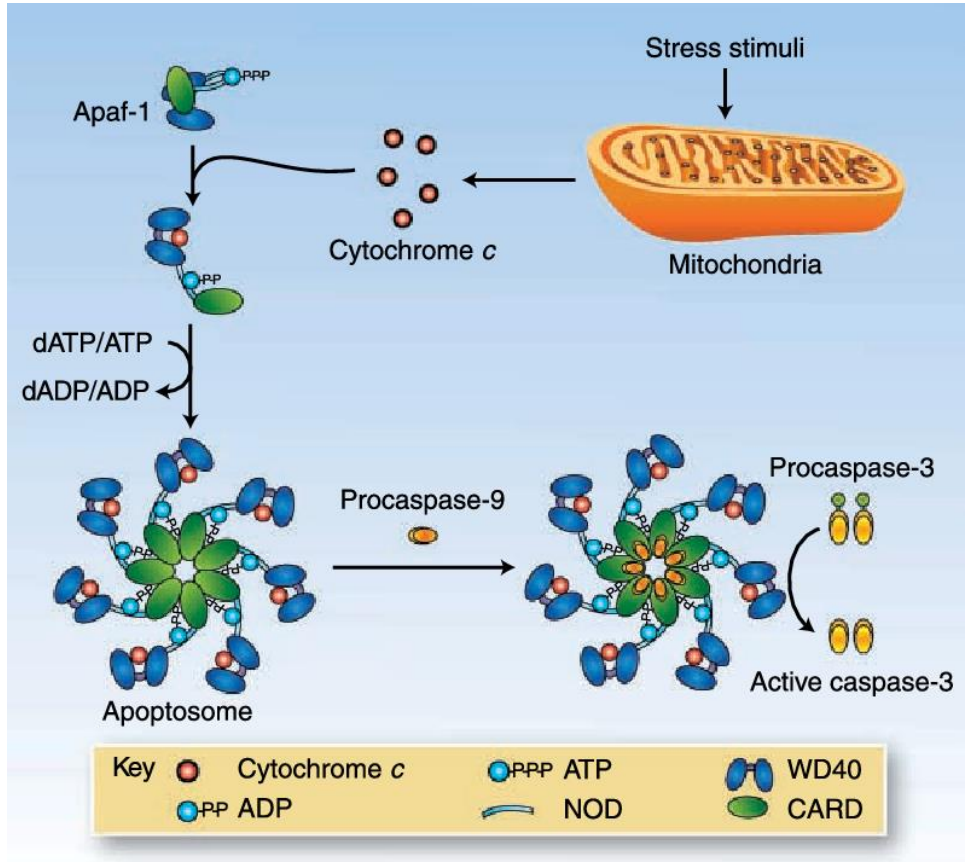
- Healthy cells: **anti-apoptotic BCL-2 proteins sequester pro-apoptotic BH3 only proteins**
- Apoptotic stimuli: upregulation of pro-apoptotic **BCL-2 BH3 only proteins** → inhibition of anti-apoptotic BCL-2 proteins → pro-apoptotic BAX & BAK oligomerization = **formation of pores in the mitochondrial outer membrane**
- **Release of cytochrome c from mitochondria into the cytosol**
- **Formation of apoptosome**

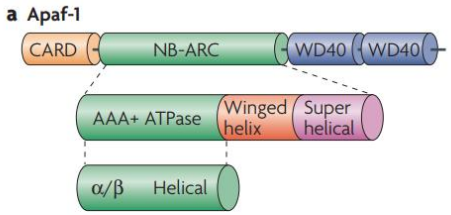
Apoptosome

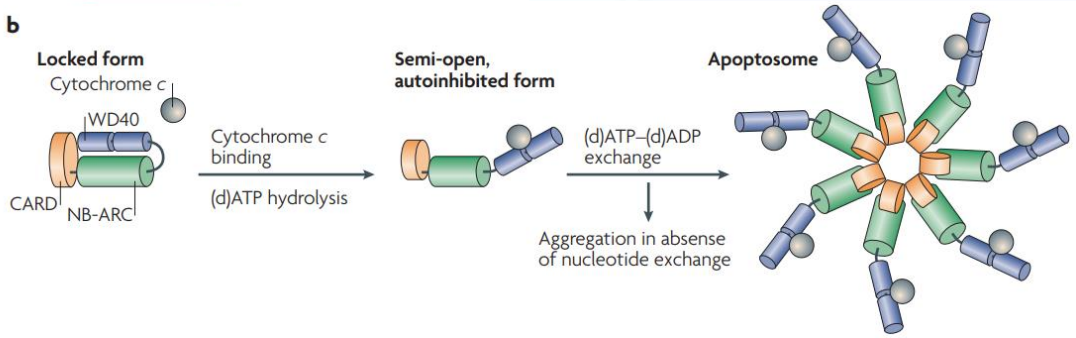
- **Cytosolic Apaf-1** + (d)ATP
- **Cytochrome c**

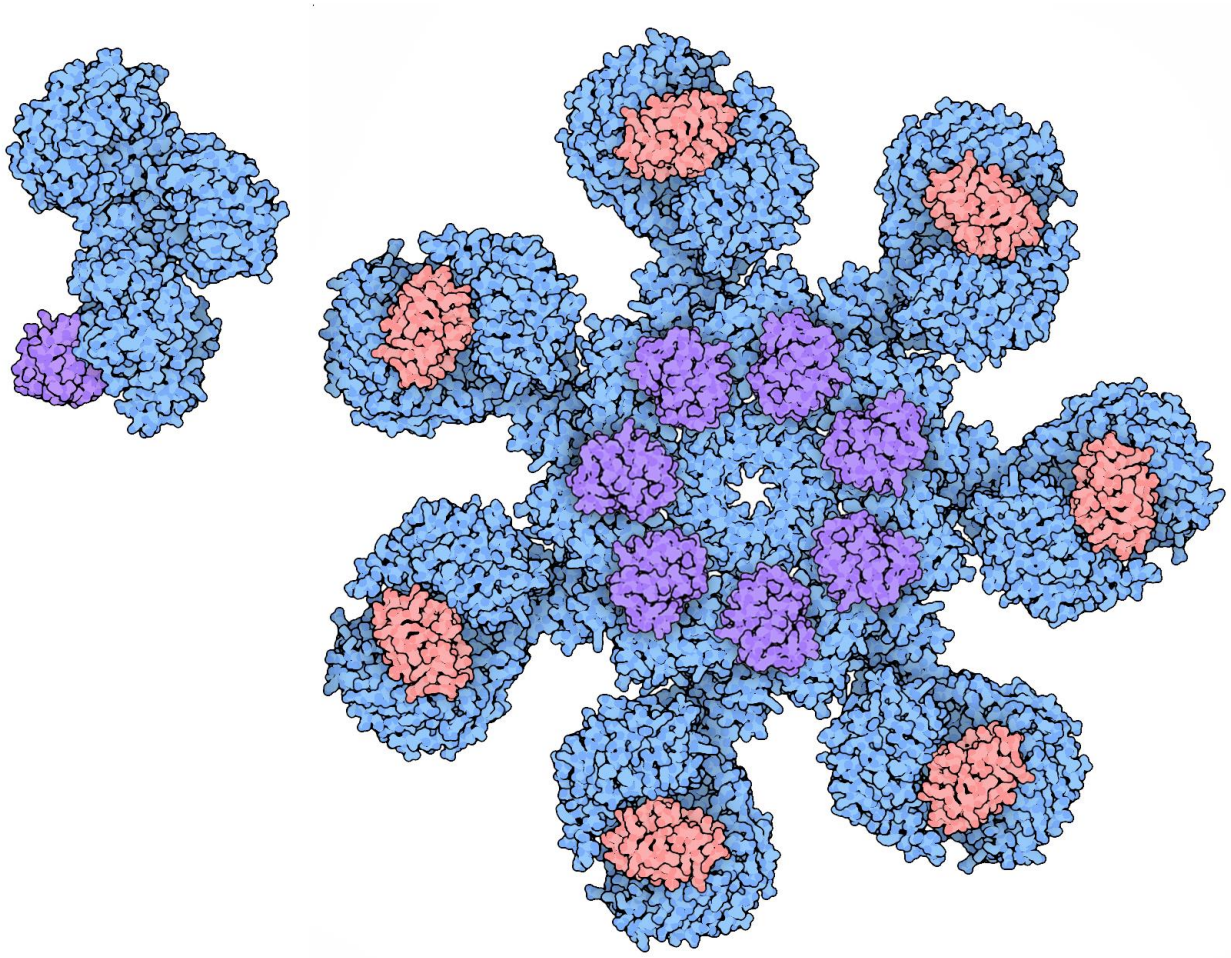
Active apoptosome:

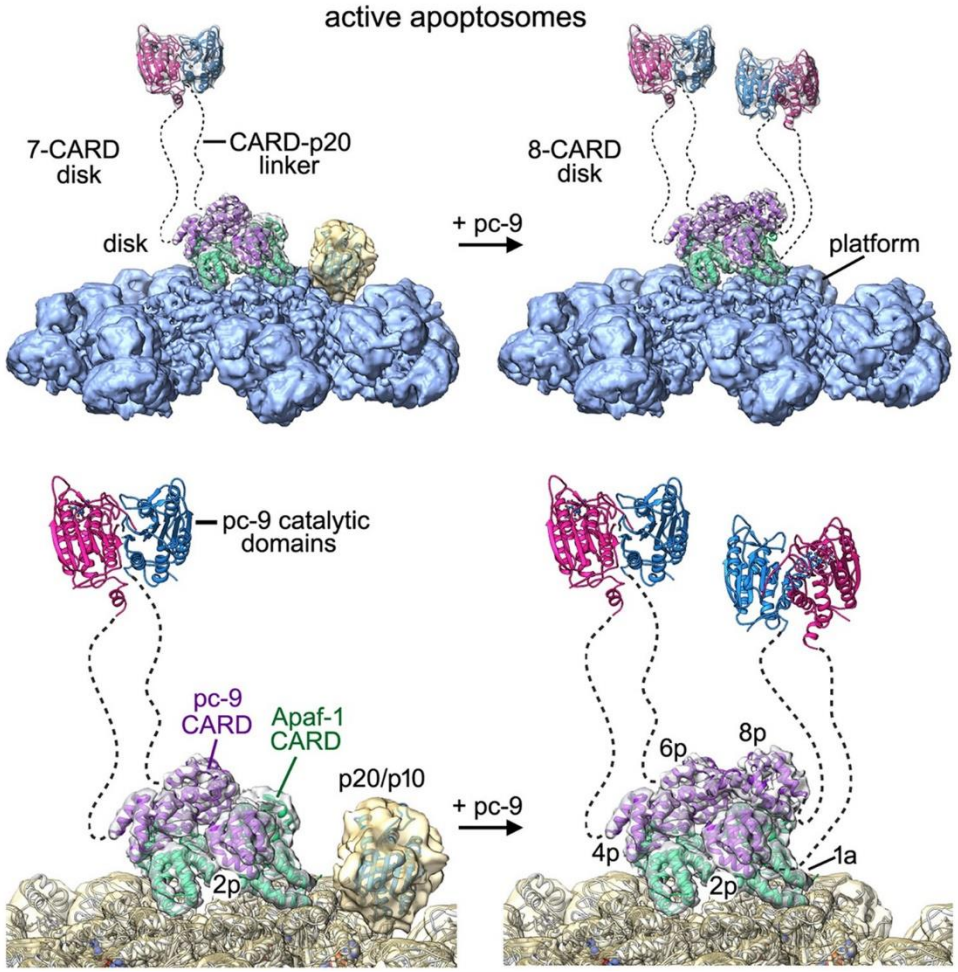
- Apaf-1 CARD domain **binds pro-caspase 9**
- **Cleavage into active initiation caspase 9: activates executioner caspases**



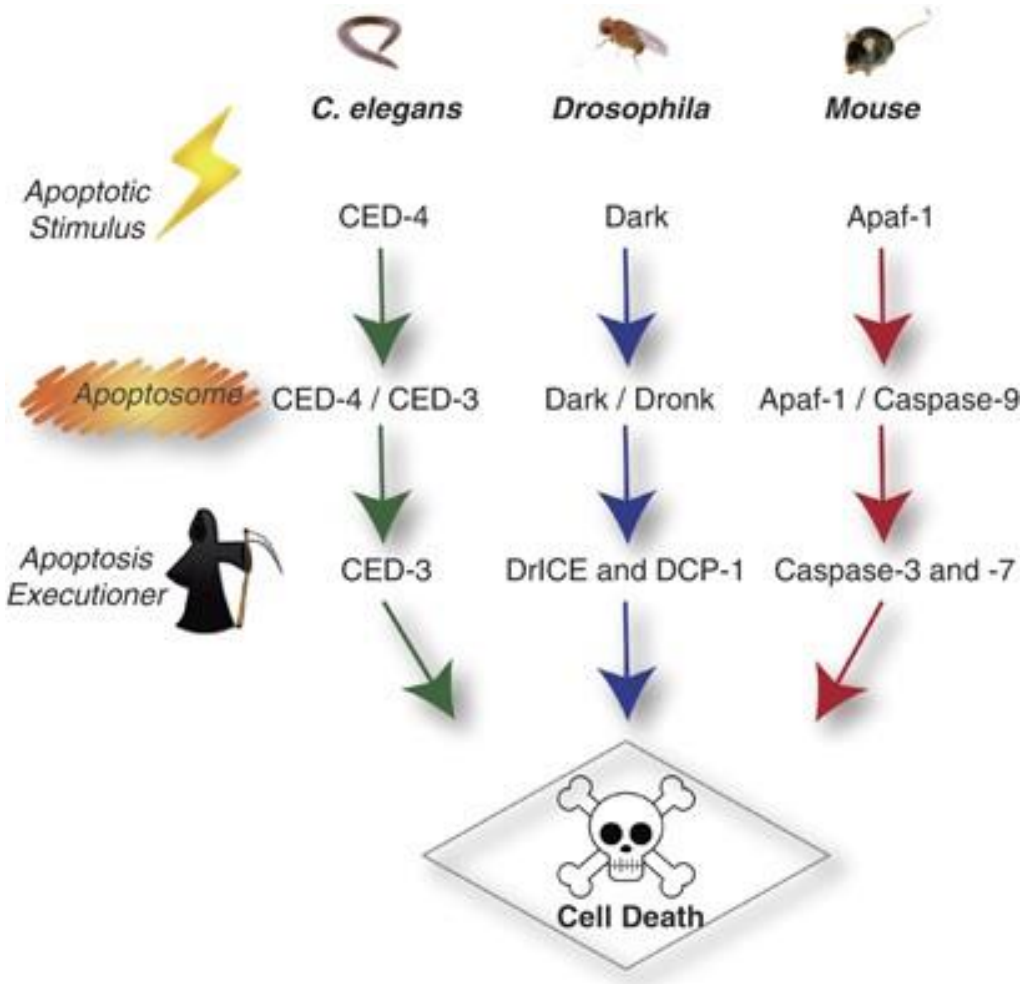







active apoptosomes
7-CARD disk
CARD-p20 linker
8-CARD disk
disk
+ pc-9
platform
pc-9 catalytic domains
pc-9 CARD
Apaf-1 CARD
p20/p10
+ pc-9
6p
8p
4p
1a
2p
2p

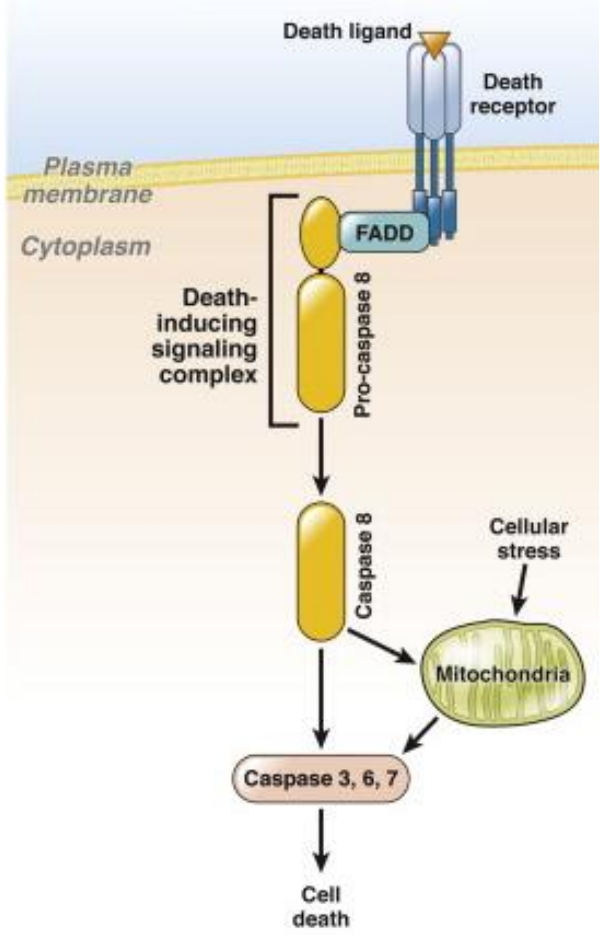
Intrinsic apoptotic pathway is evolutionary conserved



Extrinsic apoptotic pathway

- **Death ligands** activate specific **death receptors** at the plasma membrane:
- Fas ligand (FasL) – Fas receptor (CD95)
- Tumor necrosis factor (TNF) α – TNF receptor
- TRAIL – death receptor (DR) 4 and DR5
- Tweak – DR3

- **Activation of caspase 8** (2, 10): **proteolytic cascade → executioner caspases**



Extrinsic vs. intrinsic

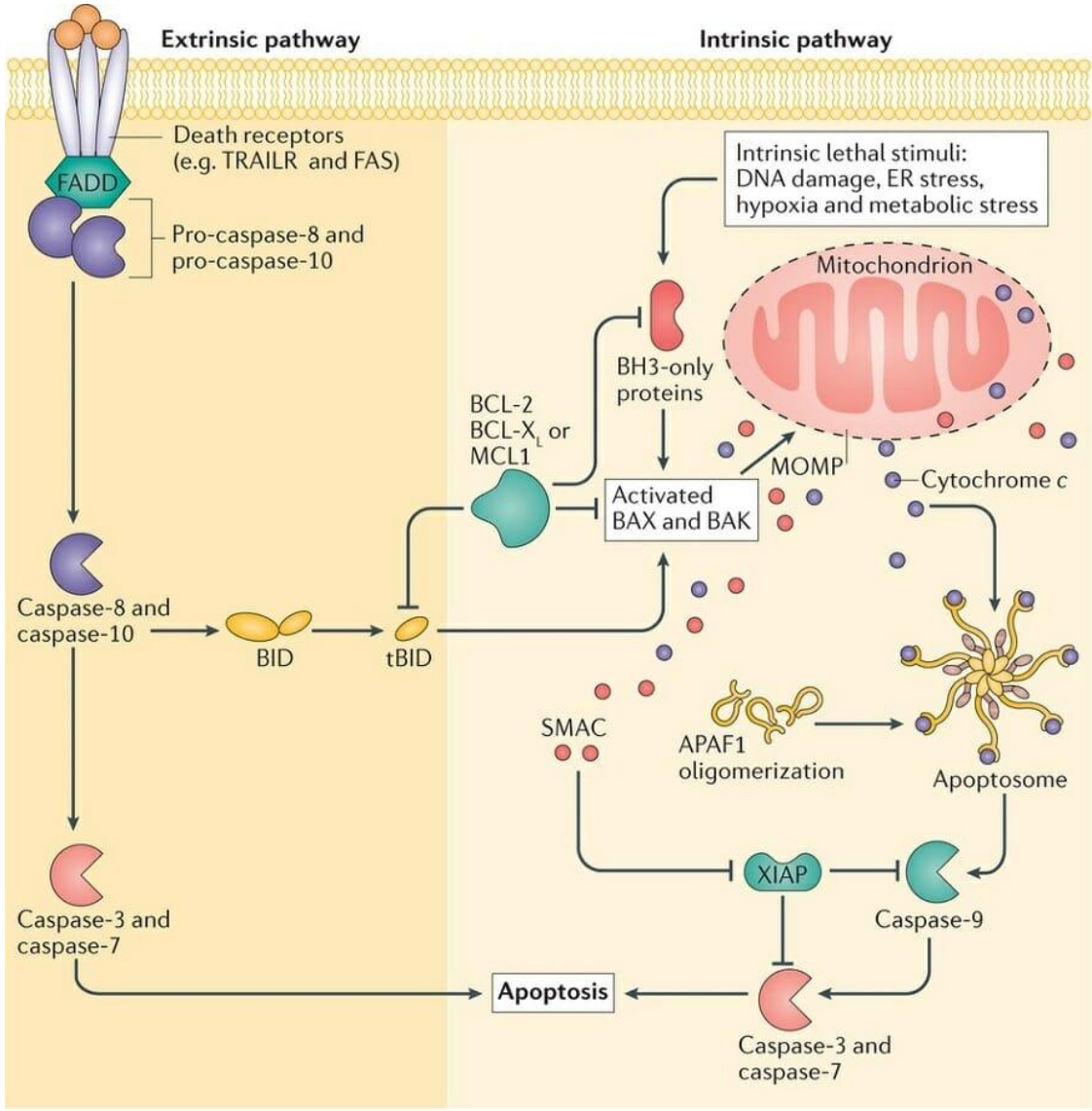
Extrinsic

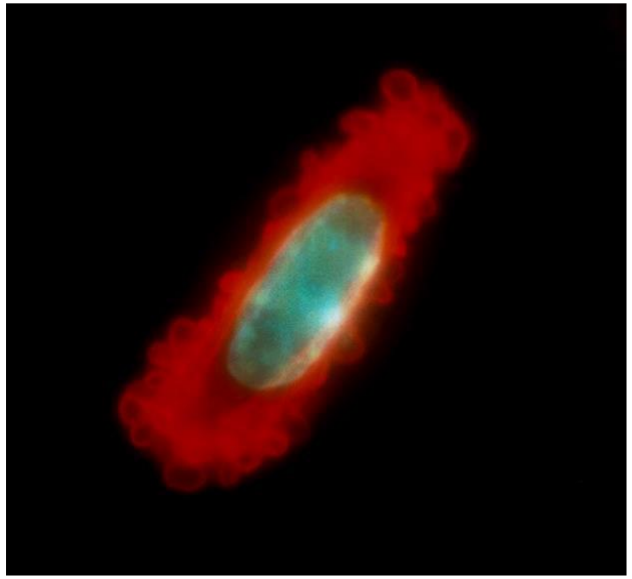
- Death receptors
- Caspase 8 (and 2,10)

Intrinsic

- MOMP and cytochrome c release
- Caspase 9

Executioner caspases shared



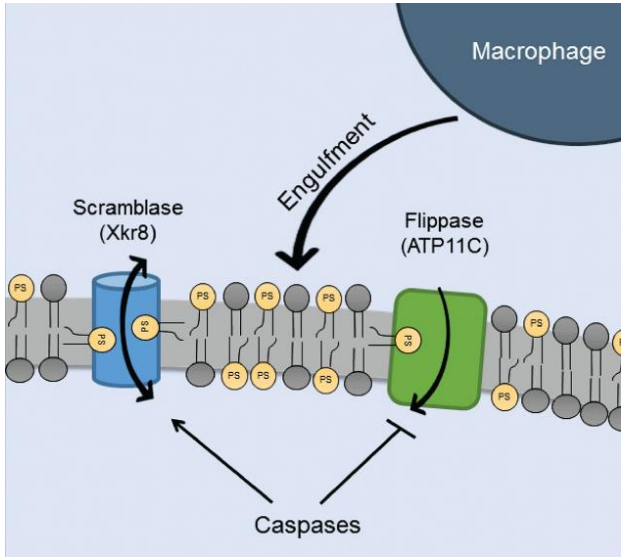


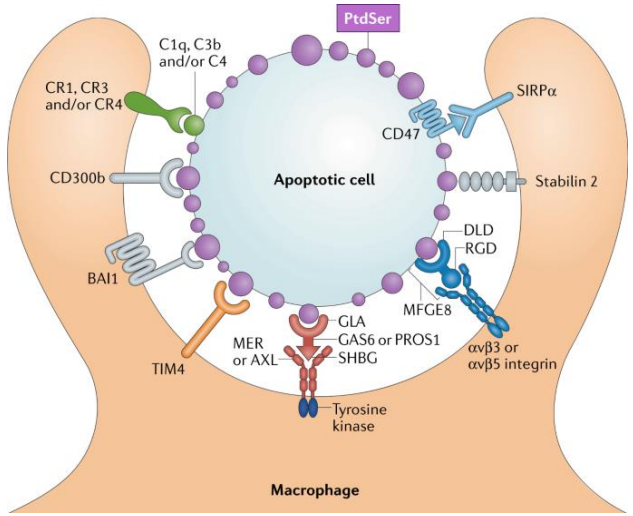
Plasma membrane blebbing

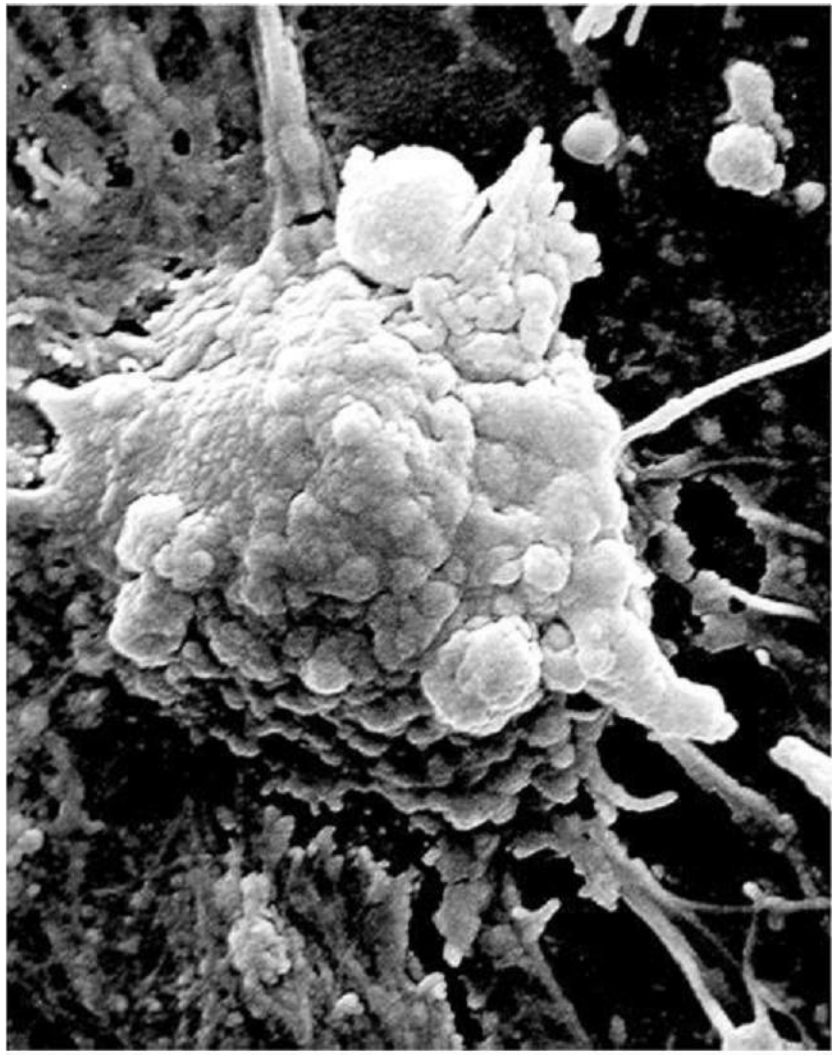
– Defects and degradation of cortical cytoskeleton

Changes in the plasma membrane

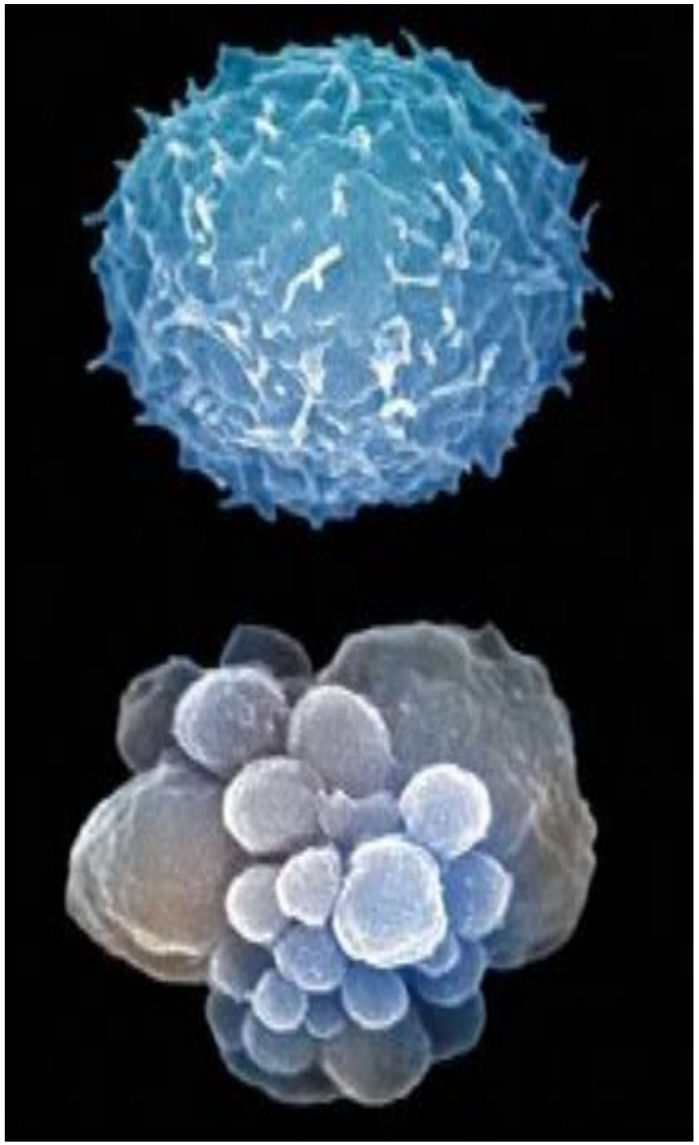
– Externalization of phosphatidylserine: signal for phagocytosis





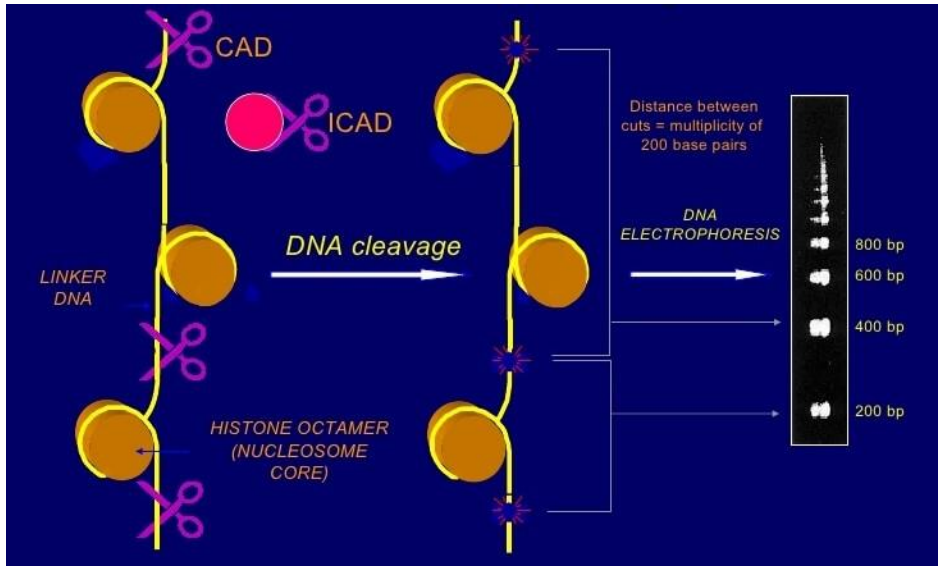


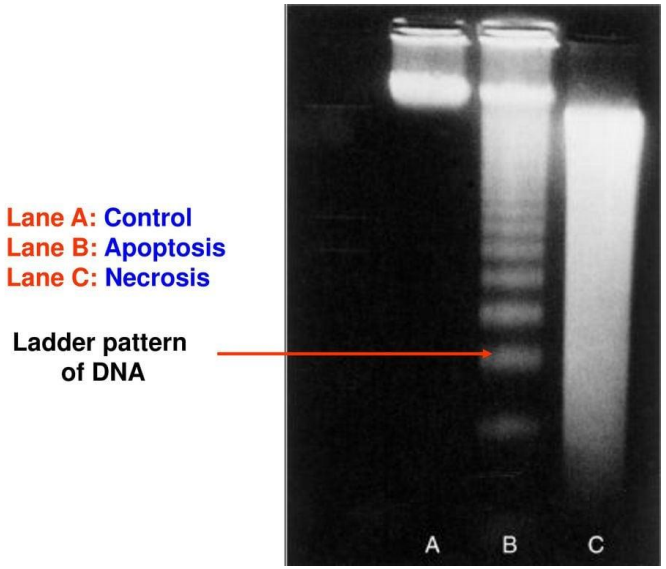
Motoneuron disease: an apoptopic neuron seen by scanning electron microscopy

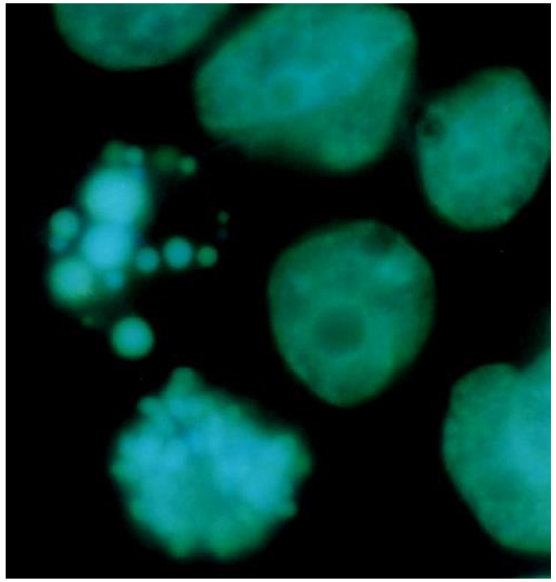


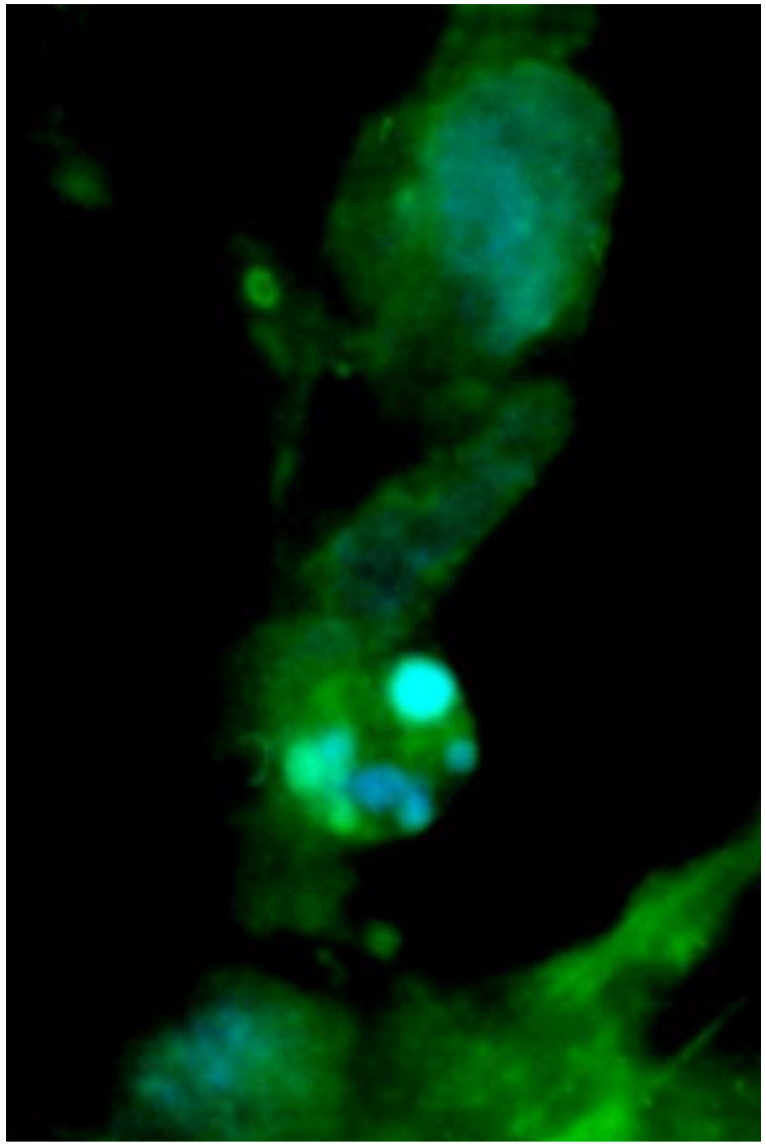
Nuclear collapse

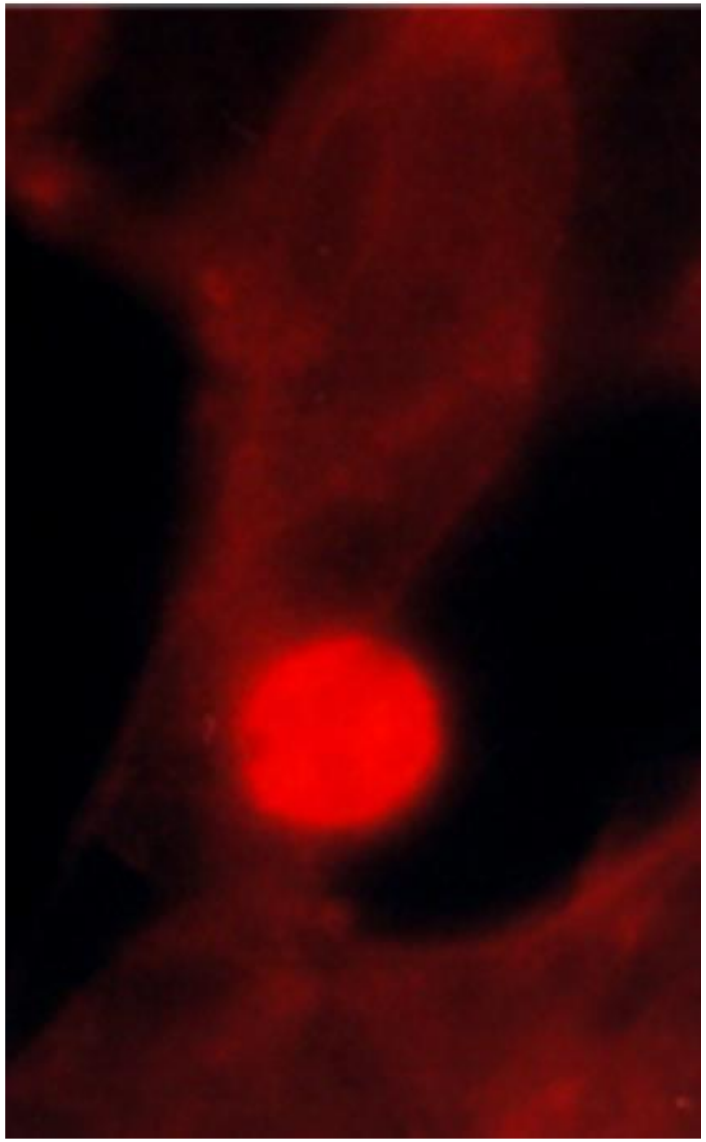
- Chromatin condensation and degradation of nuclear lamina
- Internucleoasomal cleavage of DNA: DNA ladder
- Nuclear fragmentation





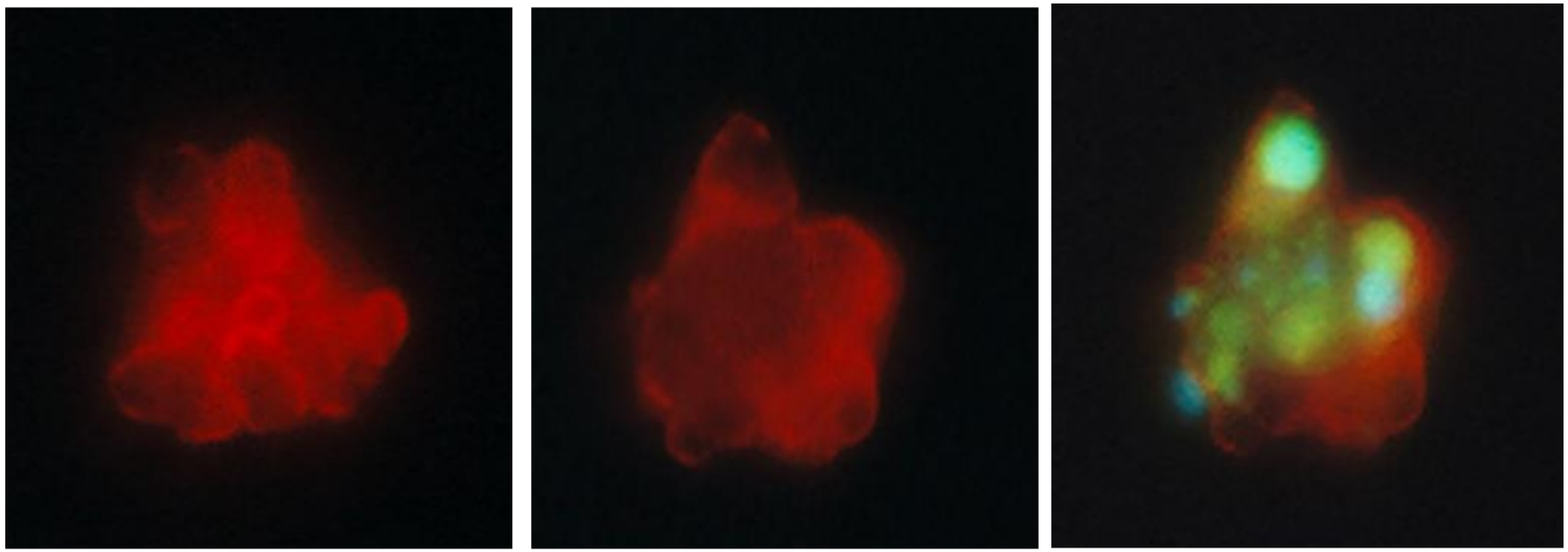






α-tubulin, DNA, cleaved caspase 3

Cell fragmentation into apoptotic bodies

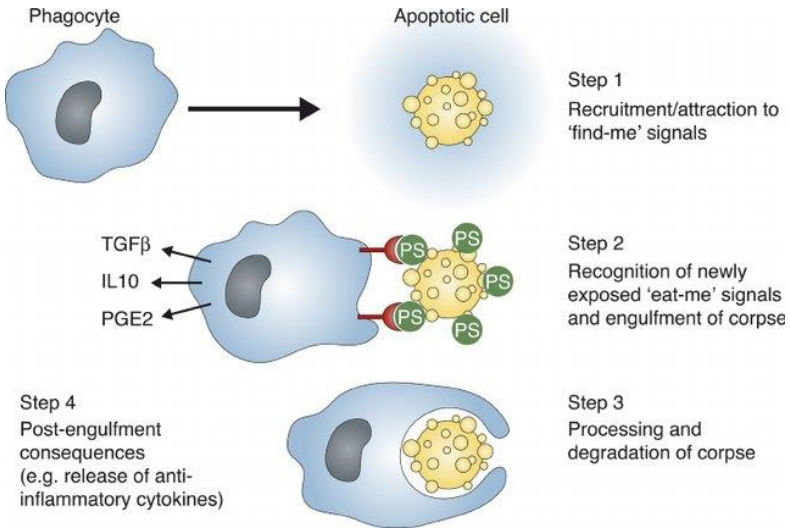


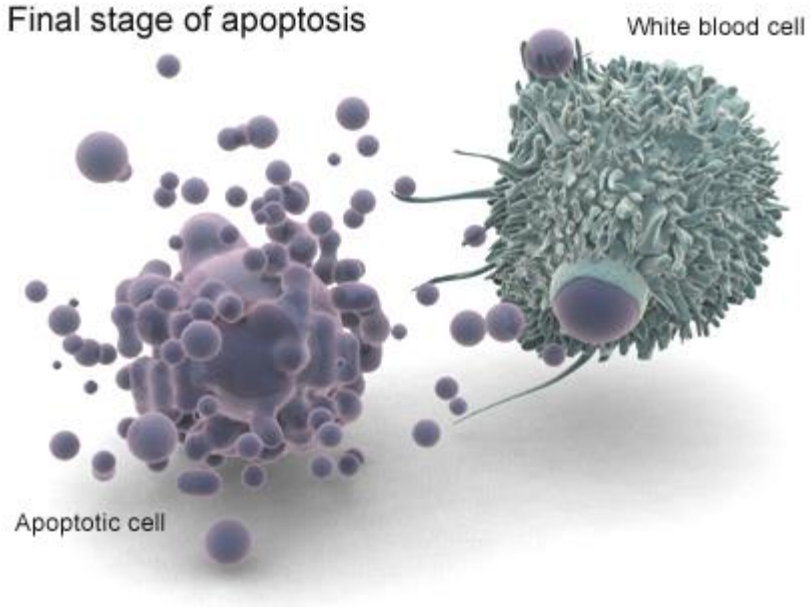
F-actin, DNA

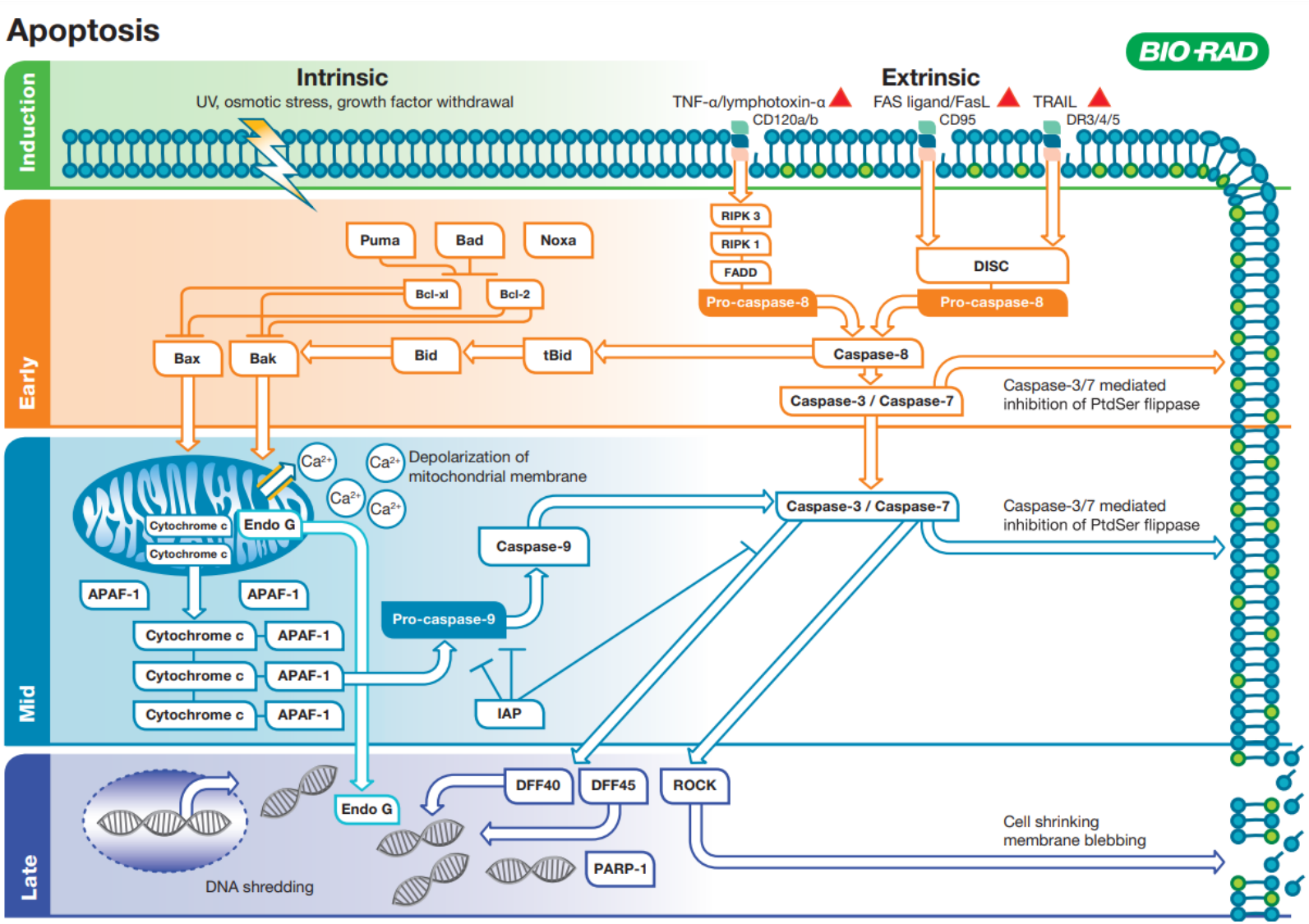
- **Actin/non-muscle myosin II** contraction – blebbing and apoptotic bodies formation
  - Plasma membrane integrity remains intact
  - Apoptotic bodies comprise nuclear fragments, organelles, cytoplasm

Phagocytosis of apoptotic bodies

- Engulfment of apoptotic cells/apoptotic bodies by neighboring phagocytes (macrophages and dendritic cells)
- Phagocytes secretes anti-inflammatory cytokines





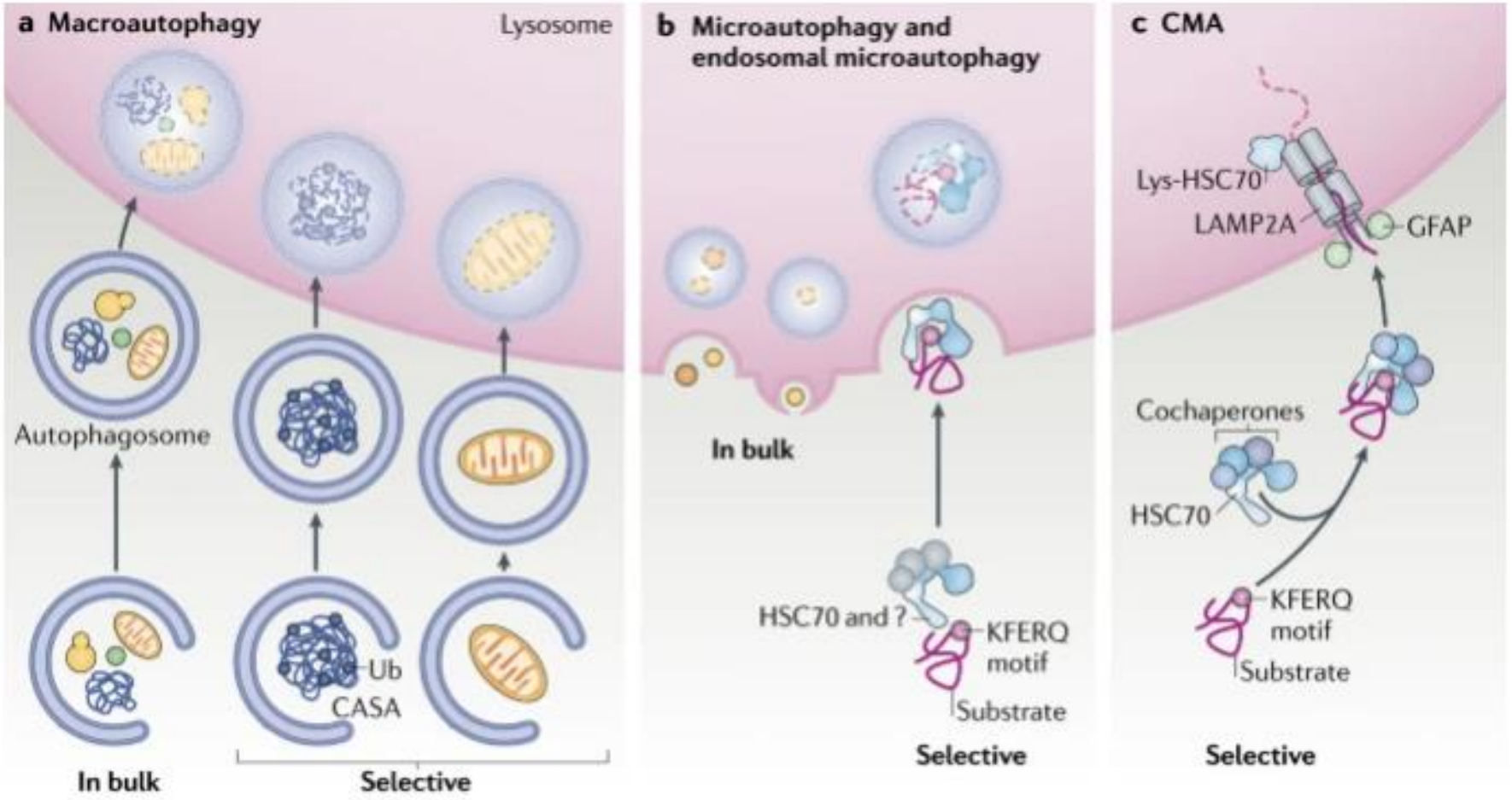

Apoptosis
BIO-RAD
Induction
Intrinsic
UV, osmotic stress, growth factor withdrawal
Extrinsic
TNF-α/lymphotoxin-α
CD120a/b
FAS ligand/FasL
CD95
TRAIL
DR3/4/5
Early
Puma
Bad
Noxa
Bcl-xl
Bcl-2
Bax
Bak
Bid
tBid
RIPK 3
RIPK 1
FADD
Pro-caspase-8
DISC
Pro-caspase-8
Caspase-8
Caspase-3 / Caspase-7
Caspase-3/7 mediated inhibition of PtdSer flippase
Mid
Ca2+
Depolarization of mitochondrial membrane
Cytochrome c
Endo G
Cytochrome c
APAF-1
APAF-1
Caspase-9
Caspase-3 / Caspase-7
Caspase-3/7 mediated inhibition of PtdSer flippase
Pro-caspase-9
Cytochrome c
APAF-1
Cytochrome c
APAF-1
Cytochrome c
APAF-1
IAP
Late
DFF40
DFF45
ROCK
Endo G
Cell shrinking membrane blebbing
PARP-1
DNA shredding

Cell death: Autophagic cell death

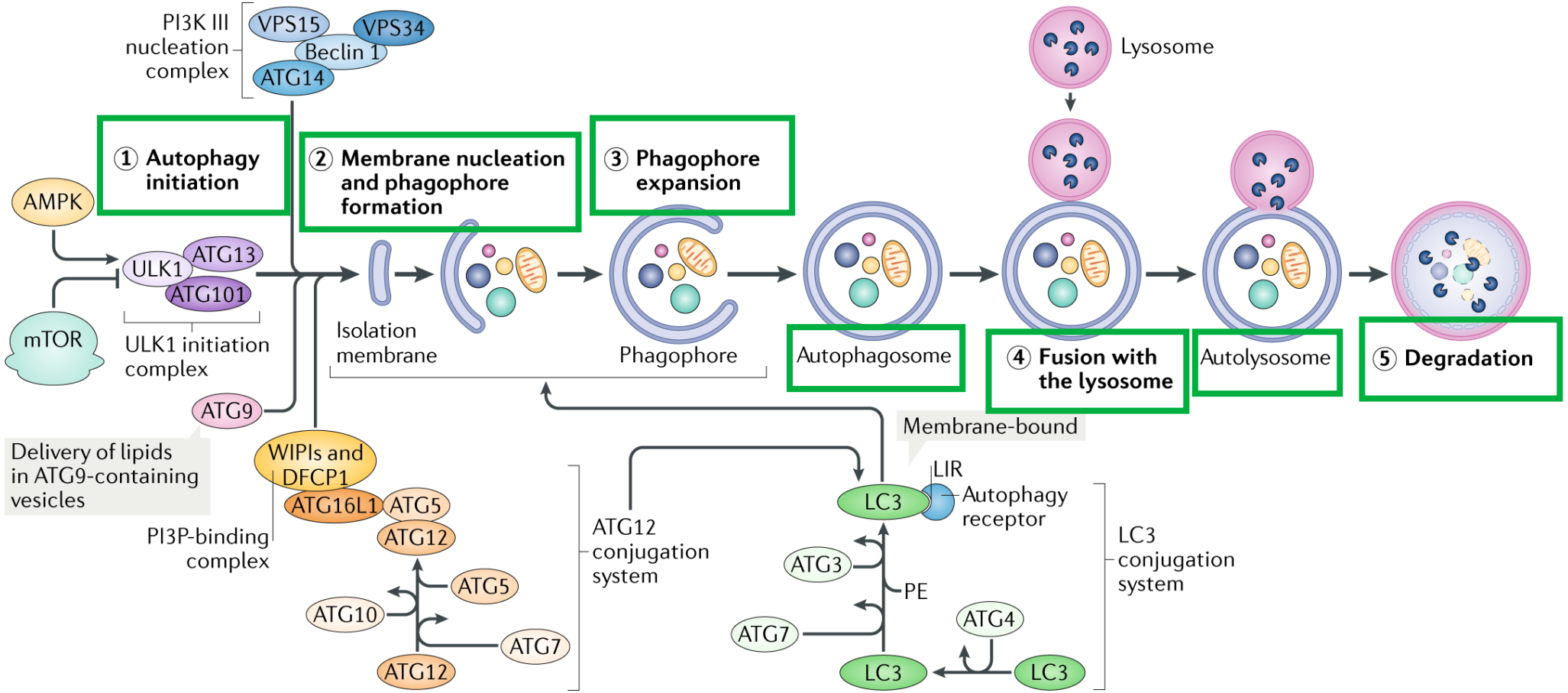
Autophagy

- Regulated process of targeting and delivery of cellular components and organelles into lysosomes for degradation (and recycling)

- **Macroautophagy**
  - best described, autophagosome formation; selective/non-selective
- **Microautophagy**
  - direct invagination of lysosomes; selective/non-selective
- **Chaperone-mediated autophagy**
  - selective

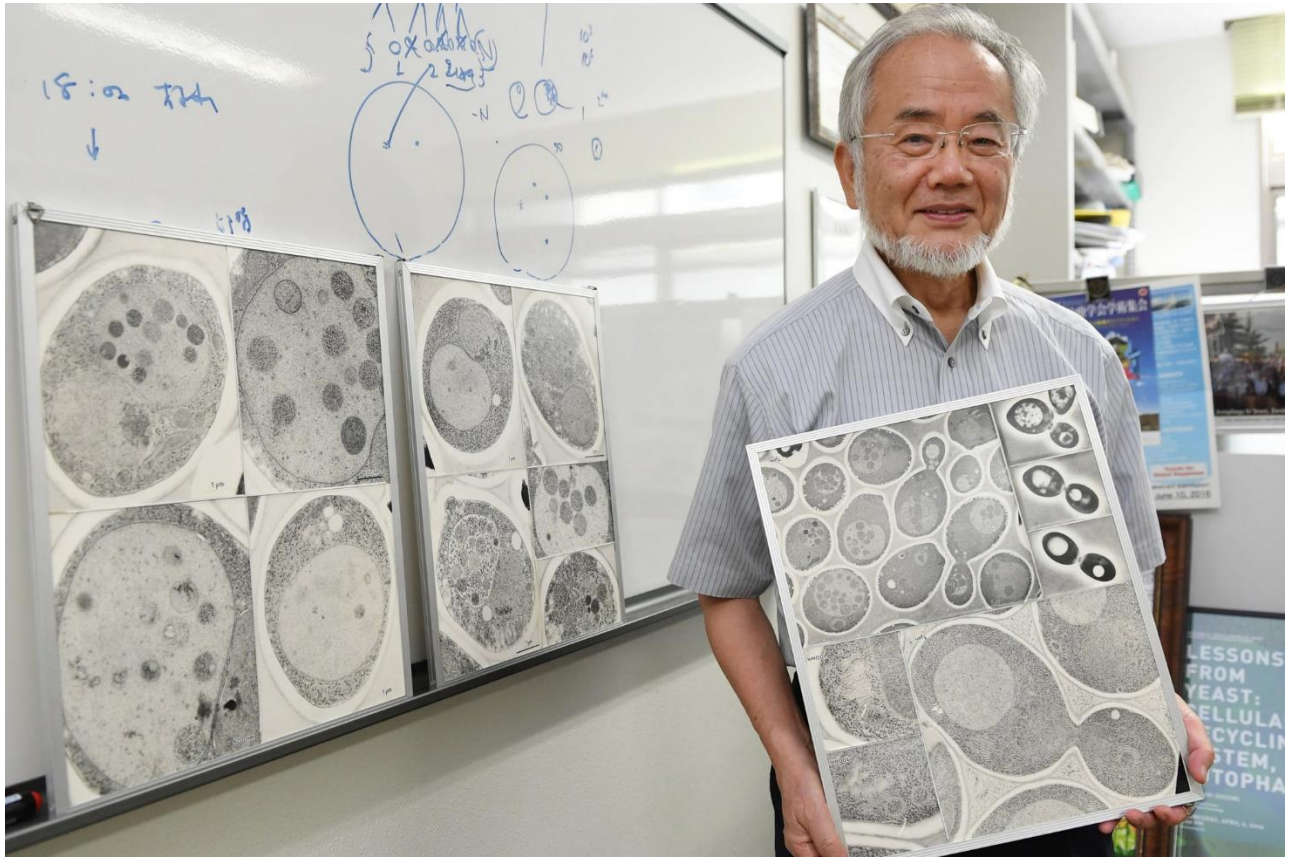

a Macroautophagy
Lysosome
Autophagosome
Ub
CASA
In bulk
Selective
b Microautophagy and endosomal microautophagy
In bulk
HSC70 and ?
KFERQ motif
Substrate
Selective
c CMA
Lys-HSC70
LAMP2A
GFAP
Cochaperones
HSC70
KFERQ motif
Substrate
Selective

Macroautophagy process



2016 Nobel Prize in Physiology or Medicine

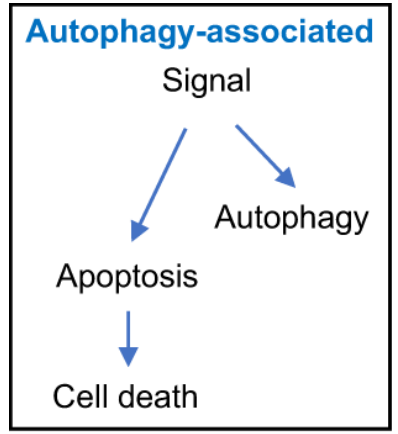
Yoshinori Ohsumi



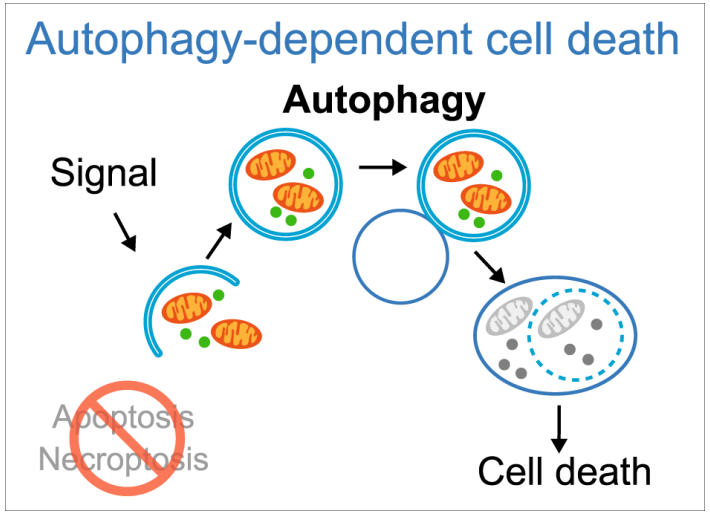
– for his discoveries of mechanisms for autophagy

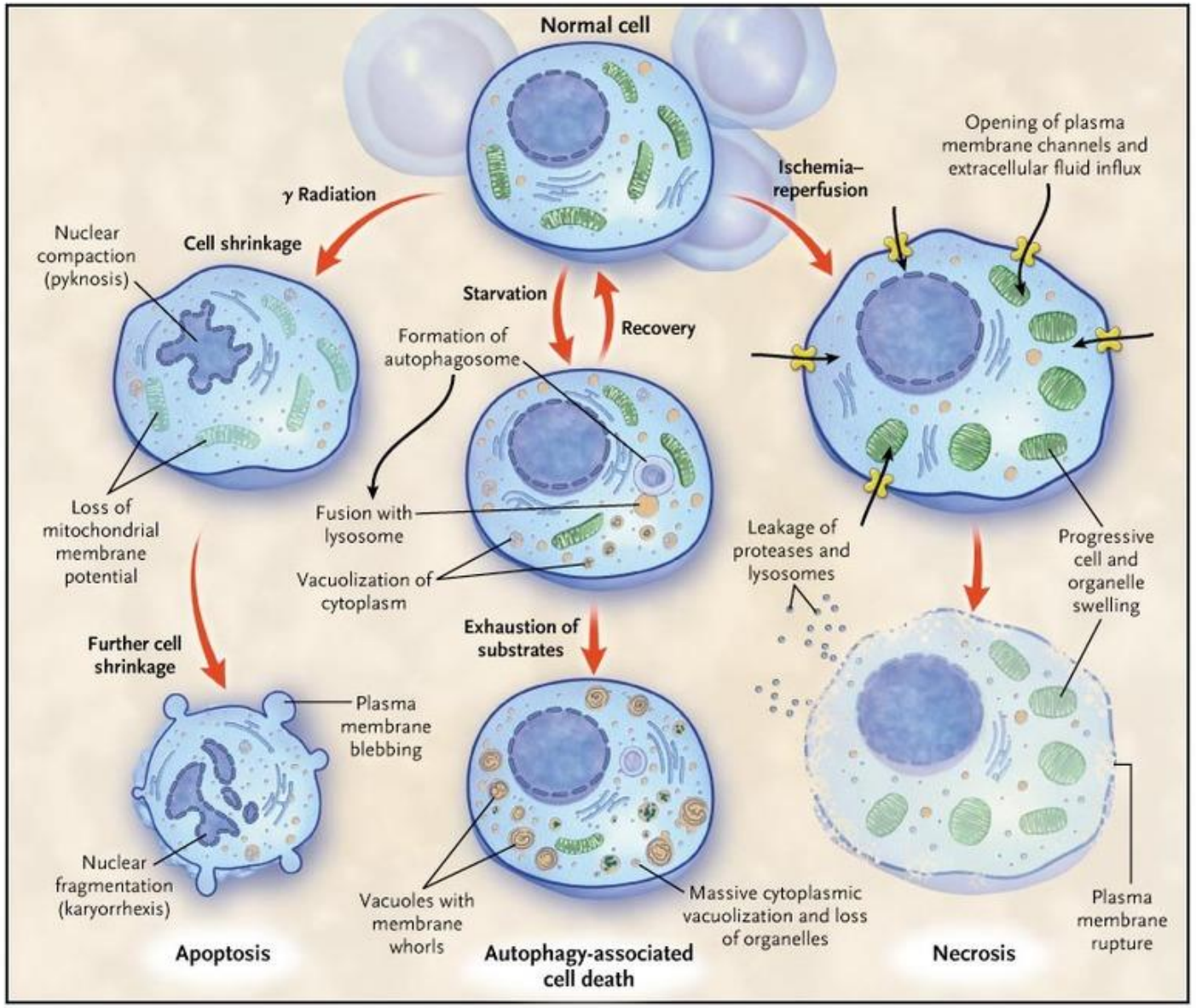
Autophagic cell death

- **Autophagy-associated cell death**
  - Excessive autophagy that accompanies apoptosis



- **Autophagy-dependent cell death**
  - Inhibition of autophagy prevents cell death, apoptosis or necrosis not involved
  - Context dependent: e.g., midgut of Drosophila larvae; hippocampal neural stem cells after insulin withdrawal…




Normal cell
γ Radiation
Ischemia–reperfusion
Opening of plasma membrane channels and extracellular fluid influx
Nuclear compaction (pyknosis)
Cell shrinkage
Starvation
Recovery
Formation of autophagosome
Loss of mitochondrial membrane potential
Fusion with lysosome
Vacuolization of cytoplasm
Leakage of proteases and lysosomes
Progressive cell and organelle swelling
Further cell shrinkage
Exhaustion of substrates
Plasma membrane blebbing
Nuclear fragmentation (karyorrhexis)
Vacuoles with membrane whorls
Massive cytoplasmic vacuolization and loss of organelles
Plasma membrane rupture
Apoptosis
Autophagy-associated cell death
Necrosis

Cell death: Ferroptosis

Ferroptosis

- **Iron-dependent programmed cell death**
- Characterized by large amount of iron accumulation and **iron-catalyzed lipid peroxidation** during the cell death process
- Dysregulation of iron metabolism, glutathione (GSH, antioxidant) depletion…
- Excessive ROS production → rupture of mitochondrial outer membrane


CSI: BODY UNIT
WELL, DETECTIVE?
LOOKS LIKE AN OPEN AND SHUT CASE TO ME, JIM...
CRIME CELL: DO NOT CR
Bye Cruel Body
...APOPTOSIS.