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Cell Death and Disease

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Regulated Cell Death in Disease

Programmed cell death pathways can become pathological and promote chronic inflammation and many other diseases.

Damage-associated molecular patterns, which are associated with various diseases, are host-derived molecules that might be released from dying cells and then function as danger signals, enhancing local inflammation.

Lytic forms of cell death, such as necroptosis, pyroptosis and NETosis, are highly pro-inflammatory owing to the release of cell contents, which can contribute to inflammation.

Even apoptotic cell death, which is typically non-inflammatory, can cause pathology when upregulated or when cell debris is improperly cleared, resulting in the release of inflammatory mediators.

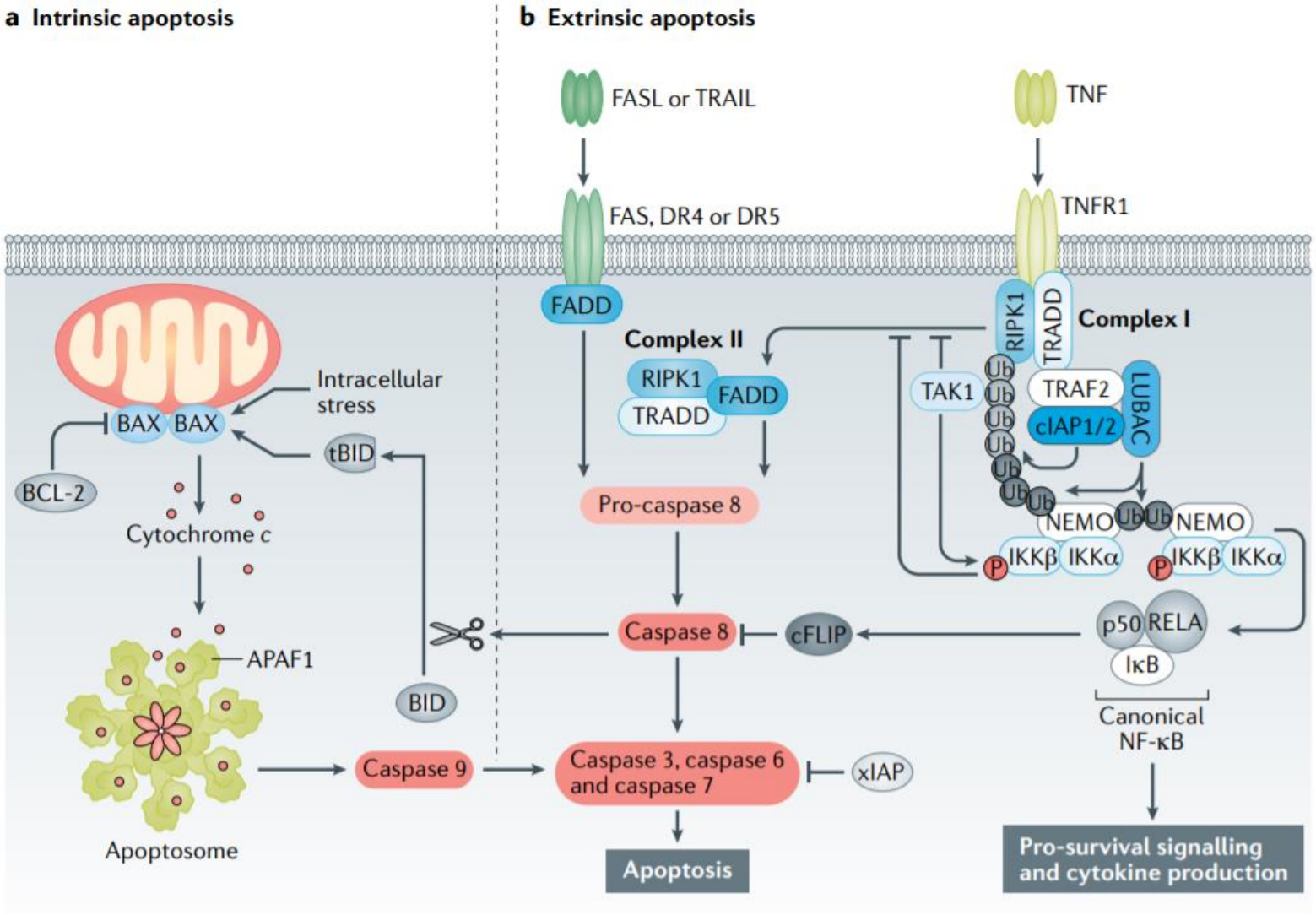
Anderton, H., Wicks, I.P. & Silke, J. Cell death in chronic inflammation: breaking the cycle to treat rheumatic disease. *Nat Rev Rheumatol* **16,** 496–513 (2020).

Apoptosis

Typical apoptotic cell death during development or homeostasis is non-inflammatory, and the cell debris is rapidly cleared. Intrinsic apoptosis pathways that lead to the activation of caspases instigate mechanisms that actively suppress potentially inflammatory responses. For example, the apoptotic caspase cascade functions to prevent type I interferon production during BAX/BAK-dependent apoptosis; furthermore, during apoptosis, genomic DNA is cleaved into small fragments, and HMGB1 remains bound to chromatin, limiting its pro-inflammatory potential.

Ligation of the TNF receptor 1 (TNFR1) receptor can result in either pro-survival signals or pro-apoptotic signals.

These events lead to phosphorylation of RIPK1 (via the IKKs and TAK1), preventing the formation of RIPK-dependent death complexes, and activation of canonical NF-κB signalling, which promotes the transcription of pro-inflammatory cytokine genes as well as genes encoding anti-apoptotic factors such as cellular FLICE-like inhibitory protein (cFLIP).



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Apoptosis in Chronic Inflammation

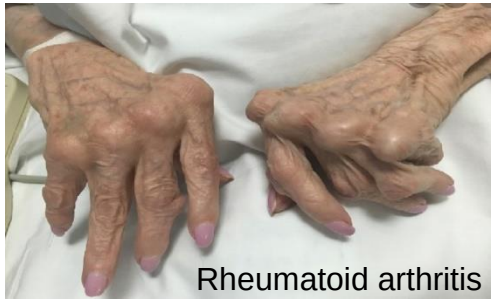
Apoptosis of neutrophils is another critical step in the resolution of acute inflammation. Defects in apoptosis and a failure to clear inflammatory neutrophils can prolong inflammatory responses (e.g. Rheumatoid arthritis).

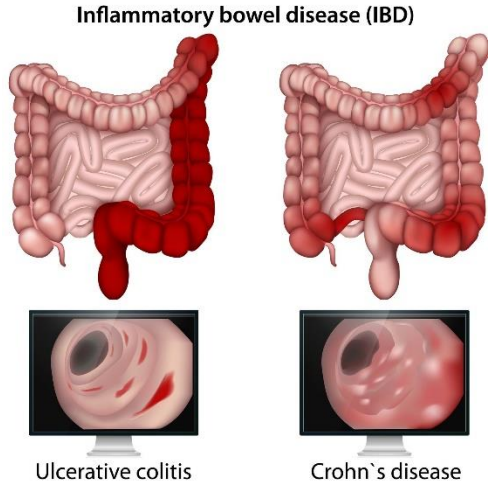
Apoptosis is key to developing immunological tolerance, as negative selection in the thymus and bone marrow removes self-reactive T cells and B cells by apoptosis.

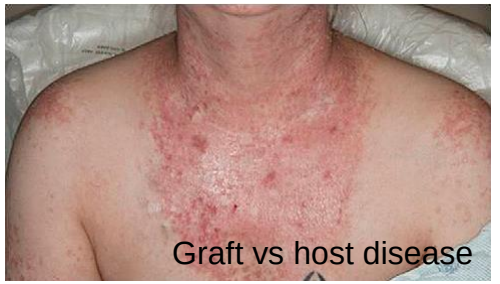
Too much apoptosis causes inflammatory disease.

If a large number of apoptotic cells cannot be cleared rapidly by efferocytosis, cells undergoing apoptosis can progress to secondary necrosis, with concomitant membrane permeabilization and release of pro-inflammatory cell contents. Excessive cell death can also result in tissue atrophy or a loss of barrier function, which might contribute to inflammation

The skin and gut are exposed continuously to commensals and pathogens, making them more vulnerable to inflammatory consequences. Loss of barrier function in epithelial surfaces can result in prolonged exposure to PAMPs and a more intense inflammatory milieu. Increased cell death, both apoptotic and necrotic, has been associated with chronic inflammation in inflammatory bowel disease (IBD) and is particularly prominent in paediatric patients.
Apoptotic bodies, suggestive of excessive apoptosis, have also been found in colonic biopsy samples from patients with ulcerative colitis. Furthermore, skin diseases such as lichen planus, eczema, acute and chronic graft versus host disease, bullous pemphigoid and chronic diabetic skin ulcers feature excessive apoptosis.


Rheumatoid arthritis




Graft vs host disease

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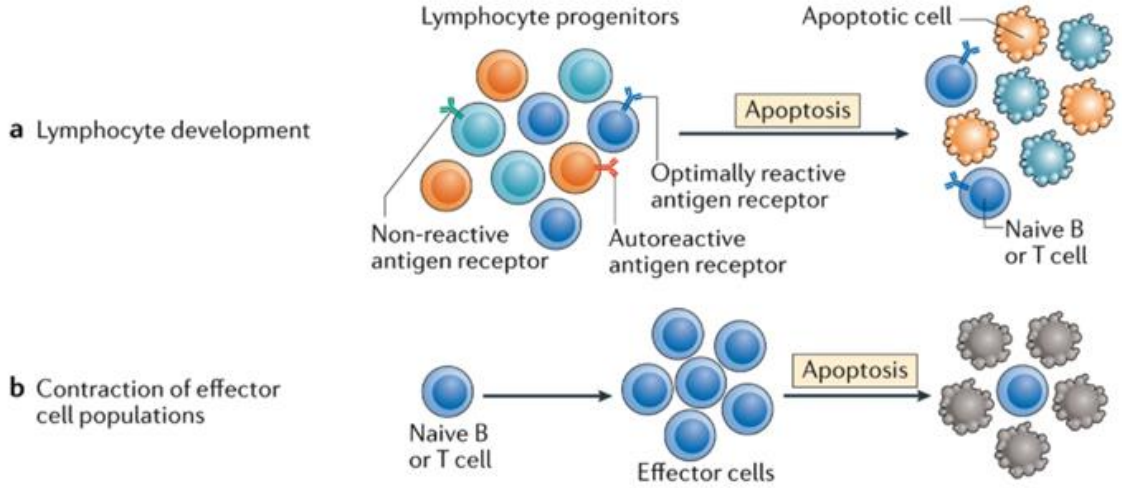
Apoptosis in Chronic Inflammation

Too much or too little apoptosis causes inflammatory disease.

In SLE (systemic lupus erythematosus), FAS polymorphisms that lead to defective apoptosis are thought to contribute to the persistence of autoreactive T cells and B cells that generate autoantibodies. Interestingly, an alternative SLE associated FAS mutation is associated with the increased apoptosis of activated lymphocytes.

The fact that both decreased and increased apoptosis can cause essentially the same disease highlights how context-specific dysregulated apoptosis can be.

Apoptosis and necroptosis are intimately linked. Necroptosis is triggered by many of the same stimuli as apoptosis and seems to function as a backup, or ‘emergency’ type of cell death when apoptosis is inhibited by pathogens.



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Acute versus Chronic Inflammation

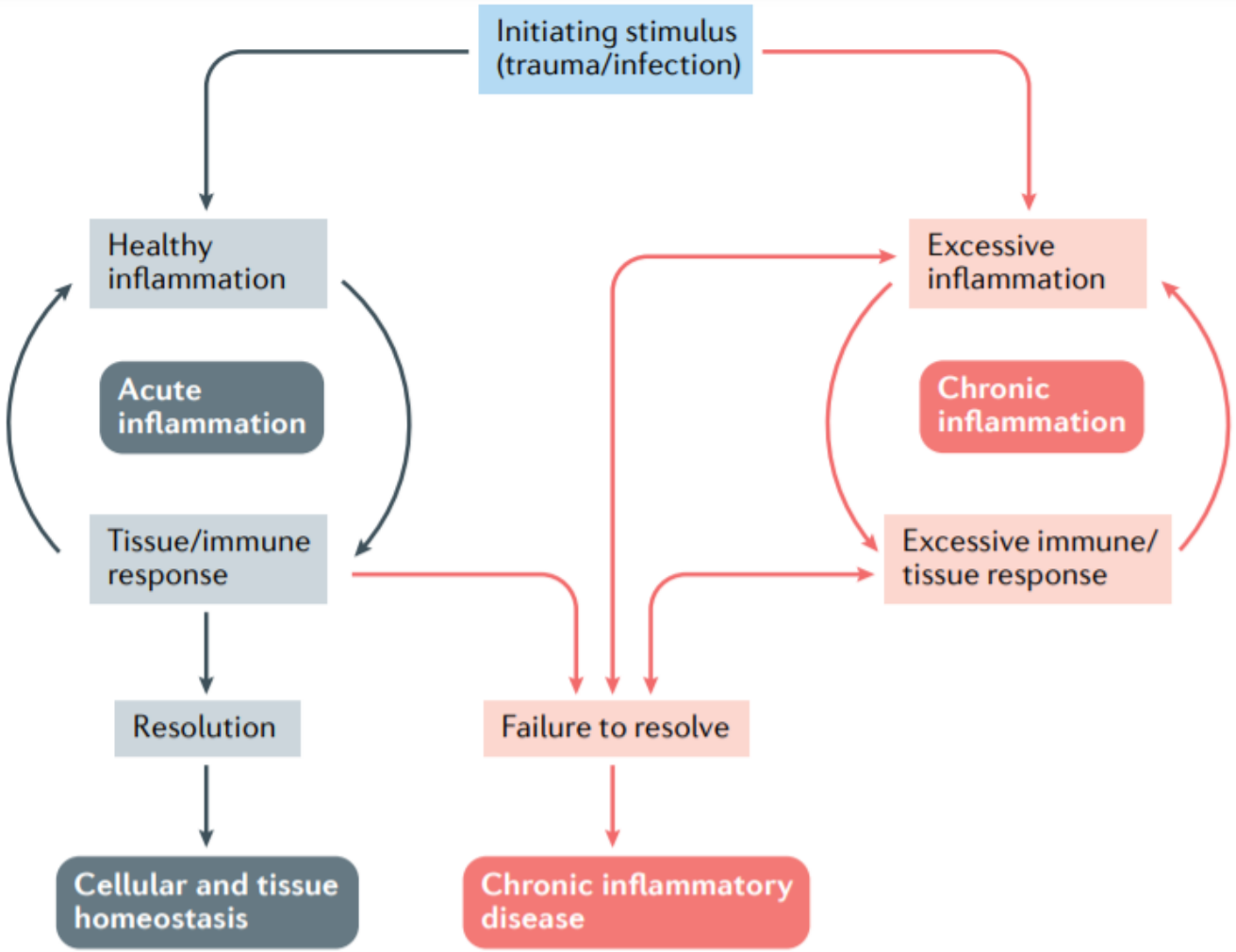
Acute inflammation is a healthy response to a danger signal, such as trauma, stress or infection.

Individual cells respond to such insults by initiating acute inflammation, but amplification loops derived from the surrounding cells are probably required to generate tissue and immune responses.

Once an insult is dealt with, the resolution of inflammation is vital to restore cellular and tissue homeostasis.

Failure to deal with an insult or resolve acute inflammation results in amplification loops that generate damage-associated molecular patterns (DAMPs).

Persistent amplification loops can generate a vicious cycle of inflammation, leading to disease.



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Regulated Cell Death and Inflammation

Acute inflammation is a defensive response, usually initiated through the detection of an extracellular stimulus by local immunoreactive cells, and mediated by cytokines, chemokines and other second messengers. The initiating signals can include damage-associated molecular patterns (DAMPs) or pathogen-associated molecular patterns (PAMPs), which activate cellular receptors on, or within, individual cells within exposed tissues (e.g. macrophages). Such stimuli include endogenously derived crystals, such as cholesterol or urate, and exogenous particulates, such as silica crystals. In response, signalling molecules induce and regulate varying degrees of local and systemic inflammation, chemotaxis, cell proliferation and tissue repair.

Cytokines often form amplification loops that increase the production of inflammatory mediators, including themselves, orchestrating local tissue and systemic immune responses. Cytokines, such as TNF or other so-called ‘death ligands’ of the TNF superfamily, can also induce cell death programmes via death receptors that in turn generate more DAMPs. Certain DAMPs, such as high mobility group protein B1 (HMGB1) and ATP, serve important functions in tissue regeneration following acute inflammation; these DAMPs can recruit stem cells and immune cells to the site of inflammation, promote proliferation and differentiation of tissue-resident stem cells and stimulate angiogenesis.

Once danger or damage has been dealt with, resolution of acute inflammation is essential for restoring homeostasis. Failure to resolve the inflammatory response can lead to chronic inflammation. The amplification loops that are necessary to ensure a sufficient acute inflammatory response can instead promote excessive inflammation and persistent immune responses, resulting in ongoing tissue damage and eventually, chronic inflammatory diseases.

Chronic inflammation is an important feature of a wide range of diseases that affect barrier surfaces, including inflammatory diseases of the gut (such as Crohn’s disease and colitis) and of the skin (such as eczema and psoriasis). Common rheumatic conditions such as, rheumatoid arthritis (RA), psoriatic arthritis (PsA), osteoarthritis (OA), ankylosing spondylitis (AS) and chronic tophaceous gout are also associated with varying degrees of chronic inflammation. However, compared with inflammatory diseases of the gut and skin, the aetiology of other chronic inflammatory diseases associated with sterile inflammation is less clear.

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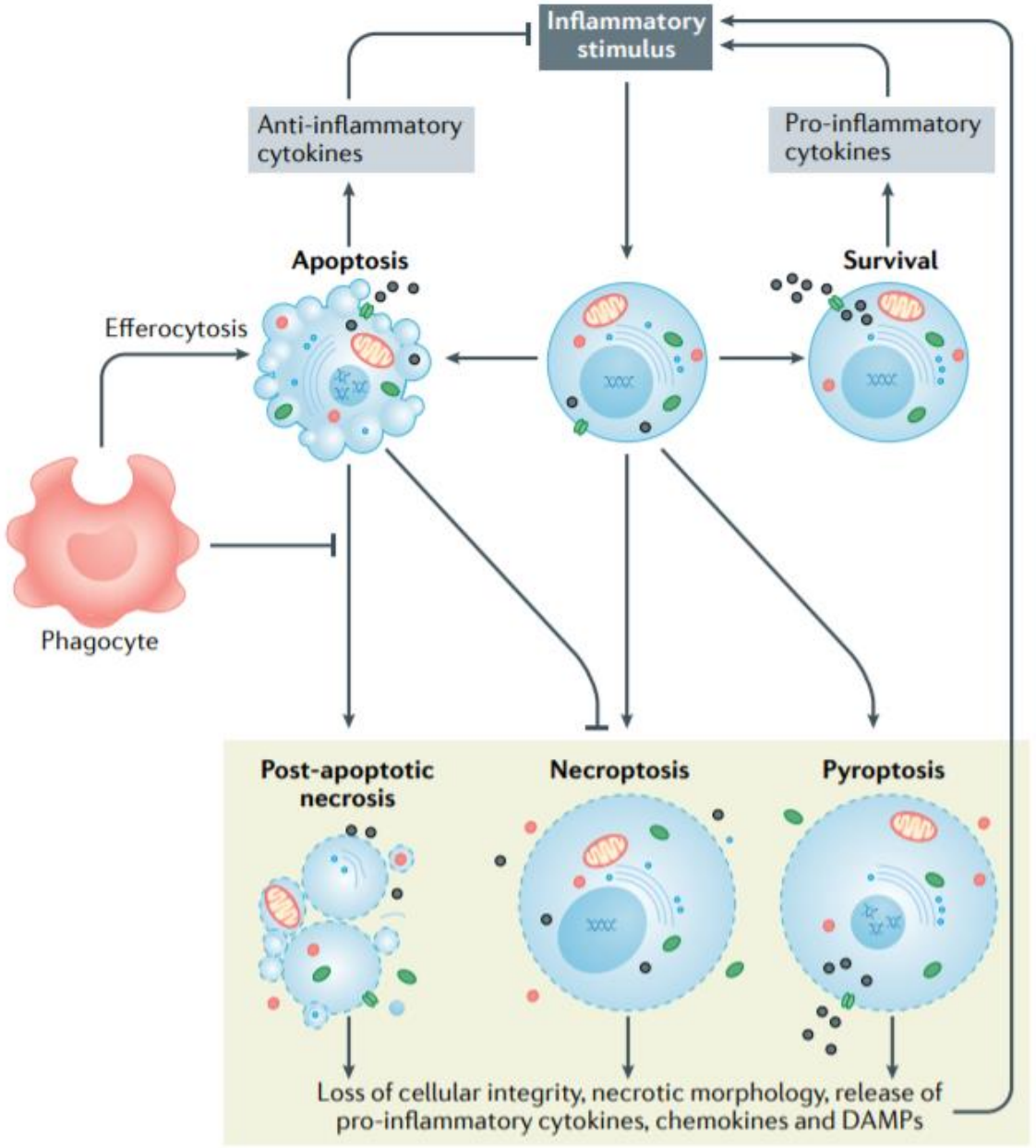
Cell Death and Inflammation

Cell death is both a cause and a consequence of inflammation.
A cell exposed to an inflammatory stimulus has several potential fates:
survival, production of inflammatory cytokines and possibly proliferation;
non-inflammatory or even anti-inflammatory apoptotic cell death; or
pro-inflammatory programmed cell death such as necroptosis and pyroptosis.

Phagocytes clear non-inflammatory apoptotic cells by efferocytosis, preventing progression to late apoptosis and post-apoptotic necrosis.
Functional apoptotic machinery can inhibit necroptosis.

Post-apoptotic necrosis, necroptosis and pyroptosis lead to the uncontrolled release of damage-associated molecular patterns (DAMPs) and inflammatory cytokines into the extracellular environment. DAMPs and cytokines can then function as pro-inflammatory stimuli, perpetuating a cycle of inflammation and cell death.



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Cell Death and Inflammation

Lytic forms of programmed cell death, including necroptosis, pyroptosis and NETosis, are thought to promote inflammation by releasing damage-associated molecular patterns(DAMPs), and other inflammatory mediators, into the extracellular environment.

Apoptosis counters the effects of DAMPs by ensuring the rapid removal of a dying cell and its contents before the contents are released.

Billions of cells undergo apoptotic cell death daily without provoking an inflammatory response. It might be that apoptosis and lytic forms of cell death have evolved to provide opposing effects on inflammation.

The availability of inhibitory drugs that target the pro-inflammatory cytokines involved in inflammation amplification loops has transformed the treatment of many inflammatory diseases. The success of TNF antagonists such as etanercept, infliximab and adalimumab has confirmed the importance of TNF in the pathology of many chronic inflammatory diseases, including RA, PsA, AS, psoriasis and inflammatory bowel disease. TNF can amplify the initial inflammatory response by transcriptionally upregulating the production of additional cytokines and chemokines. Thus, the presumption has been that TNF inhibitors function by dampening these amplification loops.

Key features	Intrinsic apoptosis	Extrinsic apoptosis	Necroptosis	Pyroptosis	NETosis
Initiators	Biochemical stress and DNA damage	The binding of death receptor ligands (FASL, TNF, TRAIL) to their receptors (FAS, TNFR1 and TRAIL receptors, respectively)	The binding of TNF to TNFR1 (or sometimes ligation of TLR3 or TLR4), plus inhibition of caspase activity	The binding of PAMPs or DAMPs to PRRs	ROS production, which might be triggered by binding of PAMPs or DAMPs to PRRs
Mediators and regulators	Mediators: BAX/BAK, BH3-only proteins, APAF1 and caspase 9	Mediators: RIPK1, Caspase 8, BH3 and BID	Mediators: RIPK1 and RIPK3	Mediators: the inflammasome (including the sensor molecules NLRP3, NLRP1, NLRC4, AIM2 and pyrin, as well as ASC), caspase 1, caspase 4 and caspase 5	Mediators: neutrophil elastase and MPO
	Negative regulators: pro-survival members of the BCL-2 family (such as MCL1 and BCL-X_L)	Negative regulators: cIAPs, xIAP, LUBAC, TAK1 and cFLIP	Negative regulator: caspase 8		
Executors	BAX/BAK	Caspase 3, caspase 6 and caspase 7	MLKL	Caspase 1, caspase 4, caspase 5 (or caspase 11 in mice) and gasdermin D	Gasdermin D
Morphology	Cytoplasmic shrinkage, condensation and margination of nuclear chromatin, DNA fragmentation, membrane blebbing and formation of apoptotic bodies		Cytoplasmic swelling, swelling of organelles, perforation of plasma membrane, osmotic lysis and release of cellular contents	Cytoplasmic swelling, nuclear condensation, pore formation in the cell membrane, release of pro-inflammatory cytokines, osmotic lysis and release of cellular contents	Disruption of intracellular membranes and extrusion of a histone-containing and chromatin-containing proteinaceous mesh (NETs)
Inflammatory response	Can be anti-inflammatory or pro-inflammatory (context dependent)		Pro-inflammatory	Pro-inflammatory	Pro-inflammatory
Featured DAMPs	Minimal DAMPs are released in early apoptosis owing to efferocytosis; however, failure to engulf early apoptotic cells leads to post-apoptotic necrosis, associated with the release of IL-1α, uric acid, EMAP II, low molecular weight nucleotides and HMGB1–nucleosome complexes[72]		Long genomic DNA, HMGB1, histones, intact or damaged mitochondria (and potentially mtDNA), full length IL-33, IL-1α, ATP and S100A9 (REFS[111,160])	IL-1β, IL-18, IL-1α, HMGB1, cytochrome *c*, mtDNA and ASC specks[160]	Chromatin, histones and mtDNA[72,184]
Disease associations	Defective apoptosis of immune cells is associated with autoimmune disease including RA[85,86] and SLE[3]		Necroptosis contributes to various inflammatory phenotypes in mouse models[81,82,128,132–134] including MSU-induced arthritis[135,136]	Gain-of-function mutations in *NLRP3* (REFS[167,168]) or *MEFV*[168] are implicated in CAPS and FMF, respectively; mouse models support a function for pyroptosis in these diseases[170,171]	NET formation has been associated with lupus nephritis, vasculitis, SLE, RA, psoriasis and gout[184]
	Excessive apoptosis owing to defective NF-κB signalling is associated with inflammatory phenotypes in mice[76–88]		Necroptosis might contribute to systemic inflammation in individuals with *RIPK1* mutations[138,140]	PAPA[168] and hidradenitis suppurativa[174,175] are associated with increased inflammasome activity and potentially pyroptosis	
	Excessive apoptosis can also occur in various human diseases, including lichen planus[93], eczema[93], acute and chronic GVHD[92], bullous pemphigoid[93] and IBD[93–95]; aberrant apoptotic death of chondrocytes also occurs in OA[95,96]		Pyroptosis is possibly implicated in the pathogenesis of Alzheimer disease[210–215] and atherosclerosis[164,177]	Necroptosis might contribute to systemic inflammation in individuals with *RIPK1* mutations[138,140]	
Therapeutic targets for inflammatory disease	Death receptor ligands (TNF, FASL and TRAIL), RIPK1 and caspases		RIPK1, RIPK3 and MLKL	IL-1β, IL-18, caspase 1 and gasdermin D	Gasdermin D

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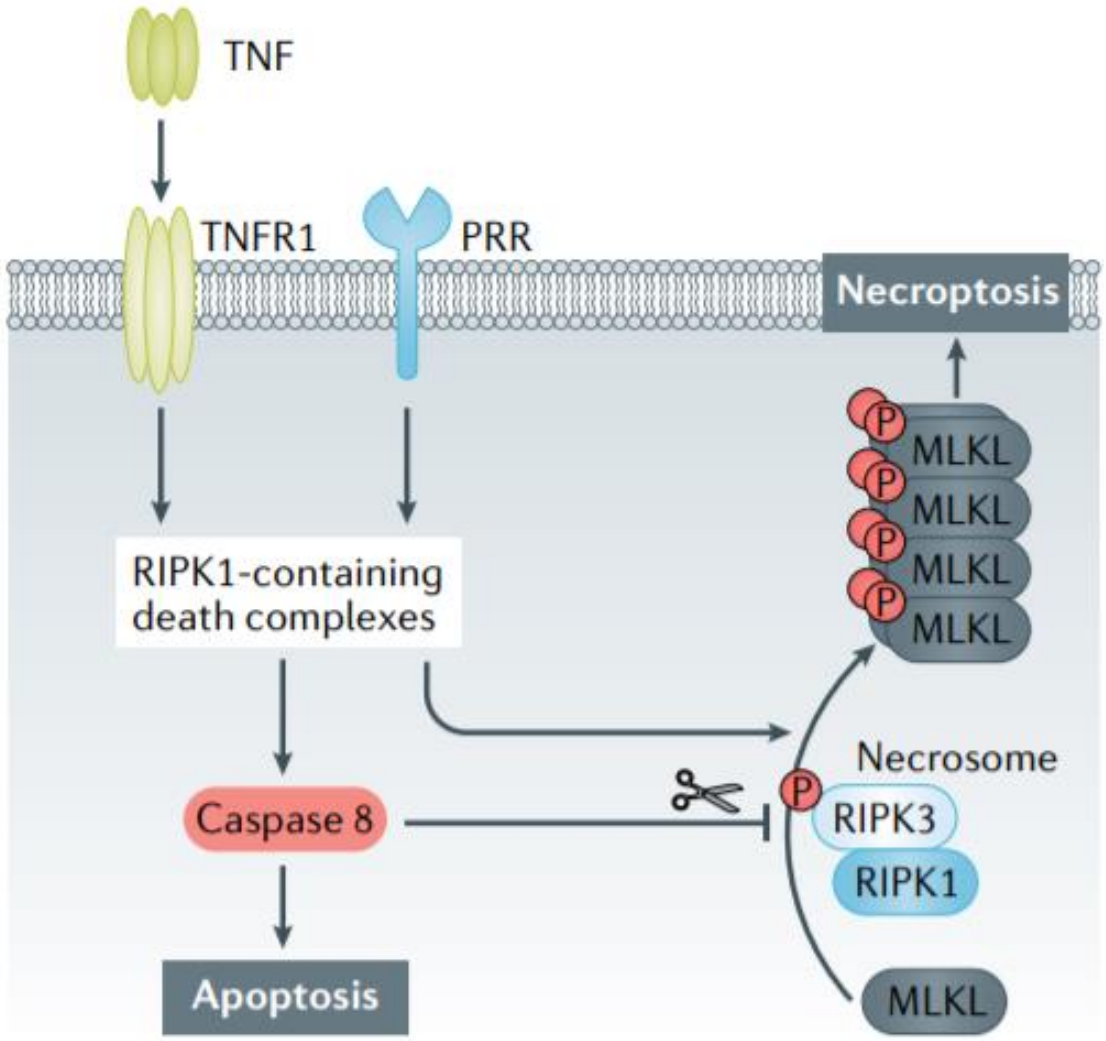
Necroptosis

Necroptosis is mediated by the necrosome, a complex consisting of receptor interacting serine/threonine-protein kinase 1 (RIPK1), RIPK3 and mixed lineage kinase domain-like protein (MLKL).

During extrinsic apoptotic signalling, following ligation of TNF receptor 1 (TNFR1) or pattern recognition receptors (PRRs), activated caspase 8 cleaves RIPK1 and possibly RIPK3, preventing the formation of the necrosome.

Complete inhibition of caspase 8 (e.g. HNSCC), for example by the long isoform of cellular FLICE-like inhibitory protein, enables the formation of the necrosome and subsequent phosphorylation and activation of MLKL.

Activated MLKL oligomerizes and translocates to the cell membrane, generating pores that result in the release of cell contents, cellular swelling and rupture, and necroptotic death.



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Necroptosis and disease

homozygous loss-of-function mutations in RIPK1 have been described in patients with a range of inflammatory disease phenotypes, including arthritis, lymphopenia and early-onset IBD. Freshly derived monocytes from these patients were more sensitive to TNF-induced necroptosis, but, in contrast to RIPK1-deficient mice, intestinal inflammation was not associated with increased apoptosis in those patients with early-onset.

These data suggest that genetic deficiency of RIPK1 can sensitize cells to necroptosis; however, given the pleiotropic role that RIPK1 has in the immune system, whether cell death has a primary role in other human inflammatory diseases is not yet clear.

Activation of the RIPK3–MLKL axis has been particularly observed in neutrophilic diseases, such as cutaneous vasculitis, ulcerative colitis and psoriasis; although the extent to which necroptotic cell death is a cause, consequence or an exacerbating factor in these diseases is unknown.

An emerging theme suggests that key mechanisms of neurodegeneration involve the interaction of cell-autonomous mechanisms mediated by RIPK1 in CNS glial cells to promote the degeneration of axons and neurons in cell-non-autonomous manners. This deleterious environment is established by activated microglia and astrocytes, as well as infiltrating immune cells such as T cells and macrophages, through their ability to release disease-associated inflammatory mediators and promote the vicious cycles of neuroinflammation and neurodegeneration. In this environment, RIPK1 not only may act as a key effector of inflammatory cell death but also may mediate deleterious inflammatory signalling to provide a feedforward mechanism to accelerate neurodegeneration.

Yuan, J., Amin, P. & Ofengeim, D. Necroptosis and RIPK1-mediated neuroinflammation in CNS diseases. *Nat Rev Neurosci* **20,** 19–33 (2019). https://doi.org/10.1038/s41583-018-0093-1

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Necroptosis and disease

The necroptotic signalling pathway has been implicated in several pathologies based on disease models, which include retinal degeneration, brain impact trauma, cerulein-induced pancreatitis, ethanol-induced liver injury, septic shock, multiple sclerosis, Huntington disease and tumour progression.

Virus-induced necroptosis can be beneficial to host cells by limiting the lifespan of the cells in which the virus replicates or by inducing necroptosis-mediated inflammatory responses.
Virus-mediated regulation of necroptosis can be detrimental to the host under some circumstances: for example, when viruses induce necroptosis in immune cells that are required for infection control, such as $CD4^+$ T cells during HIV infection. HIV-infected T cells have increased necroptosis rates, which were correlated with a higher sensitivity to TNF-induced cell death and decreased membrane-associated caspase 8 activity.

Bacterial infection.
Enteropathogenic *Escherichia coli* (EPEC) express the pathogenicity effector protein NleB1, which blocks apoptosis and necroptosis. NleB1-deficient EPEC was unable to effectively colonize the host, which indicated that bacterium-induced cell death protected the host organism. In agreement with bacterium-induced cell death being beneficial, RIPK3 deficiency, especially when combined with FADD or caspase 8 deficiency, results in a much higher susceptibility to *Yersinia* infection.

By contrast, *Staphylococcus aureus* toxins induce RIPK3-mediated necroptosis in lung epithelium, which is detrimental to the host. Other bacteria such as *Salmonella enterica* subsp. *enterica* serovar Typhimurium, *Clostridium perfringens* and *Mycobacterium tuberculosis* have been shown to induce necroptosis *in vitro* (potentially, any organism that expresses TLR3 and TLR4 ligands can induce necroptosis), but the actual role of necroptosis during *in vivo* infection by these bacteria is yet to be defined.

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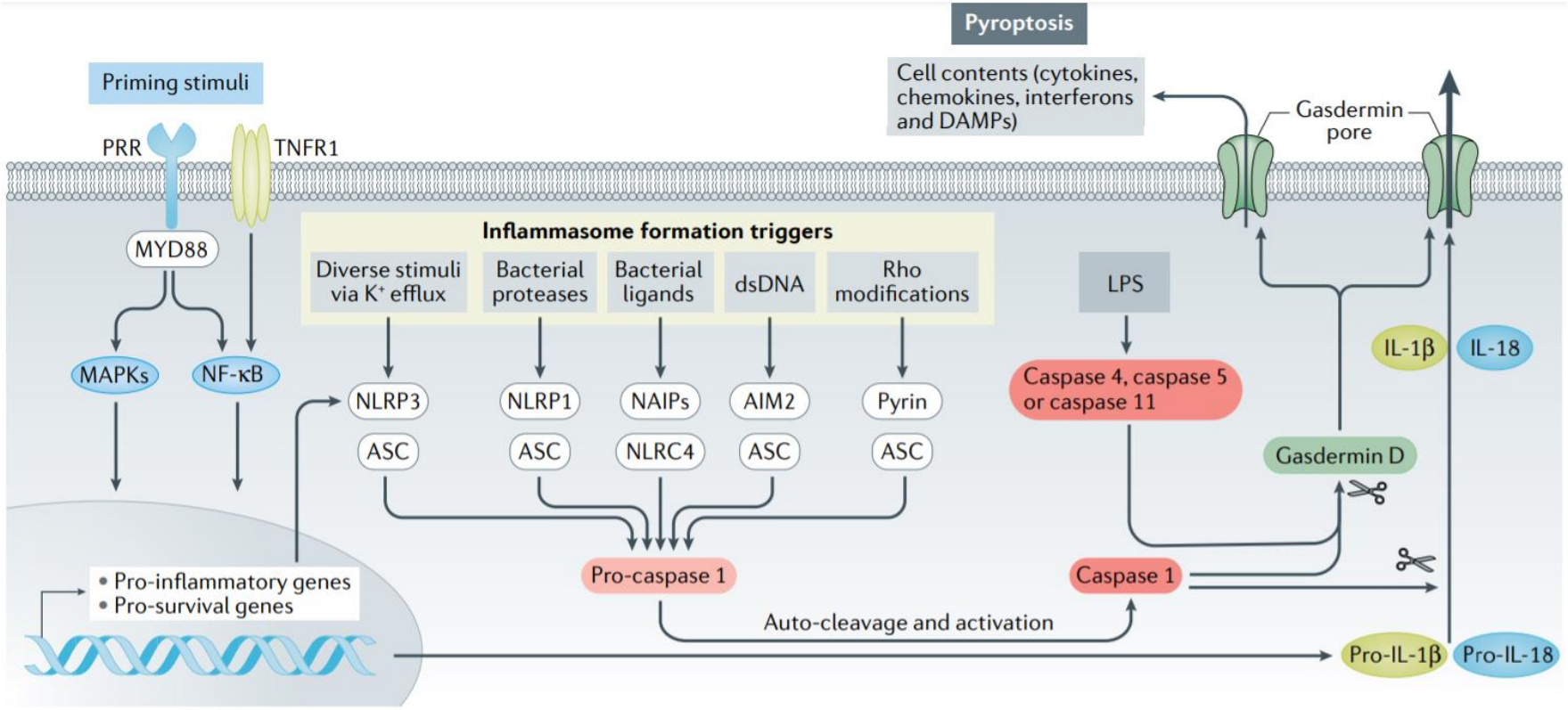
Pyroptosis

Pyroptosis is inflammatory form of cell death, characterized by formation of pores in the cell membrane, the liberation of pro-inflammatory cytokines such as IL-1β and IL-18, DNA fragmentation and chromatin condensation. Cellular swelling is followed by loss of membrane integrity and the release of cellular contents (including any intracellular pathogens).

The physiological function of pyroptosis is thought to be prevention of intracellular pathogen replication, control of such pathogens through IL-1β-mediated and IL-18-mediated inflammatory signalling and the exposure of those pathogens to extracellular killing mechanisms.

However, pyroptosis can also be activated in response to DAMPs, and sterile, DAMP-triggered inflammation is a potential contributor to inflammatory diseases.



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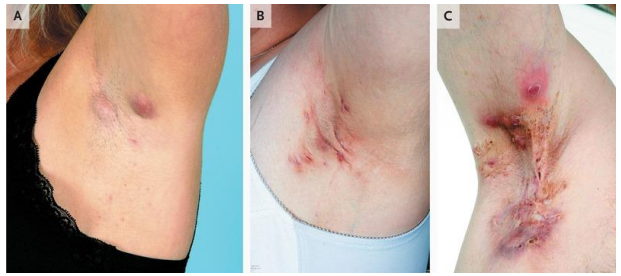
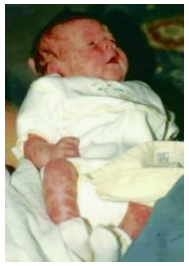
Pyroptosis and Inflammatory Disease

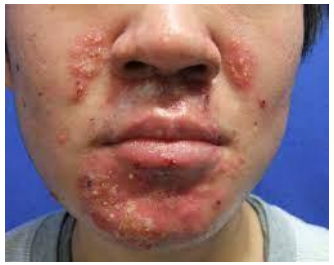
Although pyroptosis is one physiological response to infection, as are apoptosis and necroptosis, inappropriate overactivation of this pathway can lead to inflammatory disease. Furthermore, **DAMPs can trigger formation of the inflammasome and pyroptotic cell death in the absence of infection.**
These characteristics are demonstrated in periodic fever syndromes, such as familial cold autoinflammatory syndrome, Muckle–Wells syndrome and chronic infantile neurological cutaneous and articular syndrome, also known as neonatal-onset multisystem inflammatory disease (NOMID).
These inherited autoinflammatory diseases present with diverse symptoms, including periodic fever, urticaria, joint pain and swelling, headaches and conjunctivitis. They are collectively referred to as the cryopyrin-associated periodic syndromes (CAPS) and are associated with gain-of-function mutations in NLRP3.

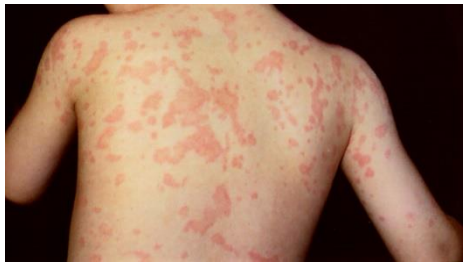
For some inflammatory diseases, inflammasome activation has been implicated, but pyroptosis has not been directly demonstrated (Gout is caused by MSU crystal deposition in and around joints, leading to acute inflammation and intense neutrophilic infiltration).
Other examples of diseases associated with inflammasome activation and the release of IL-1β and IL-18 include pyogenic arthritis, pyoderma gangrenosum and acne (PAPA) syndrome and hidradenitis suppurativa.

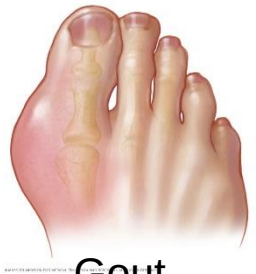


Hidradenitis suppurativa


NOMID


Pyogenic arthritis


Muckle–Wells syndrome


Gout

Jemec, G.B.E., *Hidradenitis Suppurativa.* New England Journal of Medicine, 2012. **366**(2): p. 158-164.
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Pyroptosis and Disease

Cancer

Pyroptosis can not only inhibit tumor cell proliferation, but also form a microenvironment suitable for tumor cell growth and promote tumor growth.

Chronic tumor necrosis caused by pyroptotic cell death of a small number of tumor cells in the central hypoxic area of the tumor inhibits antitumor immunity and accelerates tumor development.

The acute inflammation induced by pyroptosis in the tumor microenvironment enhances the immune response and suppresses the progression of the tumor.

Pyroptosis is also involved in the negative effects of radiotherapy. The AIM2 inflammasome played an unexpected role in responding to radiation-induced DNA damage and induced caspase-1-mediated pyroptosis in intestinal epithelial cells and bone marrow cells, which is one of the causes of radiation-induced gastrointestinal and hematological toxicity.

Cardiovascular disease

NLRP3 and caspase-1 are the most widely involved in cardiovascular diseases. By affecting angiogenesis, myocardial hypertrophy, destabilizing plaques on the arterial wall, myocardial fibrosis, endothelial injury and other pathological processes, they play an important role in myocardial infarction/reperfusion, arrhythmia, Kawasaki disease and other cardiac diseases.

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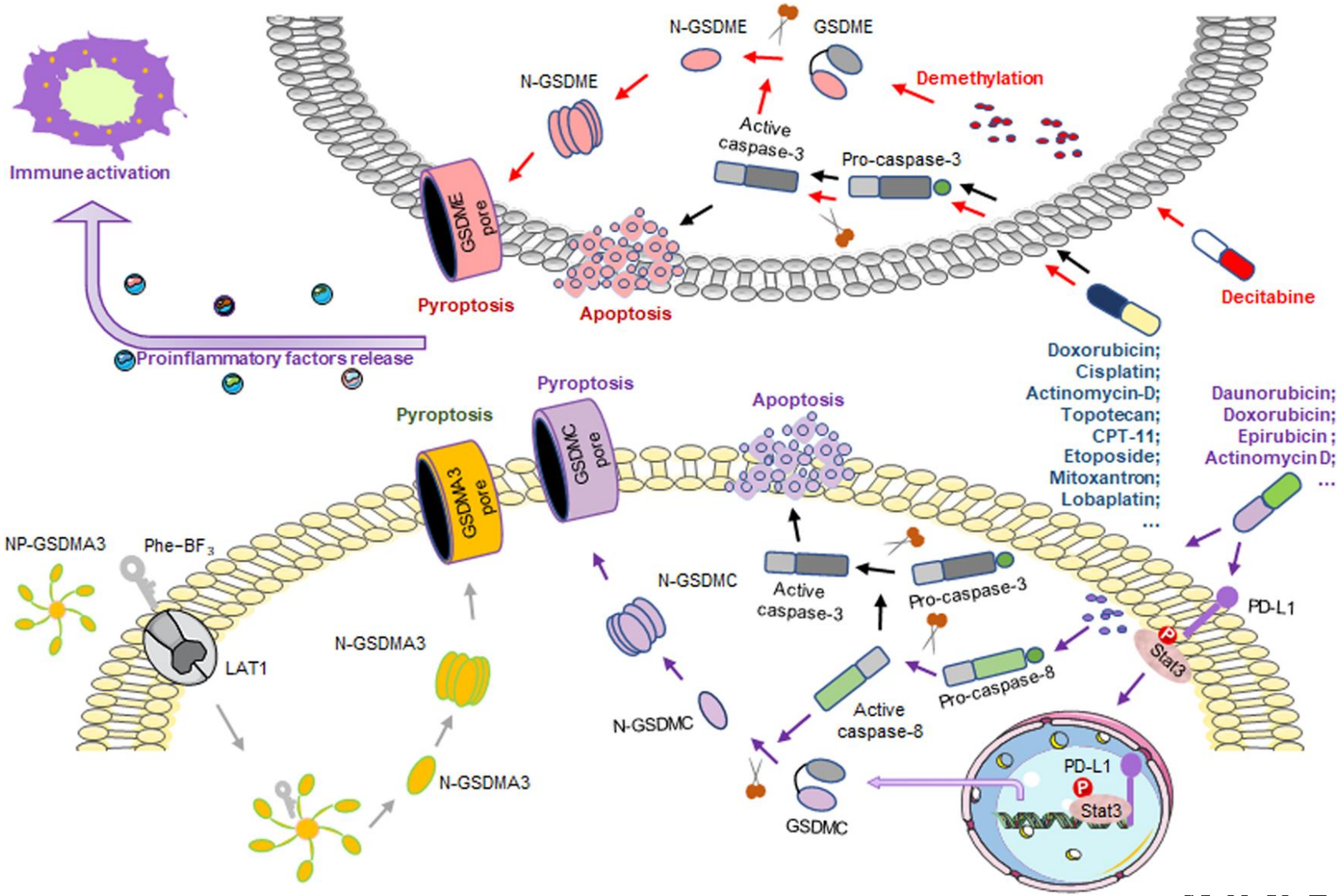
Gasdermin-related therapy

Gasdermins are the effectors of pyroptosis, and activation of gasdermins might prevent tumor formation. The researchers developed a bioorthogonal chemical system mediated by the probe phenylalanine trifluoroborate (Phe-BF_3, a cancer-imaging probe that is significantly and specifically absorbed by tumors) at the cellular and in vivo levels. The study revealed that the pyroptosis of a small percentage of tumor cells can effectively regulate the tumor immune microenvironment and activate a strong T cell-mediated antitumor immune response.



Regulated Cell Death in Heart Disease

Regulated and unregulated forms of cell death have been implicated in the pathogenesis of multiple forms of heart disease: ranging from MI without reperfusion, MI with reperfusion (I/R), heart failure of diverse etiologies, myocarditis, congenital heart disease, and others.

MI results from acute and prolonged deficits in the supply of oxygen, nutrients, and survival factors to the myocardium relative to the demands of this tissue.

During acute MI, cardiomyocyte death is the central event in pathogenesis. Acute loss of these cells in the infarct zone drives subsequent adverse remodeling in the remaining myocardium leading to heart failure.

much of this acute cell death occurs through regulated death programs and, therefore, may be amenable to therapeutic manipulation.

Recent data prompt reconsideration of the relative contributions of apoptosis and necrosis in I/R. Early studies suggested that apoptosis was the primary form of cell death in this syndrome. In some cases, this conclusion was based on genetic manipulations that were thought at the time to impact only apoptotic cell death but were later recognized to also affect necrosis. Raising further questions concerning a role for apoptosis in I/R are data suggesting that caspase-dependent cell death is less robust in adult as compared with fetal/neonatal cardiomyocytes

Regulated Cell Death in Heart Disease

In most studies, genetic and pharmacological inhibition of cell death signaling reduces cardiomyocyte death and infarct size only in the context of reperfused MI (I/R).

Studies predating the regulated cell death era have traditionally considered unregulated necrosis to be the primary mode of cardiomyocyte death in this syndrome based primarily on morphological criteria

Non-apoptotic cell death mediating cardiomyocyte loss during I/R.

MPT-mediated necrosis and necroptosis,
ferroptosis, although it remains unclear whether this program is functioning as an independent cell death modality or an amplification loop for the necrotic cell death. Regardless, the molecules that mediate ferroptosis may provide new therapeutic targets.
PARP-1-dependent processes also appear important in I/R. The significance of PARP-1 activation may be more related to its depletion of NAD and disruption of cellular energetics.
The data regarding autosis in ischemic neuronal injury are intriguing, and encourage further study of this form of autophagy-dependent cell death in myocardial I/R.
Pyroptosis may also contribute to I/R, but the major challenge is in understanding the cell types in which it is taking place. Current data suggest that pyroptosis operates primarily in non-cardiomyocytes, bone marrow-derived cells recruited to the heart during MI and perhaps cardiac fibroblasts, but further study is needed.

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Thanks for your
attention.