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Review

Caspase-1: is IL-1 just the tip of the *ICEberg*?

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Caspase-1, formerly known as interleukin (IL)-1-converting enzyme is best established as the protease responsible for the processing of the key pro-inflammatory cytokine IL-1β from an inactive precursor to an active, secreted molecule. Thus, caspase-1 is regarded as a key mediator of inflammatory processes, and has become synonymous with inflammation. In addition to the processing of IL-1β, caspase-1 also executes a rapid programme of cell death, termed pyroptosis, in macrophages in response to intracellular bacteria. Pyroptosis is also regarded as a host response to remove the niche of the bacteria and to hasten their demise. These processes are generally accepted as the main roles of caspase-1. However, there is also a wealth of literature supporting a direct role for caspase-1 in non-infectious cell death processes. This is true in mammals, but also in non-mammalian vertebrates where caspase-1-dependent processing of IL-1β is absent because of the lack of appropriate caspase-1 cleavage sites. This literature is most prevalent in the brain where caspase-1 may directly regulate neuronal cell death in response to diverse insults. We attempt here to summarise the evidence for caspase-1 as a cell death enzyme and propose that, in addition to the processing of IL-1β, caspase-1 has an important and a conserved role as a cell death protease.
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Facts

- Caspase-1 cleaves the pro-inflammatory cytokine pro-interleukin (IL)-1β to an active secreted molecule in monocytes and macrophages.
- Pyroptosis is a caspase-1-mediated macrophage cell death following infection by intracellular pathogens as part of the host response.
- The inflammasome is a molecular scaffold that forms in response to pathogen, or damage-associated signals to activate caspase-1.
- The caspase-1 cleavage site is present only in mammalian pro-IL-1β and is absent in the sequences of other vertebrates.
- Caspase-1 inhibitors inhibit cell death in mammals and other vertebrates.

Open Questions

- How is caspase-1 regulated during cell death processes in non-immune cells?
- Is caspase-1-dependent cell death a conserved mechanism across vertebrates?
- Have the non-caspase-1-dependent mechanisms of IL-1β secretion in sterile inflammation been underestimated?

Caspase-1 is an enzyme involved in the processing of pro-IL-1β to active secreted IL-1β, a key inflammatory mediator driving the host response to infection, injury, and disease. During disease, IL-1β-driven inflammation has often disastrous consequences, and thus represents a therapeutic target.[1] Independent of IL-1β there is unheralded, yet convincing, evidence to suggest that caspase-1 can execute cell death processes. The most extensive evidence for both the inflammatory and direct cell death activities of caspase-1 exists in neuronal injury. Thus, caspase-1 represents a therapeutic target for the treatment of brain injury/disease, conditions for which there is considerable unmet clinical need because of limited clinical options available, and because of the limited regenerative capacity of the brain.[2]

IL-1β is the best characterised of the 11 IL-1 family members. It is produced by numerous cell types, although the majority of studies focus on its production by cells of the innate immune system, such as monocytes and macrophages.[3] It is produced in response to 'pathogen-associated molecular patterns' (PAMPs), or 'damage-AMPs' (DAMPs) as an inactive 31-kDa precursor, called pro-IL-1β. PAMPs and DAMPs function through pattern recognition receptors (PRRs) on macrophage membranes to regulate pathways that control gene expression.[4,5] Stimuli that control pro-IL-1β expression are, however, generally inefficient as secretion

stimuli, but render the cell 'primed' for subsequent exposure to more secretion competent stimuli. These further stimuli are additional PAMPs or DAMPs that function on cytosolic PRRs, commonly of the NOD-like receptor (NLR) family.[3]

An IL-1 processing activity was initially identified in the lysates of LPS-activated monocytes and ascribed as an IL-1 convertase, or IL-1-converting enzyme (ICE).[6,7] Significant homology of ICE with the cell death gene, *ced-3*, from *Caenorhabditis elegans* was identified that subsequently led, along with the discovery of multiple related proteases involved in mammalian apoptosis, to the reclassification of ICE as a member of the caspase family of proteases (caspase-1).[8–10] Members of the caspases fall into one of two sub-families; apoptotic or inflammatory; caspase-1 is considered to belong to the inflammatory group.[11] Thus, the vast majority of the literature on caspase-1 has focussed on its role in inflammation, with a wider role in cell death rarely considered, except for the pyroptotic cell death of macrophages associated with infection by intracellular pathogens.[12] Here, we discuss evidence that caspase-1-dependent cell death is important beyond pyroptosis.

The Activation of Caspase-1

Caspase-1 is activated by recruitment to a molecular platform called an inflammasome.[13] The known caspase-1-activating inflammasomes are composed of a PRR of the NLR family such as NLRP1, NLR family pyrin domain (PYD) containing 3 (NLRP3), NLRP6, NLRP7, NLR family CARD domain-containing protein 4 (NLRC4), or the DNA-sensing absent in melanoma 2 (AIM2) and RIG-1 receptors.[14–16] The best-characterised inflammasomes to date are formed by PRRs of the NLR family, NLRP3 and NLRC4. These are composed of several domains including a leucine-rich repeat, important for PAMP/DAMP sensing, a nucleotide-binding domain required for oligomerisation, and a caspase activation and recruitment (CARD) and/or a PYD, for recruitment to caspase-1 directly, or *via* the adaptor protein apoptosis-associated speck-like protein containing a CARD (ASC), respectively.[14] NLRP3 is activated in response to a variety of structurally diverse PAMPs and DAMPs, and is thought to be the main sensor for sterile inflammatory stimuli (i.e., in response to injury/disease in the absence of infection). NLRC4 is thought to function mainly as a sensor of bacterial infection by sensing flagellin, but also the type III secretion system rod protein PrgJ.[14] Although regulation of the inflammasome is an area of enormous interest currently, there are still many outstanding questions regarding the mechanisms of its activation.

The most reported consequence of caspase-1 activation is the rapid secretion of IL-1β. An additional consequence of caspase-1 activation in macrophages following infection by NLRC4-activating pathogens is a rapid, and caspase-1-dependent cell death called pyroptosis.[12] Pyroptosis is a pro-inflammatory form of cell death that causes an infected macrophage to kill itself, and at the same time release IL-1β.[12] The rapid, caspase-1-dependent pyroptotic cell death caused by *Salmonella typhimurium*,[17] and the caspase-1-dependent clearance of NLRC4-activating pathogens *in vivo*[18] do not depend upon IL-1β processing. Pyroptosis is suggested to serve principally to eliminate the intracellular niche required

for pathogen growth.[19] The process of pyroptosis is not bactericidal *per se*, and the released pathogens are killed by the cytotoxic mechanisms of neutrophils recruited to the inflamed tissue.[18] However, cell death associated with IL-1β release does not occur only in response to infection with NLRC4-activating pathogens. Stimulation of LPS-primed peritoneal macrophages with the NLRP3-activating stimulus ATP (*via* the P2x7 receptor[20]) or allospecific cytotoxic T-lymphocytes induces cell death in addition to IL-1β processing and release.[21] Brief (30-min) incubation with ATP causes LPS-primed murine peritoneal macrophages to 'round up' and bleb, which is closely followed by the release of the cytolytic marker lactate dehydrogenase.[22] ATP-induced death of LPS-treated mouse peritoneal macrophages is caspase-1-dependent and completely independent of IL-1 secretion.[20] NLRP3-inflammasome-dependent pyroptosis is also activated by infection of macrophages with *Staphylococcus aureus*.[23] Caspase-1 activation *via* the AIM2 inflammasome also results in pyroptotic cell death,[24] as does activation of the NLRP1 inflammasome.[25] Thus, pyroptotic cell death can be activated by many diverse stimuli and by multiple inflammasomes, and is independent of IL-1β.[18,20] Interestingly, caspase-1-dependent cleavage of pro-IL-1β appears to be an exclusively mammalian trait, as other vertebrate pro-IL-1β sequences lack a caspase-1 cleavage site.[26] Thus, in these organisms pro-IL-1β must be cleaved by additional proteases, and there is also evidence for alternative processing in mammals.[27–30] Does caspase-1 therefore have a conserved role in cell death independent of IL-1β?

Caspase-1 substrates. The specificity of caspase-1 for cleavage of pro-IL-1β is suggested to be due to the labile nature of its activity, while it appears a rather promiscuous enzyme based on substrate cleavage profiles.[31] Several independent proteomic-based approaches to identify caspase-1 substrates have identified numerous proteins, the cleavage of which could result in rapid cell death.[31–34] Identified caspase-1 substrates from these and other studies[35–39] (there are 121 in total, see Supplementary Table 1) suggest a diverse substrate specificity, the cleavage of which could result in the rapid dismantling of the cell, characteristic of pyroptosis. The activation of classical apoptotic caspases, and associated regulators, in addition to cytoskeletal proteins and other proteins essential for cell sustaining processes will give rise to the pyroptotic phenotype of a rapid oncolytic-like cell death with features of apoptosis. Some of these substrates and their ontologies are summarised in Figure 1. The full list of identified caspase-1 substrates and their UniProt identification are supplied in Supplementary Table 1.

Caspase-1 and Cell Death in Non-mammalian Vertebrates

Chicken pro-IL-1β does not contain a caspase-1 cleavage site,[26] although chickens do express caspase-1.[40] Cell death induced by trophic factor withdrawl in primary cultured chick dorsal root ganglia (DRG) neurones is inhibited when *crmA* (*cytokine response modifier A* gene from cowpox virus that encodes an inhibitor of caspase-1[41]) or bcl-2 are overexpressed,[42] and in chick motoneurones treated with the
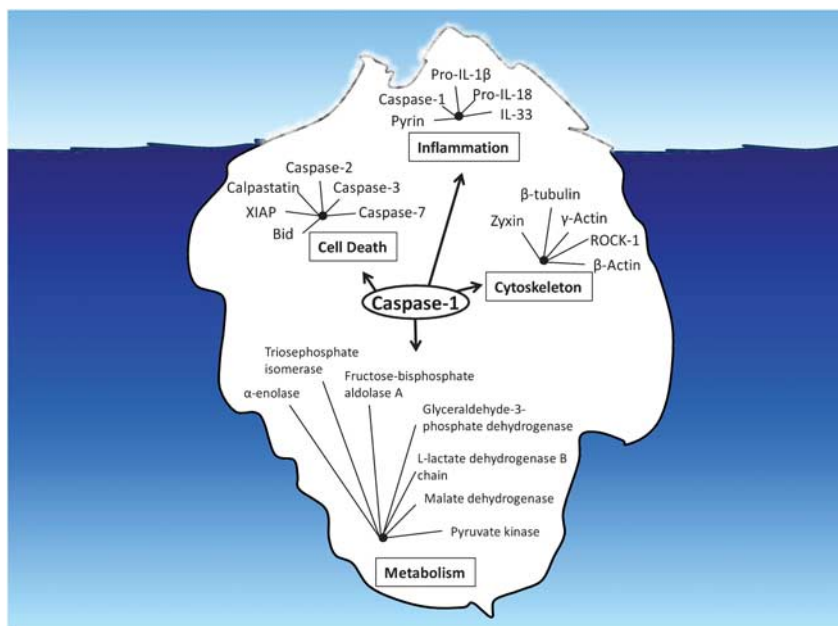
Figure 1 Is IL-1 just the tip of the ICEberg? Caspase-1 has a broad range of substrate specificity that extends far beyond inflammation. Depicted here is an iceberg of caspase-1 substrates in which IL-1- and inflammation-related protein substrates are situated at the tip of the iceberg. The uppercase ICE in ICEberg relates to the former name for caspase-1, ICE. Also shown are some selected substrates that may contribute to the phenotype of a pyroptotic cell death. In addition to inflammation, substrates related to the ontologies of cell death, cytoskeleton and metabolism are shown. The full list of substrates is provided as Supplementary information (Supplementary Table 1)

caspase-1 inhibitor YVAD.[43] Chicken DRG neurones that over express a dominant-negative caspase-1 enzyme are protected from cell death induced by trophic factor withdrawal.[44] The lack of a caspase-1-cleavage site on chicken pro-IL-1β[26] suggests that this protective effect of caspase-1 inhibition must be independent of pro-IL-1β processing.

Caspase-1 orthologues have also been identified in fish. In zebrafish (*Danio rerio*) two orthologues of caspase-1 have been identified, caspy1 and caspy2, as have ASC- and NLR-like molecules.[45,46] Caspy activity is activated by oligimerisation of the zebrafish orthologue of ASC and induces apoptosis when expressed in mammalian 293 T cells.[45] YVAD also protects zebrafish embryos from camptothecin-induced cell death.[47] Seabream (*Sparus aurata L*) express caspase-1, and its activity is also effectively blocked by YVAD.[48] Classical DAMPs that activate caspase-1 in mammalian cells such as ATP and mono sodium urate do not induce activation of caspase-1 in seabream macrophages.[49] However, infection of seabream macrophages with *S. typhimurium* induces a caspase-1-dependent pyroptotic cell death, and caspase-1-independent processing and secretion of IL-1β.[49] These data suggest that the association between caspase-1 activation and IL-1β developed later in evolution, thus further suggesting a conserved role for caspase-1 in cell death (Figure 2).

Caspase-1 and Cell Death in Mammals

In mammals, caspase-1 cannot be considered a typical regulator of apoptosis. Caspase-1 KO mice develop normally and KO cells undergo apoptosis in response to typical apoptotic stimuli.[50,51] However, there are examples where ectopic overexpression of caspase-1 and its substrates can cause cell death. These effects are due either to the effects of

IL-1β, or the direct cell-death-inducing effects of caspase-1, and caspase-1-dependent cleavage of pro-IL-1β may induce apoptosis differently to exogenously administered mature IL-1β. For example, apoptosis in COS cells induced by co-expression of caspase-1 and pro-IL-1β is inhibited by IL-1 receptor antagonist (IL-1Ra). However, the addition of exogenous mature IL-1β before hypoxia is anti-apoptotic *via* the downregulation of IL-1RI.[52] As with the zebrafish caspy described above, overexpression of murine caspase-1 in the rat fibroblast cell line Rat-1 results in cell death and this can be blocked by co-expression of crmA, and of the anti-apoptotic bcl-2.[48] There are, however, many examples where endogenous caspase-1 is involved directly in cell death in disease and tissue injury.

Brain injury/neuronal cell death. Acute brain injuries such as stroke, trauma, and haemorrhage, and chronic neurodegenerative diseases, including Alzheimer's and Parkinson's diseases, are devastating conditions with pathologies that are exacerbated by inflammation and IL-1.[2,53] Transgenic mice overexpressing a dominant-negative caspase-1 under the control of a neurone-specific promoter exhibit reduced ischaemic brain injury compared with wild-type mice.[44] Caspase-1 KO mice also have reduced infarcts compared with wild type after experimental stroke induced by occlusion of the middle cerebral artery (MCAo),[54,55] and intracerebroventricular (i.c.v.) administration of the caspase-1 inhibitor Ac-YVAD-cmk is neuroprotective in this model.[54,56] Following stroke in mice (permanent MCAo) neuronal caspase-1 is activated rapidly (within 30 min), preceding the activation of caspase-3.[57] Caspase-1 is also reported to be expressed in neurones in the mouse brain after thromboembolic stroke (as are inflammasome components) but is not expressed by
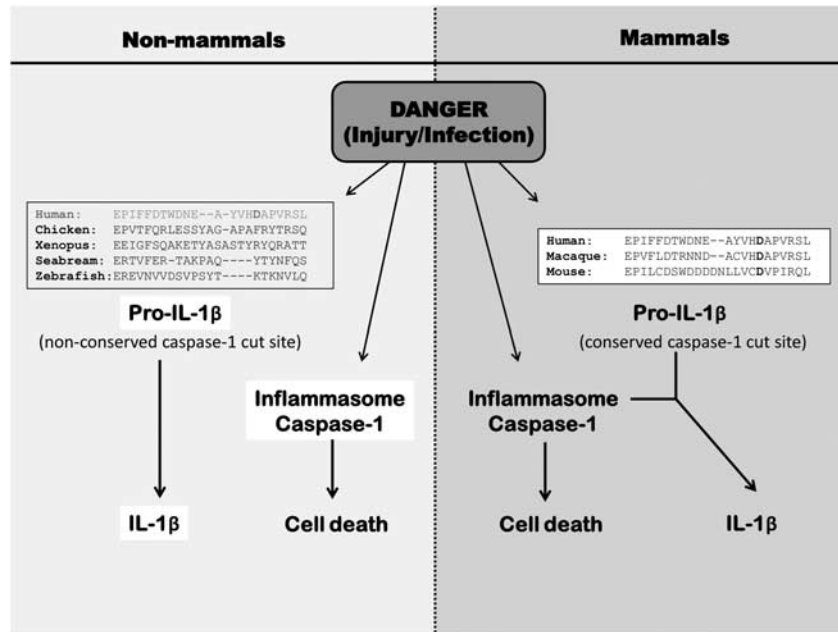
Figure 2 Conservation of caspase-1-dependent cell death and IL-1β processing. The development of caspase-1 as an inflammatory, in addition to a cell death protease occurred in mammals. Highlighted here are conserved caspase-1 cleavage sites in mammalian vertebrate pro-IL-1β that are not observed in non-mammalian pro-IL-1β sequences. The schematic diagram shows the link between caspase-1, cell death, and inflammation in mammals, and that the link is not present between caspase-1 and inflammation in non-mammalian vertebrates. DANGER represents any source of stress that could drive an inflammatory response such as tissue injury, disease, or infection

microglia until 24 h post stroke.[58] After spinal cord injury in rats, caspase-1 expression is induced rapidly in neurones.[59] In addition to the activation of caspase-1 in macrophages (in response to various DAMPs[60–62]), lysosomal destabilisation and cathepsin B are also required for caspase-1 activation in neurones after stroke.[63] A selective caspase-1 inhibitor is protective after MCAo in rats when injected i.c.v. up to 3 h following reperfusion, but not after 6 h,[64] even though IL-1β, protein or message, is below detection limits in the brain parenchyma at this time,[65] and IL-1β KO mice are not protected.[66] The major IL-1 form present early after stroke is IL-1α,[65] which is consistent with the temporal profile of IL-1 family member expression in other paradigms of sterile inflammation.[67,68] Although i.c.v. injection of an anti-IL-1β antibody (given at reperfusion) reduces ischaemic brain injury,[69] it may be neutralising low levels of IL-1β in the cerebrospinal fluid rather than parenchymal IL-1β processed by caspase-1. IL-18, another IL-1 family member and the only other cytokine activated by caspase-1 is suggested to have no role in ischaemic brain injury in adult animals.[70] In contrast, in rodent neonatal hypoxia/ischaemia, protection against ischaemic brain injury was observed in IL-18-deficient mice.[71] In cultured mouse cortical neurones oxygen glucose deprivation (OGD) induces a caspase-1-dependent cell death where caspase-1 activation is apical to the cleavage of BH3-interacting domain death agonist (Bid) and the mitochondrial-dependent activation of caspase-3.[72] Furthermore, OGD-induced neuronal cell death in rat organotypic hippocampal slices is blocked by the caspase-1 inhibitor Ac-YVAD-cmk, and this is neither reversed by the addition of IL-1β to the culture, nor is IL-1Ra protective in the absence of Ac-YVAD-cmk.[73] In vivo IL-1Ra is protective only when administered within 3 h after MCAo in rats,[74] suggesting that its effects may be via the inhibition of IL-1α, and that caspase-1 inhibition in acute brain injury may be targeting cell death directly and independently of IL-1.

In rat pheochromocytoma (PC12) cells, apoptosis induced by the downregulation of Cu^{2+}/Zn^{2+} superoxide dismutase (SOD1), or by trophic factor/nerve growth factor deprivation, can be prevented by caspase-1 inhibition. Cell death induced by SOD1 suppression is prevented by interventions against IL-1, but a neutralising IL-1β antibody does not protect against trophic factor withdrawal-induced cell death.[75] Murine caspase-1 KO DRG neurones are also protected from trophic factor withdrawal-induced death.[44] Caspase-1-dependent Bid cleavage drives neurodegeneration in a mouse model of amyotrophic lateral sclerosis induced by transgenic expression of mutant SOD1.[76] Inhibition of caspase-1 or caspase-3 also delays mortality in mouse models of amyotrophic lateral sclerosis (mSOD1(G93A) or SOD(G93R) mice).[77,78] This effect is generally thought to be dependent on IL-1β.[79,80] However, chronic expression of IL-1β mRNA in the spinal cord or the absence of IL-1β in SOD1G37R mice does not modify disease progression and motorneuron death.[81] In neuroAIDS gp120, a membrane glycoprotein of HIV-1, elevates cytochrome C immunoreactivity, which is blocked by the caspase-1 inhibitor Ac-YVAD-(acyloxy)mk. Ac-YVAD-(acyloxy)mk did not affect IL-1β levels or gp120-induced cleavage of pro-IL-1β.[82] It has been suggested that gp120-induced processing of pro-IL-1β and neuronal apoptosis are matrix metalloproteinase-dependent.[83] These data indicate that both caspase-1 and its substrates can be involved in neuronal injury

Table 1 Caspase-1 mediates vertebrate cell death independently of its classical role in inflammation

Description	Tissue, cell type, parameters affected	Species	References
Caspase-1 inhibition protects against cell death independently of IL-1β processing	Embryo, macrophages	Fish	38–40
Caspase-1 inhibition protects against trophic factor-induced cell death independently of IL-1β processing	DRG neurones	Chicken	33–35
Caspase-1 inhibition protects against trophic factor-induced cell death, which is independent of IL-1β and partially independent of IL-1R1	PC12 cells	Rat	75
Ac-YVAD-cmk, but not IL-1β or IL-1Ra blocks neuronal death	Organotypic brain slices	Rat	73
Caspase-1 activates mitochondrial cell death pathways in hypoxia/ischaemia	Cortical neuron cultures	Mouse	72
Caspase-1 is involved in cell death in SOD1 models of ALS, but IL-1β can be dispensable	Cell death, mortality *in vivo*	Mouse	76–81
Ac-YVAD-(acyloxy)mk-mediated neuroprotection in neuroAIDS is independent from IL-1β procession	Neocortex	Rat	82
Caspase-1 is involved in Fas-ligand-induced hepatocyte apoptosis and induces liver injury independently of IL-1β and IL-18	Liver, fibroblasts, hepatocytes,	Mouse, rat	84–87
Acute renal failure is attenuated in caspase-1 KO animals, independently of IL-1 or IL-18	Kidney	Mouse	89
Caspase-1-mediated effects can be independent of IL-1 or IL-18 in renal ischaemia models	Kidney, proximal renal tubules	Mouse	90–92
Caspase-1 has a proapoptotic role in heart failure, independently of IL-1 or IL-18 induction and inflammation	Heart, cardiomyocytes	Human, mouse	97
Caspase-1 ablation protects photoreceptors in a model of autosomal dominant retinitis pigmentosa independently of IL-1	Retina	Mouse	99
Caspase-1 KO or zVAD-fmk protects against septic shock and apoptosis, which is not seen in IL-1β/IL-18 double KO	Mortality *in vivo*, B-cell apoptosis	Mouse	101

Abbreviations: DRG, dorsal root ganglion; IL, interleukin; SOD, superoxide dismutase
Examples illustrate IL-1- or IL-18-independent actions of caspase-1 both in *in vivo* and *in vitro* models of cell death, tissue injury, or after systemic inflammatory challenge. See the text for a detailed explanation

independently of each other. Some examples of the direct cell death-related activities of caspase-1 independent of IL-1 are presented in Table 1.

Other tissue injury. Similarly to the effects of inhibiting caspase-1 or its pro-inflammatory substrates in the brain, there is evidence for the involvement of these pathways in many other models of tissue injury and disease. Caspase-1 is strongly implicated in TNF-α or Fas-ligand-induced hepatocyte apoptosis,[84,85] and a caspase-1 inhibitor completely inhibits Fas-induced mortality *in vivo*.[86] Liver injury induced by major trauma is also caspase-1-dependent, independently of its effects on IL-1β and IL-18 processing.[87] There is evidence that IL-18 can also be secreted by macrophages *via* a caspase-1-independent, Fas/Fas-ligand-mediated manner and contribute to acute liver injury in mice.[88] Endotoxemic acute renal failure is attenuated in caspase-1 KO mice, and in these mice blockade of IL-1 by IL-1Ra or neutralisation of IL-18 is not protective.[89] In renal ischaemia/reperfusion models, caspase-1 inhibition may be beneficial owing to an inhibition of pro-IL-18 processing,[90] whereas no protection is observed in IL-1RI KO mice, or after IL-1Ra administration.[91] However, inhibition of IL-18 has no effect against caspase-1-dependent hypoxia-induced death in proximal renal tubules *in vitro*,[92] suggesting that caspase-1 also has a role in renal injury that is independent of IL-1 and

IL-18 processing. In renal ischaemia/reperfusion injury NLRP3 KO mice are protected independently of NLRP3's inflammasome function.[93] Inhibition or deletion of caspase-1 also improves outcome after myocardial infarction,[94–96] and this protection may also occur independently of IL-1β and IL-18. Caspase-1 KO mice are protected from ischaemia/reperfusion-induced cardiomyocyte apoptosis, whereas mice with cardiomyocyte-specific overexpression of caspase-1 develop heart failure, in the absence of IL-1β or IL-18.[97] Ischaemia/reperfusion injury in transgenic mice overexpressing caspase-1 results in myocardial infarcts that are 50% larger than their non-transgenic littermates and this is suggested to depend upon cross talk with caspase-3.[98] Caspase-1 ablation protected photoreceptors in a model of autosomal dominant retinitis pigmentosa, although no protective effect was observed in IL-1R1 KO mice.[99] Caspase-1 KO mice are resistant to sepsis induced lethality,[50] yet there is no protection in IL-1β KO mice.[100] Caspase-1 KO mice are also completely protected from septic shock induced by administration of live *Escherichia coli* while IL-1β and IL-1β/IL-18 double KO mice suffered the same mortality as the wild-type controls, but were protected by administration of a caspase-1 inhibitor.[101] Histological analysis revealed high levels of apoptosis within the B-cell population in the spleen of septic mice that was not present in the caspase-1 KO mice,[101] again suggesting that the effects of caspase-1 on

cell death are independent of the cleavage of its classical substrates pro-IL-1β and pro-IL-18.

Caspase-1 in humans. IL-1-driven pathology defines a new emerging family of diseases classified as autoinflammatory.[102] Within this group of diseases there is some where a link between caspase-1 and IL-1β processing is clearly established, while it remains to be seen in others. Currently, evidence implicating caspase-1 in direct cell death processes in human disease is lacking, although the animal studies described above provide evidence that a role for caspase-1 in cell death processes in humans should not be entirely unexpected. A group of diseases where a role for caspase-1-dependent IL-1β-driven responses is unequivocal are the cryopyrin-associated periodic syndromes (CAPS). These diseases share many features including recurrent bouts of fever, elevated acute phase proteins, fatigue and hearing loss.[102] CAPS are caused by gain of function mutations in NLRP3 leading to increased inflammasome formation, caspase-1 activation, and subsequently increased release of IL-1β.[103] Disease symptoms resolve following treatment with anti-IL-1β therapies.[102]

Studies describing clinical use of anti-IL-1 therapies focus almost exclusively on the use of biologicals such as IL-1Ra (anakinra) or anti-IL-1β antibodies such as canakinumab.[1] Clinical data on drugs that target caspase-1 are much more limited. Pralnacasan is an orally available caspase-1 inhibitor, that when trialled in phase II for rheumatoid arthritis showed amelioration of disease symptoms, but not for osteoarthritis.[104] Trials using pralnacasan were subsequently suspended when a preclinical study in dogs reported liver abnormalities when treated long term with high doses.[104] Pralnacasan is currently in phase II trials for the treatment of drug resistant epilepsy. Currently, we can only speculate based upon the animal studies described above, that

caspase-1 will also have a direct role in cell death processes in human disease.

Cross Talk Between Inflammatory and Apoptotic Caspases

As discussed above, there is evidence supporting a significant interaction between the pathways regulating inflammatory, and apoptotic caspases (Figure 3). For example, the anti-apoptotic protein bcl-2, which is classically associated with an inhibition of the intrinsic pathway of apoptosis, can also inhibit caspase-1-dependent cell death.[39,42] More recently bcl-2 has subsequently been discovered to bind to, and suppress activation of the NLRP1 inflammasome, inhibiting release of IL-1β in response to the NLRP1-activating ligand muramyl dipeptide,[105] and also blocks the activation of the NLRP3 inflammasome in response to apoptotic stimuli in mouse macrophages.[106] Members of the inhibitors of apoptosis (IAP) family suppress apoptotic caspases through their E3 ubiquitin ligase activity,[107] but have now been shown to regulate the activity of caspase-1 and IL-1β release.[108,109] X-linked IAP protein, a caspase-1 substrate (Figure 1), is reported to be a component of the NLRP1 inflammasome formed after spinal cord injury and after thromboembolic stroke in rodents.[58,59] In several of the models of neuronal cell death described above, caspase-1 is apical to the activation of caspase-3.[57,72] From the proteomic work summarised in Figure 1 we know that caspase-1 can function directly upon caspase-3 and Bid,[31] and in several disease models described above caspase-1 is reported to activate Bid.[72,76] Cleavage of Bid is central to the intrinsic cell death pathway of apoptosis, with the truncated form of Bid triggering the process that leads to mitochondrial outer membrane permeabilisation, cytochrome *C* release, apoptosome formation, and the subsequent activation of caspases 9 and 3/7.[110] Caspase-8 is typically associated
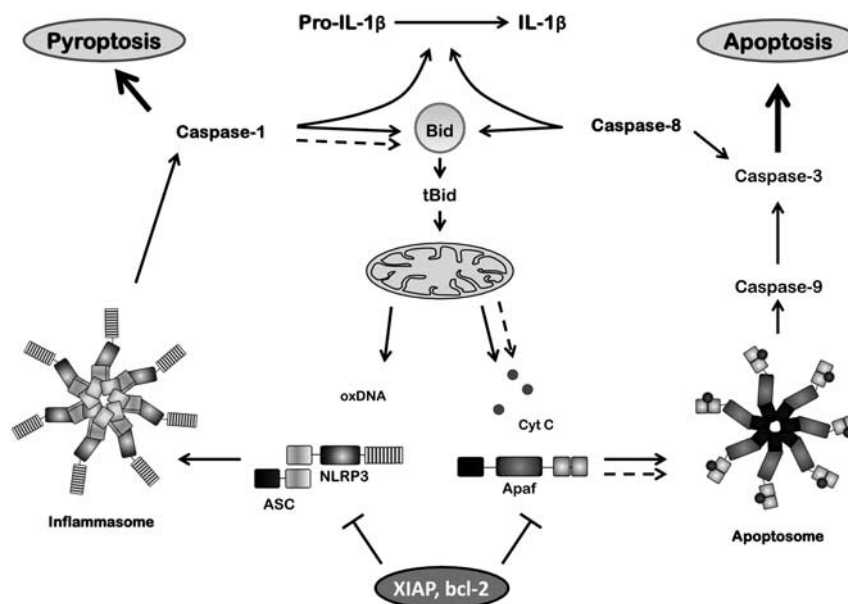

Figure 3 Inflammatory and apoptotic caspase cross talk. Shown is a summary of some of the interactions between inflammatory and apoptotic caspases. In particular, parallels and overlap between the formation of the inflammasome and the apoptosome are shown. Bold arrows are established links. The dashed arrows highlight possible interactions as suggested by the reviewed literature

with Bid cleavage, although the data discussed in this review suggest that caspase-1 could also contribute to this intrinsic cell death pathway. This cross talk between caspase-1 and apoptotic pathways has also been reported in reverse. For example, caspase-8 can cleave pro-IL-1β, at the same site as caspase-1, in response to Toll-like receptor stimulation,[111] or following treatment of LPS-primed macrophages with an IAP antagonist.[109] In addition, the pro-apoptotic drug staurosporine induces NLRP3-dependent activation of caspase-1 and IL-1β secretion from LPS-primed macrophages via release of oxidised mitochondrial DNA.[106] Inflammatory and apoptotic caspase cross talk also occurs during pyroptotic cell death in macrophages, where caspase-7 is activated downstream of NLRP3- and NLRC4-inflammasome-dependent caspase-1 activation.[112,113] Caspase-7 is also activated downstream of caspase-1 in response to LPS in the absence of cell death.[114] These data suggest that there is significant overlap between inflammatory and apoptotic caspases and that the signalling processes controlling their regulation are not exclusive to inflammation or to apoptosis.

Summary

Sterile inflammation is the inflammatory response to injury and disease in the absence of infection and is driven by DAMPs; endogenous host molecules modified during disease, or intracellular proteins released after necrosis.[5] The same indiscriminate weapons used during inflammation by recruited leucocytes to kill pathogens (e.g., reactive oxygen species and proteases) kill surrounding healthy cells and thus sterile inflammation exacerbates disease and injury.[5,115] Thus, considering the evidence discussed above for the direct role of caspase-1 in cell death processes after sterile insults, an inhibition of caspase-1 would be anti-inflammatory by preserving cell viability and therefore limiting the release of DAMPs, consequently resulting in less inflammation. In this way caspase-1 could drive an IL-1-dependent inflammation across all vertebrate classes. In mammals, caspase-1-dependent processing of pro-IL-1β can occur although there are additional pathways of pro-IL-1β processing that have been described in disease.[27–30] Thus, a challenge when devising future studies and interpreting current literature will be to dissociate the effects of caspase-1 on cell death and on the processing of IL-1β as it is possible that caspase-1-dependent cell death could lead to an IL-1-dependent inflammatory response, independent of caspase-1-processing of pro-IL-1β. The conserved caspase-1-dependent cell death in non-mammalian vertebrates and the cross talk between inflammatory and apoptotic caspases discussed above, suggest that the involvement of caspase-1 in cell death pathways is much greater than is considered currently.

Conflict of Interest

The authors declare no conflict of interest.

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