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Beyond canonical inflammasomes: emerging pathways in IL-1-mediated autoinflammatory disease

John R. Lukens[1] and **Thirumala-Devi Kanneganti**[1,*]

[1]Department of Immunology, St. Jude Children's Research Hospital, Memphis, TN, 38105, USA

Abstract

In recent years non-communicable chronic diseases that are potentiated by sterile inflammation have replaced infectious diseases as the major threat to human health. Sterile inflammation that results from aberrant tissue damage plays pivotal roles in the pathogenesis of numerous acute and chronic inflammatory diseases including atherosclerosis, type 2 diabetes, cancer, obesity, and multiple neurodegenerative diseases. The cellular events and molecular signaling pathways that govern sterile inflammation currently remain poorly defined, however emerging data suggest central roles for IL-1 in driving autoimmune and inflammatory disease pathogenesis. Improved characterization of the immunological pathways that contribute to sterile inflammation are desperately needed to develop effective therapeutics to treat these devastating diseases. In this review we discuss recent advances in our understanding of how IL-1 is regulated in response to tissue damage. In particular, we highlight recent studies that describe novel roles for conventional cell death molecules in the regulation of IL-1β production.

Keywords

Sterile inflammation; interleukin-1; innate immunity; inflammasome; NOD-like receptor; autoinflammation

Introduction

Inflammation that is mediated by immune cells is vital for host protection against pathogens. In response to an infection, the immune system orchestrates a coordinated response to eradicate the pathogen and to restore tissue integrity. Innate immune cells constitute the first line of defense and are involved in recognizing the initial threat, containing the infection and promoting the recruitment of additional immune cells through the release of cytokines and chemokines. Adaptive immune cells, which comprise of T and B cells, then arrive at the site of invasion and promote the clearance of infected cells. An inability to mount protective responses against pathogens can have debilitating and even fatal consequences for the host

[*]**Correspondence should be addressed to:** Thirumala-Devi Kanneganti Department of Immunology, St Jude Children's Research Hospital MS #351, 262 Danny Thomas Place, Suite E7004 Memphis TN 38105-2794 Tel: (901) 595-3634; Fax. (901) 595-5766. Thirumala-Devi.Kanneganti@StJude.org.

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and, as a result, the immune system has evolved an arsenal of effector mechanisms to combat infection.

However inflammation can be a double-edged sword, and the same inflammatory pathways that are required for host protection against microbes can also be provoked in response to tissue damage in the absence of apparent infection. Inflammation and tissue destruction that results from trauma, cellular and metabolic dysfunction, ischemia-reperfusion injury or environmental irritants typically ensues in the absence of infection and is commonly referred to as sterile inflammation [1]. Controlled immune responses to sterile stimuli are needed to neutralize and sequester the irritant, clear damaged cells, and to promote wound healing. Innate immune cells, including most prominently neutrophils and macrophages, are the major mediators of sterile inflammation [2–5]. Following tissue damage, neutrophils and macrophages are recruited into the area of injury where they play essential roles in the removal of the irritant and the induction of repair pathways. The process of immune cells aiding in the resolution of sterile tissue damage typically occurs in the absence of overt pathology. However, continuous exposure to an injurious agent can cause unrestrained inflammation, fibrosis and potentially organ failure. Mounting evidence indicates that unchecked immune responses are centrally involved in a spectrum of acute and chronic inflammatory disorders. Indeed, dysregulated production of proinflammatory cytokines, reactive oxygen species (ROS), growth factors and proteases by immune cells are known to cause the aberrant tissue destruction, collagen deposition and fibrosis that underlie inflammatory and autoimmune disease [6, 7].

Acute disorders that result from sterile inflammation include ischemia-reperfusion injury, trauma and particulate-induced lung injury. In these settings, rapid perturbations to tissue integrity cause inflammatory forms of cell death such as necrosis. Immune cells respond to danger-associated molecular patterns (DAMPs) released by necrotic cells and rapidly up-regulate factors to limit the spread of tissue damage and to promote wound-healing responses. Immune-based inflammatory responses that ensue in response to acute tissue damage are directly responsible for the pain, vasodilation and scarring that are associated with trauma, exposure to environmental irritants, and tissue hypoxia.

Dysregulated immune responses are also centrally responsible for driving inflammation and tissue destruction in chronic autoimmune and inflammatory diseases. For example, deposition of cholesterol crystals around arterial walls provokes inflammatory cytokine production by macrophages and this contributes to subsequent plaque formation in atherosclerosis [8]. Sterile inflammation is also involved in the pathogenesis of multiple neurodegenerative diseases including Alzheimer’s disease and amyotrophic lateral sclerosis (ALS). In these disorders, the buildup of amyloids and unfolded proteins in the central nervous system (CNS) incites the release of neurotoxic pro-inflammatory cytokines by microglial cells and other innate immune cells [9]. Further, immune cell-mediated inflammation is now recognized to contribute to the development and progression of obesity and associated metabolic disorders, which include type 2 diabetes and fatty liver disease [10–13]. In this context, saturated fatty acids and danger signals (e.g. islet amyloid polypeptide, uric acid and damaged mitochondria) produced as a result of metabolic dysfunction provoke inflammatory cytokine production and tissue damage.

Extensive work now shows that IL-1, in particular, plays overarching roles in the inflammatory process and, as a result, the immune system has evolved numerous mechanisms to regulate IL-1 production. Indeed, aberrant IL-1 signaling has been identified to underlie many monogenic and polygenic human inflammatory disorders including cryopyrin-associated periodic syndromes (CAPS) and familial Mediterranean fever (FMF). Generation of IL-1 by caspase-1 in canonical inflammasome complexes is by far the most well established mechanism for IL-1 production, however recent studies have implicated prominent roles for additional pathways and molecules in the regulation of IL-1 secretion. In this review we discuss that pivotal roles that IL-1 plays in inflammatory disease and draw attention to emerging pathways that are involved in the regulation of IL-1 production.

The IL-1 family cytokines: central mediators of inflammation

The IL-1 family cytokines, IL-1α and IL-1β, have been established to play key roles in infectious and sterile inflammatory diseases [1, 14–19]. Both IL-1α and IL-1β provoke potent proinflammatory events by engaging the IL-1 receptor (IL-1R). Following tissue damage, IL-1 release serves as the primary initiating signal to coordinate the mobilization of immune cells to the damaged area (Figure 1). Indeed, induction of IL-1 signaling results in dramatic production of chemokines and cytokines that function to orchestrate the expansion and recruitment of phagocytes to the site of damage. The early recruitment of neutrophils appears to be mediated primarily via IL-1-dependent production of granulopoietic factors including IL-6, KC and G-CSF [20–23]. The release of these mediators rapidly induces the expansion of neutrophils in the bone marrow (termed granulopoiesis) and also provides cues to direct the trafficking of neutrophils to the damaged tissue. IL-1 can also directly coordinate the mobilization and activation of macrophages during autoinflammatory responses by promoting the production of IL-12, M-CSF and IP-10 [23].

In addition to acting on innate cells, IL-1 signaling is also known to influence aspects of the sterile inflammatory process by affecting adaptive cells [24, 25]. For instance, IL-1 secretion in the periphery directs recruitment of B and T cells out of circulation through the blood and lymphatic system and into the inflamed tissue [26, 27]. Once mobilized in inflamed organs, B cells can secrete antibodies that help to opsonize irritants and remove cellular debris [28]. Furthermore, B cells participate in sterile inflammatory responses by secreting cytokines (IL-10, IL-12 and IL-18) that are known to regulate the activity of macrophages and neutrophils in inflamed areas [29, 30]. T cells aid in the containment and removal of irritants and cell damage by secreting cytokines that further promote the recruitment of additional phagocytes to the injured area and by producing cytolytic factors that eliminate injurious agents [31]. T cells have also been found to centrally contribute to the wound healing process. In particular, the production of anti-inflammatory cytokines such as IL-10 and TGF-β by regulatory T cells (Tregs) is needed to facilitate effective resolution of inflammatory responses and to promote tissue repair [32]. Although T cells contribute to successful containment and resolution of tissue damage, unchecked T cell responses can also provoke tissue pathology. Interestingly, dysregulated IL-1 signaling has emerged as a major mechanism that promotes pathogenic T cells responses during autoinflammatory disease and work by multiple laboratories has clearly shown that IL-1 signaling in T cells markedly induces T cell expansion and promotes enhanced inflammatory cytokine production [33–

35]. For example, IL-1R signaling promotes the generation of GM-CSF and IL-17 producing autoreactive T cells that are required to cause demyelinating neuroinflammatory disease in experimental autoimmune encephalomyelitis (EAE) [36, 37].

Historically, IL-1α and IL-1β have been considered to have overlapping functions. Despite their ability to evoke similar immunological outcomes, IL-1α and IL-1β differ substantially in their expression and regulation. Furthermore, non-redundant roles for IL-1α or IL-1β have recently been established in multiple inflammatory diseases [20, 21, 38–42]. Below we highlight the specific molecular pathways that are known to regulate IL-1α and IL-1β production and discuss their contributions to autoinflammatory disease.

IL-1α and inflammatory disease

Aberrant cell death that results from cellular stress, trauma, environmental insults and hypoxia are known trigger to inflammatory disease and, accordingly, the release of IL-1α under these conditions has been shown to prominently affect such disease [43]. Indeed, IL-1α has been discovered to be a central driver of immune responses that are generated in response to sterile tissue damage. Early studies demonstrated that IL-1α instigates the sterile inflammatory response to necrotic cells in mice [7, 44], and subsequent studies have shown that IL-1α critically regulates aspects of wound healing [45]. Following catastrophic tissue damage, IL-1α is released by cells and serves as an “alarmin” molecule to recruit other immune cells to the site of injury. IL-1α can also lead to potent up-regulation of inflammatory cytokines including proIL-1β, IL-6, and TNFα following IL-1R-mediated NF-κB signaling in nearby cells (Figure 1). IL-1α has been proposed to be an apical initiator of autoinflammatory responses due to the fact that it does not require up-regulation or processing to provoke inflammation once it is released. Indeed, IL-1α has been shown to centrally orchestrate the inflammatory responses that develop in response to ischemia-reperfusion injury, and altered IL-1 signaling has been identified to be a major culprit in the pathology of many ischemia-related diseases, including stroke and myocardial infarction [46–51].

IL-1α was also shown to centrally drive inflammatory immune responses in a mouse model of neutrophilic dermatosis [20]. Mutation in the phosphatase, SHP-1, causes a severe autoinflammatory syndrome that resembles neutrophilic dermatosis in humans and is characterized by persistent footpad swelling and suppurative inflammation [52–55]. Excessive production of inflammatory cytokines, neutrophilia and hyperactive T cell responses are associated with this SHP-1-mediated disease pathology [56, 57]. Genetic abrogation of IL-1R was found to protect SHP-1 mutant mice from cutaneous inflammation [58], suggesting that IL-1-mediated events potentiate disease. Surprisingly, inflammasome activation and IL-1β expression were dispensable for SHP-1-mediated footpad disease. In contrast, dysregulated IL-1α-mediated events were discovered to be responsible for chronic inflammation in this model, as genetic deletion of *Il*1α provided complete protection from disease [20]. IL-1α is also chiefly responsible for driving inflammation in models of trauma-induced skin damage [20], artery rejection [27], atherosclerosis [41], and DNA damage-induced senescence and tumorigenesis [21]. Additional studies that seek to characterize the

discrete roles of IL-1α and IL-1β in sterile inflammation will provide much needed insight into the etiology of many inflammatory diseases.

Regulation of IL-1α

In comparison to IL-1β, our understanding of the roles and regulation of IL-1α in sterile inflammatory disease is severely limited. IL-1α is one of the few known cytokines that can exert transcriptional functions in the nucleus while also promoting immunological activities once it is released into the extracellular compartment. IL-1α possesses a nuclear localization sequence in its N-terminus, which allows it to translocate into the nucleus where it can affect transcription [59–61]. Interestingly, the only other two known dual function cytokines, IL-33 and HMGB1, have also been implicated to play instrumental roles in regulating inflammatory responses to tissue damage [62, 63]. In comparison to IL-1β, which requires cleavage to provoke its inflammatory activities, full-length IL-1α can incite inflammation without any modification and, thus, it is critical that cells employ protective measures to ensure that IL-1α is not released during cell death. Turnover of cells occurs at astounding rates in humans and it is estimated that one million cells die each second through a silent or non-inflammatory form of cell death known as apoptosis [64]. During homeostasis IL-1α exists both in the cytoplasm and nucleus, however following apoptotic signaling, IL-1α is rapidly shuttled into the nucleus to prevent its passive release during cell turnover [43, 65]. In contrast, the induction of catastrophic forms of cell death, including necrosis, can provoke the release of IL-1α and subsequent inflammation (Figure 1).

While IL-1α is constitutively expressed by both immune cells and parenchymal cells, IL-1β is not expressed at appreciable levels by circulating cells [66]. Rather, a priming step is required to up-regulate IL-1β before it can be processed and secreted. Once IL-1β has been expressed it requires cleavage to elicit its biological activity and secretion. In contrast, IL-1α does not require processing for it to be active and, as a result, IL-1α can promote inflammation in its full-form (precursor IL-1α) [67]. Precursor IL-1α can also be cleaved to generate two biologically active IL-1α species, which are known as the mature and propiece forms. The proteases that contribute to IL-1α cleavage and the generation of mature IL-1α remains a subject of debate. Multiple groups have reported that activators of caspase-1 in inflammasomes (see below for description of caspase-1 and inflammasomes) can promote the secretion of mature IL-α [68, 69]. In contrast, other studies suggest that calpain-like activities rather than inflammasomes are required for mature IL-1α processing [70–73]. Regardless, it is clear that additional studies are needed to ascertain the molecular players that coordinate IL-1α cleavage. Furthermore, the discrete biological functions of the three different forms of IL-1α (precursor, propiece and mature IL-1α) have not been fully characterized and this remains an important area of future investigation in the sterile inflammatory field.

The upstream pathways that regulate IL-1α production still remain poorly defined. However, in an inflammatory skin disease model it was found that the kinase RIP1 is centrally involved in driving IL-1α-mediated inflammation [20]. RIP1 has been established to play important roles in cell death pathways, however its ability to influence inflammatory responses has not been studied in detail. Additional studies are needed to unravel the

signaling pathways that are involved in RIP1-dependent control of cytokine production and inflammation.

Inflammasome-mediated processing of IL-1β

IL-1β has also been established to play pathogenic roles in multiple major inflammatory and autoimmune diseases including type 2 diabetes, Alzheimer's disease and obesity. A two-step process is required to generate and secrete biologically active IL-1β. Under steady state conditions, there is typically minimal expression of IL-1β by immune cells, thus the first step that is required for production of bioactive IL-1β is characterized by the up-regulation of IL-1β expression. This induction of IL-1β priming is typically mediated by NF-κB signaling. The most well characterized triggers that have been shown to facilitate IL-1β induction include TNF, IL-1α and Toll-like receptor (TLR)-ligands [66, 74, 75]. In the case of autoinflammatory and autoimmune disease, which typically occur in the absence of infection, it is likely that proinflammatory cytokines that are known to promote NF-κB activation (e.g. IL-1α, TNFα and IL-6) provide the necessary signal to promote IL-1β expression [75]. However, it is also possible that commensal bacteria that reside in the host can also mediate proIL-1β up-regulation by providing TLR signals. The second essential step for the generation of biologically active IL-1β involves the cleavage of precursor IL-1β by a protease.

The most well characterized mechanism for IL-1β processing is via activated caspase-1 in the canonical inflammasome complex. Canonical inflammasomes are multi-protein complexes that generally consist of three main components: a cytosolic sensor molecule, the enzyme caspase-1 and the adaptor protein ASC [14, 15, 74]. Members of the NOD-like receptor (NLR) and AIM2-like receptor (ALR) families are established cytosolic sensor molecules that mediate inflammasome formation. NLRs that have been identified to incite inflammasome activation include NLRP1, NLRP3, NLRP6, NLRP7, NLRP12 and NLRC4. NLRP1 and NLRC4 are primarily involved in initiating innate immune responses during infection. NLRP1b detects anthrax lethal toxin [76–78] and NLRC4 induces IL-1β secretion in response to certain bacterial flagellin and Type III secretion system-associated proteins [79–84]. NLRP6, NLRP7 and NLRP12 have also recently been suggested to coordinate inflammasome signaling under specific conditions. For instance, NLRP12 has been implicated in the regulation of IL-1β secretion in response to *Yersinia pestis* and malaria [85, 86], and NLRP7 was described to control inflammasome-mediated IL-1β by human macrophages following stimulation with microbial lipopeptides [87]. Interestingly, NLRP6 and NLRP12 also negatively regulate NF-κB signaling and inflammatory cytokine production in response to TLR activation [88–95]. Thus, additional studies are needed to clarify how these NLRs can exert both anti- and pro-inflammatory functions in different pathways. NLRP3, on the other hand, has been identified to be a central mediator of sterile inflammatory disease as a result of its unique ability to recognize a diverse array of endogenous danger signals that are released during aberrant cell death (ATP and uric acid), metabolic factors (saturated fatty acids and cholesterol crystals) and exogenous irritants (asbestos and silica).

Absent in melanoma 2 (AIM2) and interferon-inducible protein 16 (IFI16) are ALR (also known as pryin- and HIN-200 domain–containing proteins or PYHIN containing proteins) family molecules that have recently been described to incite inflammasome formation following detection of intracellular DNA [96–100]. The roles of AIM2 and IFI16 in autoinflammatory disease progression are currently poorly defined. Interestingly, the development of immune response to self-DNA is believed to contribute to the pathogenesis of multiple autoimmune disorders including systemic lupus erythematous (SLE) [101], psoriasis [102], type 1 diabetes [103], and polyarthritis [104]; thus it is feasible that ALRs will be discovered to contribute to autoinflammatory disease progression at some level.

Recognition of pathogen- or danger-associated molecular patterns (PAMPs and DAMPs, respectively) by NLRs or ALRs promotes the recruitment of ASC and caspase-1 into the inflammasome complex, which is required to correctly orient caspase-1 for auto-cleavage and activation. Once activated, caspase-1 subsequently cleaves proIL-1β and proIL-18, which is required for their secretion and to elicit their inflammatory properties (Figure 2). Intriguingly, many of the danger- and stress-associated signals that have been widely proposed to trigger sterile inflammation have recently been discovered to provoke inflammasome-mediated IL-1β production. For instance, it was shown that man-made and environmental irritants (silica, asbestos, alum, alloy particles, and car exhaust), metabolic factors (cholesterol, amyloids, saturated fatty acids, and glucose) and endogenous danger signals that are released as a result of aberrant cell death (ATP, reactive oxygen species, and uric acid) can all trigger inflammasome-mediated IL-1β secretion. Furthermore, work from multiple groups has clearly shown that dysregulated inflammasome activation and downstream cytokine production centrally contributes to the development of inflammation and pathology in a spectrum of metabolic, autoimmune and inflammatory disorders.

For instance, inflammasome-mediated IL-1β has emerged as a major driver of the chronic low-grade inflammation that underlies obesity-associated diseases [105– 110]. In these studies NLRP3 inflammasome-mediated sensing of saturated fatty acids and associated metabolites (e.g. ceramide and palmitate) induced potent IL-1β secretion [107, 109]. Likewise, genetic deletion of central inflammasome molecules (caspase-1, ASC, NLRP3 and IL-1β) in mice that are fed a high-fat diet leads to reduced weight gain and improved glucose tolerance and insulin sensitivity [105–109, 111].

Inflammasome activation has also been discovered to incite IL-1β maturation in response to misfolded protein and amyloids; and, thus, caspase-1 has been implicated in driving the inflammation that causes tissue destruction in Alzheimer’s disease and type 2 diabetes. The deposition of amyloid β in the brain is believed to cause Alzheimer’s disease by provoking immune cell-mediated damage to CNS cells. Studies now show that recognition of amyloid β by microglia cells induces inflammasome-dependent IL-1β production [112]. Consistent with these *in vitro* findings, genetic abrogation of NLRP3 or caspase-1 in mice carrying mutations that are associated with familial Alzheimer’s disease (APP/SP1 mouse model) protects mice from loss of spatial memory and leads to enhanced phagocytosis of amyloid β by CNS phagocytes [113]. Accumulation of amyloids, and islet amyloid polypeptide (IAPP) in particular, is also associated with beta cell destruction in type 2 diabetes. IAPP has been

described to initiate inflammasome-induced IL-1β production and this is believed to play pathogenic roles in type 2 diabetes [108].

Crystals and particulates that are of both environmental and endogenous origin have been historically linked to tissue damage and sterile inflammatory disease. For instance, the build-up of uric acid in joints is known to cause inflammatory joint destruction in gout, and the inhalation of irritants such as asbestosis and silica has been shown to cause chronic obstructive pulmonary disease (COPD) [114]. Recent studies now suggest that macrophage-mediated IL-1 production in response to particulates and crystals appears to be largely dependent on caspase-1 activation in inflammasomes [111, 115–118]. Collectively, these studies have helped to position inflammasome-mediated IL-1β as a key regulator of sterile inflammation. However, as discussed throughout this review, there are numerous important areas of both inflammasome and IL-1 biology that still require further investigation.

Regulation of IL-1β by new players in inflammasome activation

Over the last few years it has become increasingly apparent that inflammasome activation is not as simple as once thought, and additional caspases and modulators have been discovered to play critical roles in IL-1β cleavage and secretion. Interestingly, many of the newly identified contributors to inflammasome-mediated IL-1β maturation, including caspase-8 and caspase-11, have been previously described to potentiate sterile inflammatory disease through their established roles in regulating cell death. This emerging appreciation for the interface between traditional cell death pathways and IL-1β production has helped to identify new layers of complexity in IL-1β regulation.

Caspase-11

One of the first indications that additional caspases may be involved in inflammasome activation came from the important observation that the routinely studied caspase-1 knockout mouse is actually deficient in both caspase-1 and caspase-11 [119]. It turns out that embryonic stem cells from the 129 background mouse strain, which were used to target caspase-1 deletion, also lack expression of caspase-11 due to a 5-base-pair deletion that impairs exon splicing and, as a result, caspase-1 null mice also lack *casp11*. Previous work identified caspase-11 as an executioner caspase and found that caspase-11 was involved in promoting Fas-mediated apoptosis. Moreover, initial evaluation of inflammatory disease in caspase-11 deficient mice suggested that caspase-11 is involved in driving disease pathology through the regulation of cell death [120, 121]. To ascertain whether caspase-11 specifically influences the regulation of IL-1β production in the routinely studied *Casp1*$^{-/-}$ mouse, which we now know lacks both caspase-1 and caspase-11, side-by-side comparisons of IL-1β secretion and caspase activation were conducted between singly deficient *Casp1*$^{-/-}$ and *Casp11*$^{-/-}$ cells. From these studies it was discovered that caspase-11 plays non-redundant roles in the generation of IL-1β production in response to specific activators of inflammasome activation. Namely, caspase-11 was found to be required for downstream activation of caspase-1 and subsequent IL-1β maturation in response to stimulation with cholera toxin B, *E. coli*, *citrobacter rodentium*, and others (Figure 2) [119, 122, 123]. Inflammasome platforms that are dependent on upstream caspase-11 activation are now

referred to as non-canonical inflammasomes. In contrast, multiple known triggers of IL-1β production including ATP, silica, and nigericin were found to provoke IL-1β maturation independently of a role for caspase-11. These inflammasomes that do not require caspase-11 to trigger IL-1β processing have been coined canonical inflammasomes.

This discovery of a discrete role for caspase-11 in the regulation of IL-1β has been a fairly recent finding and additional studies are greatly needed to further dissect the unique roles of canonical vs. non-canonical inflammasomes in the regulation of disease. For instance, up until now our understanding of these separate inflammasome pathways comes primarily from studies performed on bone marrow-derived macrophages. Additional studies are required to formally address the distinct contributions of canonical and non-canonical inflammasomes in other cell types that are known to contribute to sterile inflammatory disease including dendritic cells, neutrophils, and tissue resident innate cells such as microglia. Recent advances have been made to highlight the specific roles of caspase-1 and caspase-11 under physiological settings. However, this work has been primarily done in infection models, thus far [124–128], and complete characterization of the distinct roles of caspase-1 and caspase-11 is still lacking in most autoimmune and sterile inflammatory disease models. Earlier *in vivo* studies that utilized singly deficient caspase-11 mice showed that caspase-11 could indeed influence tissue damage in autoinflammatory disease models, including EAE [121], and thus future studies that decipher discrete roles for caspase-1 and caspase-11 under physiologically settings are warranted. Furthermore, it is not known whether caspase-11 is required for the induction of IL-1β maturation in response to inflammasome triggers that have been identified to promote obesity-associated disease including amyloids, saturated fatty acids, and cholesterol crystals.

Caspase-8

Additional molecules that have been traditionally associated with the regulation of cell death have also recently been identified to modulate IL-1β maturation. For instance, multiple recent reports have established caspase-8 as a key regulator of IL-1β production. Caspase-8 has been extensively studied in the cell death field, where it is known to play important roles in regulating both cell survival and death. Caspase-8 is perhaps best known for its ability to drive extrinsic apoptosis in response to TNF receptor 1 (TNFR1) and CD95 (also known as Fas) activation [129]. Ligand binding to TNFR1 and CD95 promotes conformational changes in their cytoplasmic tails, which is necessary to allow for the docking of the FAS-associated death domain (FADD) adaptor protein to these death receptors. Under healthy conditions caspase-8 typically exists in a monomeric form as an inactive enzyme. However the binding of FADD to death receptors promotes the recruitment of monomeric caspase-8 zymogens, which in turn leads to homodimerization of caspase-8 and subsequent caspase-8 activation. Once activated caspase-8 directs apoptotic cell death by activating the downstream executioner caspase-3. In addition to performing its classic function in apoptosis, caspase-8 has also been demonstrated to play numerous non-apoptotic roles, including promoting NF-κB signaling, monocyte differentiation, cell survival and proliferation [129].

Multiple reports now show that caspase-8 can also influence IL-1β regulation and processing at multiple levels (Figure 2). In early *in vitro* studies, it was shown that recombinant caspase-8 is capable of cleaving proIL-1β at exactly the same site as caspase-1 [130]. Moreover, generation of biologically active IL-1β in response to poly(I:C)- and LPS-mediated stimulation was inhibited in the presence of caspase-8 inhibitors, CrmA (virally encoded caspase-8 inhibitor) or vFLIP expression (virally encoded caspase-8 inhibitor) [130]. These results helped to identify caspase-8 as a bona fide activator of IL-1β, however the embryonic lethality that is associated with caspase-8 deletion hampered complete mechanistic characterization of caspase-8 in the regulation of IL-1β maturation. Several recent genetic advancements have helped to reinvigorate interest in this area. These have included the discovery that the additional deletion of RIP3 in *Casp8*$^{-/-}$ mice rescues embryonic lethality by limiting fatal necrosis/inflammation during development [131–133]. Utilization of *Rip3*$^{-/-}$x*Casp8*$^{-/-}$ cells and conditional targeting of the *Casp8* allele has made it possible to unravel how caspase-8 influences IL-1β production at a molecular level. Genetic deletion of either caspase-8 or FADD on the *Rip3*$^{-/-}$ background was found to markedly impair both canonical and non-canonical (caspase-11 dependent) inflammasome activation and downstream IL-1β processing [134]. This effect was not the result of RIP3 deletion, as *Rip3*$^{-/-}$ cells secreted IL-1β at levels similar to wild-type cells in response to various inflammasome triggers. Rather, FADD and caspase-8 were shown to control the transcriptional priming of the NLRP3 inflammasome by regulating the expression of NLRP3 and proIL-1β. Furthermore, caspase-8 was specifically observed to dampen inflammasome activation at the post-translational level. This was accomplished by showing that treatment of wild-type macrophages with caspase-8 inhibitors following LPS priming still results in significant reductions in IL-1β secretion. To confirm that FADD/caspase-8 do in fact influence IL-1-mediated inflammatory responses under physiological settings, LPS-induced endotoxemia was induced in *Rip3*$^{-/-}$x*Casp8*$^{-/-}$ and *Rip3*$^{-/-}$x*Fadd*$^{-/-}$ mice. Deletion of either caspase-8 or FADD on the RIP3 deficient background markedly dampened IL-1β and IL-1α release into the serum in response to LPS, which further confirms a role for the FADD-Caspase-8 axis in the regulation of IL-1β production.

Caspase-8 has also been proposed to directly promote IL-1β production through pathways that are completely independent of the critical inflammasome adaptor protein, ASC. For instance, it was found that endoplasmic reticulum (ER) stress induced IL-1β maturation is fully dependent on caspase-8 and does not require ASC expression [135]. Similar to other reports, they also found that caspase-8 is involved in the transcriptional regulation of proIL-1β. ER stress that results from the accumulation of unfolded proteins has been observed in multiple inflammatory disorders and is believed to spur inflammation and disease pathology. In particular, ER stress is frequently observed in obesity-associated diseases and diabetes, and the accumulation of unfolded proteins in the ER is thought to be linked to the chronic inflammation that underlies these diseases [136–139]. Future studies are required to elucidate whether caspase-8-mediated regulation of IL-1β secretion contributes to inflammation and tissue destruction in these disease settings.

Established regulators of cell death have also been discovered to potentiate IL-1β production through caspase-8. For example, it was shown that CD95 (also known as Fas) engagement

provokes caspase-8-dependent IL-1β maturation in myeloid cells in a fashion that is not dependent on caspase-1 or RIP3 [140]. CD95 activation is known to play pathogenic roles in many inflammatory and autoimmune disorders, however whether this is directly due to CD95/caspase-8-mediated regulation of IL-1β still remains to be formally investigated. Cell death pathways that are induced by blocking the inhibitors of apoptosis proteins (IAPs) also regulate IL-1β production at least partially through caspase-8 activation. IAPs (namely XIAP, cIAP1 and cIAP2) are a family of molecules that limit the formation of the cell death inducing "ripoptosome" complex (RIP1-FADD-caspase-8-cFLIP) [141, 142]. Treatment of cells with the smac-mimetic compound A inhibits IAP activity and results in RIP3-mediated ROS production. This Smac-mimetic induced mitochondrial ROS production has been suggested to provoke both caspase-1- and caspase-8-mediated IL-1β secretion in a recent study [143]. However, a separate study arrived at opposite conclusions and found that deficiency in either cIAP1 or cIAP2 results in impaired in caspase-1 activation [144]. Further studies are thus required to ascertain the exact role(s) of IAPs in the regulation of IL-1.

Caspase-8 was also recently implicated in IL-1β secretion that can result in response to treatment with chemotherapeutic drugs such as doxorubicin (Dox) or staurosporine (STS) [145]. Many chemotherapeutic drugs rely on their ability to promote apoptosis in tumorigenic cells to limit the spread of cancer. However, proapoptotic chemotherapeutic drugs, such as Dox and STS, have also been reported to incite IL-1 production by immune cells. This induction of IL-1β maturation in response to proapoptotic chemotherapeutic drugs was found to specifically require caspase-8 activation. Furthermore, it appears that caspase-8-triggered IL-1β processing proceeds independently of a role for caspase-1 or caspase-11, as it was shown that Dox and STS treatment of *Casp1*$^{-/-}$*Casp11*$^{-/-}$ dendritic cells results in secretion of IL-1β at levels that were comparable to WT cells. In addition to helping to illuminate how proapoptotic drugs influence immune responses, these findings also have great implications for the field of sterile inflammation, where apoptosis and caspase-8 activation are hallmarks of disease pathogenesis.

Consistent with these findings, caspase-8 has also been discovered to directly regulate IL-1β production during infection [146]. For example, caspase-8 has emerged as a key inducer of IL-1β maturation in response fungal infection. The importance of IL-1-dependent signaling in the generation of protective anti-fungal responses has been widely appreciated for many years, and IL-1β has been established to be required for the induction of T_H1 and T_H17-mediated clearance [147–150]. However, the mechanism responsible for IL-1β maturation during various forms of fungal infection has remained a matter of debate since caspase-1/11 has been reported to be dispensable to mount protective responses [151, 152]. Recent findings now show that dectin-1 recognition of fungi on dendritic cells promotes caspase-8-induced cleavage of IL-1β [146]. Interestingly, IL-1β secretion in response to fungal stimulation did not require caspase-1 or NLRP3 participation, but rather involved the recruitment of the MALT1-Bcl-10-Card9 scaffold into a complex with caspase-8. *Salmonella* infection was also recently demonstrated to lead to caspase-8-dependnent modulation of IL-1β production in macrophages [153]. In these studies it was found that caspase-8 could be recruited into a complex with ASC independently of caspase-1, and that

caspase-8 is an important driver of proIL-1β synthesis. Collectively these studies further demonstrate that caspase-8 can indeed functionally impinge on IL-1β secretion, however future studies are needed to evaluate the contributions of caspase-8-mediated IL-1β in the generation of effector responses and pathogen clearance.

It should also be noted that a recent study suggests that caspase-8 can also repress IL-1β secretion by blocking RIP3-mediated activation of the NLRP3 inflammasome under certain conditions. In this study, the authors found that conditional deletion of caspase-8 in dendritic cells using the CD11c-Cre deleter results in exacerbated IL-1β production and inflammatory disease in response to LPS stimulation [154]. Deletion of RIP3 or pharmacological inhibition of RIP1 was found to rescue hyperinflammatory responses in *Casp8*$^{fl/fl}$xCD11c-Cre+ mice and this was suggested to occur through RIP1/RIP3-mediated regulation of NLRP3 inflammasome activation and not by influencing cell death. It is clear from recent studies that caspase-8 is indeed a central regulator of IL-1β maturation, however additional studies are needed to further characterize the molecular underpinnings of caspase-8-regulated IL-1β production. Such future investigation should help reconcile how under certain conditions caspase-8 promotes IL-1β secretion, whereas in other situations it has been suggested to block IL-1β production.

Inflammasome-independent sources of IL-1β

Although caspase-mediated processing of IL-1β is the most widely characterized mechanism of IL-1-mediated inflammation and disease, emerging data also suggest pivotal roles for inflammasome-independent IL-1β in autoimmune and inflammatory disease pathogenesis. Indeed, caspase-1/11-independent IL-1β has been described to play crucial roles in osteomyelitis [38, 39], particulate-induced lung inflammation [155], osteoarthritis [156, 157], acidosis-provoked inflammation [158], host defense against certain pathogens [146, 159], and other inflammatory diseases [160]. Moreover, genetic deletion of caspase-1/11 does not lead to complete abrogation of IL-1β production or disease progression in numerous IL-1-dependent disease models [111, 115, 117, 152, 160, 161], suggesting that inflammasome-independent sources of IL-1β can also potentiate disease pathology in some settings. A number of additional serine proteases including cathepsin B, cathepsin C, cathepsin G, proteinase-3 (PR3), elastase, granzyme-A, chymase, matrix metalloproteinase 9, and chymotrypsin have also been shown to cleave proIL-1β under *in vitro* conditions [19, 162–167]. The molecular mechanisms that orchestrate the activation of IL-1β by these proteases are just beginning to be elucidated under physiological settings and not much is currently known. Furthermore, whether these serine proteases contribute to IL-1β secretion and subsequent inflammatory disease *in vivo* is just beginning to be elucidated.

Recently, it was shown that inflammasome-independent IL-1β production is responsible for driving inflammatory bone destruction in a mouse model of osteomyelitis [38, 39]. In these studies, it was discovered that IL-1 signaling and IL-1β production were required to spur this osteoimmunological disorder; however, genetic abrogation of critical inflammasome components including caspase-1/11, ASC and NLRP3 did not rescue aberrant IL-1β production or osteolytic disease. These studies suggest that inflammasome-autonomous IL-1 signaling contributes to osteomyelitis, however future studies are needed to formally

identify the alternative protease that is responsible for driving excessive IL-1β processing during this disease.

IL-1β-dependent responses to necrotic cells and silica crystals have also been found to occur largely in the absence of inflammasomes [7, 160]. Although silica-induced IL-1β production by macrophages, neutrophils and mast cells appears to require inflammasome activation under *in vitro* conditions, treatment of caspase-1/11 doubly deficient mice with either silica crystals or necrotic cells still results in substantial peritonitis. It was found that cathepsin C uniquely regulates inflammasome-independent IL-1β production in these settings, and genetic deletion of cathepsin C was found to markedly diminish myeloid cell recruitment and IL-1β levels in the peritoneal cavity of mice that received silica crystals or necrotic cells [160]. Cathepsin C is known to control the downstream activation of cathepsin G, elastase and proteinase-3 by removing two inhibitory amino acids from the N terminus of these zymogens [164, 166]. Thus, the exact nature of the serine protease that promotes IL-1β generation in response to necrotic cells and silica crystal still requires formal identification. It is possible that there may be functional redundancy between the specific proteases and that combined deletion is required to have a biological effect. Regardless, these findings highlight prominent roles for inflammasome-independent IL-1β production during responses to tissue damage and crystalline particulates. Furthermore, they also underscore the important point that *in vitro* settings do not always completely recapitulate the complexity of *in vivo* IL-1 regulation, and thus it is imperative to characterize IL-1 processing in physiological settings.

Caspase-1/11-independent IL-1β production has also been described to drive joint inflammation and disease in two separate models of arthritis [156, 157]. In the K/BxN serum transfer model of arthritis, it was shown that inflammatory joint destruction is dependent on IL-1 signaling. However, genetic deletion of caspase-1/11 in mice did not provide significant protection against joint destruction and caspase-1/11 deficient neutrophils and mast cells were found to secrete potent amounts of IL-1β even in the absence of inflammasomes. Instead, pharmacological inhibition of elastase and chymase were discovered to dampen aberrant IL-1β production and to limit the development of arthritis [157]. Inflammasome-independent IL-1β production has also been suggested to centrally promote disease in the streptococcal cell wall (SCW)-induced model of arthritis. In this study it was shown that wild-type and caspase-1 deficient mice develop inflammatory joint swelling to a similar extent in the SCW-arthritis model, and that genetic and pharmacological inhibition of the neutrophil serine protease PR3 is capable of attenuating IL-1β-mediated inflammation [156]. Collectively these studies indicate that IL-1β production by neutrophils and mast cells is not exclusively dependent on inflammasome activation, and that additional serine proteases can promote IL-1β-mediated inflammatory disease by processing proIL-1β.

Concluding Remarks

Infection and cellular injury are the two principal stimuli that provoke inflammatory disease. Much attention in recent years has been paid to define the receptors and signaling pathways that are responsible for pathogen recognition and subsequent inflammatory immune

responses. In comparison, less is known about the molecular pathways that regulate sterile inflammatory responses. Sterile inflammation that results from aberrant cell death plays pivotal roles in the pathogenesis of numerous acute and chronic inflammatory diseases including atherosclerosis, multiple sclerosis, type 2 diabetes, myocardial infarction, arthritis, and multiple neurodegenerative diseases. Non-communicable chronic diseases that are potentiated by sterile inflammation have recently surpassed infectious diseases as the leading cause of worldwide morbidity and mortality. Thus, improved understanding of the sterile inflammatory process has emerged as one of the most important areas of biomedical investigation.

The identification of the central role of IL-1 signaling in inflammatory disease progression and the discovery of the specific danger signals that trigger IL-1-mediated inflammation has provided an important foundation in our understanding of the etiology of many human diseases. Although caspase-1 activation in canonical inflammasomes is the most well established mechanism for IL-1 production in many disease settings, recent studies now clearly demonstrate critical roles for additional pathways in IL-1-medated inflammation. For instance, aberrant IL-1α release that occurs in the absence of caspase-1/11 has been shown to specifically cause inflammation and tissue destruction in multiple disease models. Mounting evidence also suggests that IL-1β secretion is not solely dependent on caspase-1, and new regulators of IL-1β processing including caspase-8, caspase-11 and cathepsins have recently been described. Continued identification of novel pathways that contribute to non-canonical inflammasome activation and the discovery of additional mechanisms that contribute to inflammasome-independent IL-1 production will undoubtedly aid in the discovery of novel therapeutics to treat autoimmune and inflammatory disease.

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Abbreviations

IL	interleukin
PAMPs	pathogen-associated molecular patterns
DAMPs	danger-associated molecular patterns
IL-1R	IL-1 receptor
NLR	NOD-like receptor
ALR	AIM2-like receptor
TLR	Toll-like receptor
CNS	central nervous system

EAE	experimental autoimmune encephalomyelitis
ALS	amyotrophic lateral sclerosis
Tregs	regulatory T cells
IAPP	islet amyloid polypeptide
SLE	systemic lupus erythematosus
RIP	receptor-interacting protein
FADD	FAS-associated death domain
TNFR1	TNF receptor 1
IAPs	inhibitors of apoptosis proteins
COPD	chronic obstructive pulmonary disease
ER	endoplasmic reticulum

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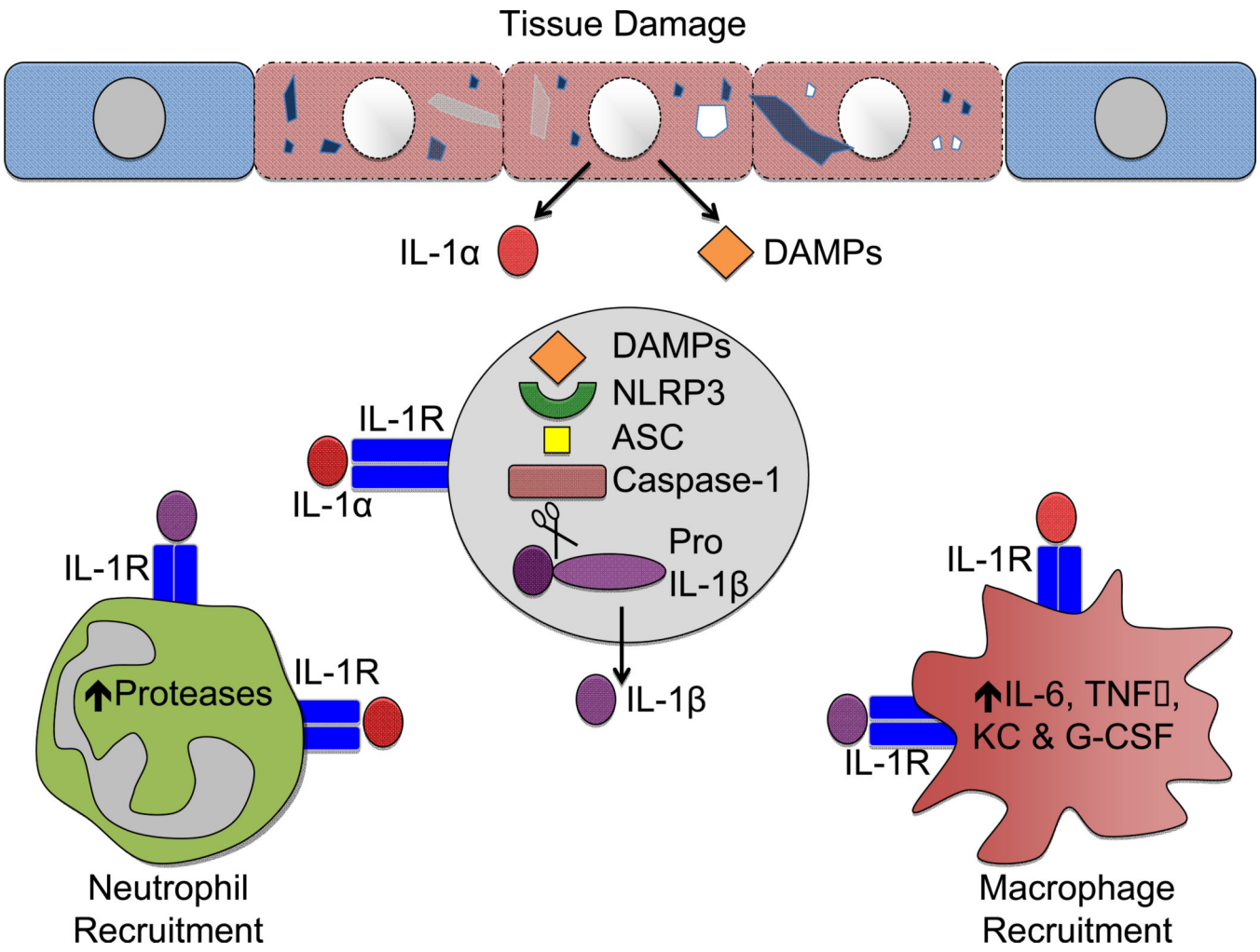

Figure 1. IL-1 signaling centrally regulates sterile inflammation

Cell death that results from trauma, ischemia, environmental irritants and cellular stress provokes the recruitment and activation of immune cells in areas of tissue damage. Inflammatory forms of cell death that ensue as a result of these triggers provoke the release of IL-1α and danger-associated molecular patterns (DAMPs). DAMPs such as ATP, uric acid, and damaged mitochondria are recognized by the cytosolic sensor NLRP3 in surrounding cells and this initiates the recruitment of NLRP3, the adaptor protein ASC and caspase-1 into multiprotein complexes that are referred to as inflammasomes. Formation of inflammasome molecular platforms triggers self-cleavage and activation of caspase-1. Active caspase-1 subsequently cleaves the pro-forms of IL-1β and IL-18, which is required for their secretion and biological activity. This is in contrast to IL-1α, which does not require processing to elicit its inflammatory activity. Both IL-1α and mature IL-1β induce potent proinflammatory singling following engagement of the IL-1 receptor (IL-1R). IL-1-dependent signaling promotes the up-regulation of additional inflammatory cytokines such as IL-6, TNFα, KC and G-CSF in macrophages and neutrophils. The release of these inflammatory mediators helps to promote the removal of cellular debris and to instruct the recruitment of additional immune cells to damaged tissue. IL-1 also triggers the expression

of proteases and growth factors, which are needed to restore tissue integrity in the damaged areas. Inflammatory responses that are mounted in response to aberrant cell death are required to restrain the insult, phagocytize damaged cells, and to promote wound healing. However, excessive or sustained sterile inflammation can adversely cause fibrosis and tissue destruction. As a result, immune responses that ensue in response to tissue damage are directly responsible for driving the inflammation and pathology that cause inflammatory and autoimmune disease.

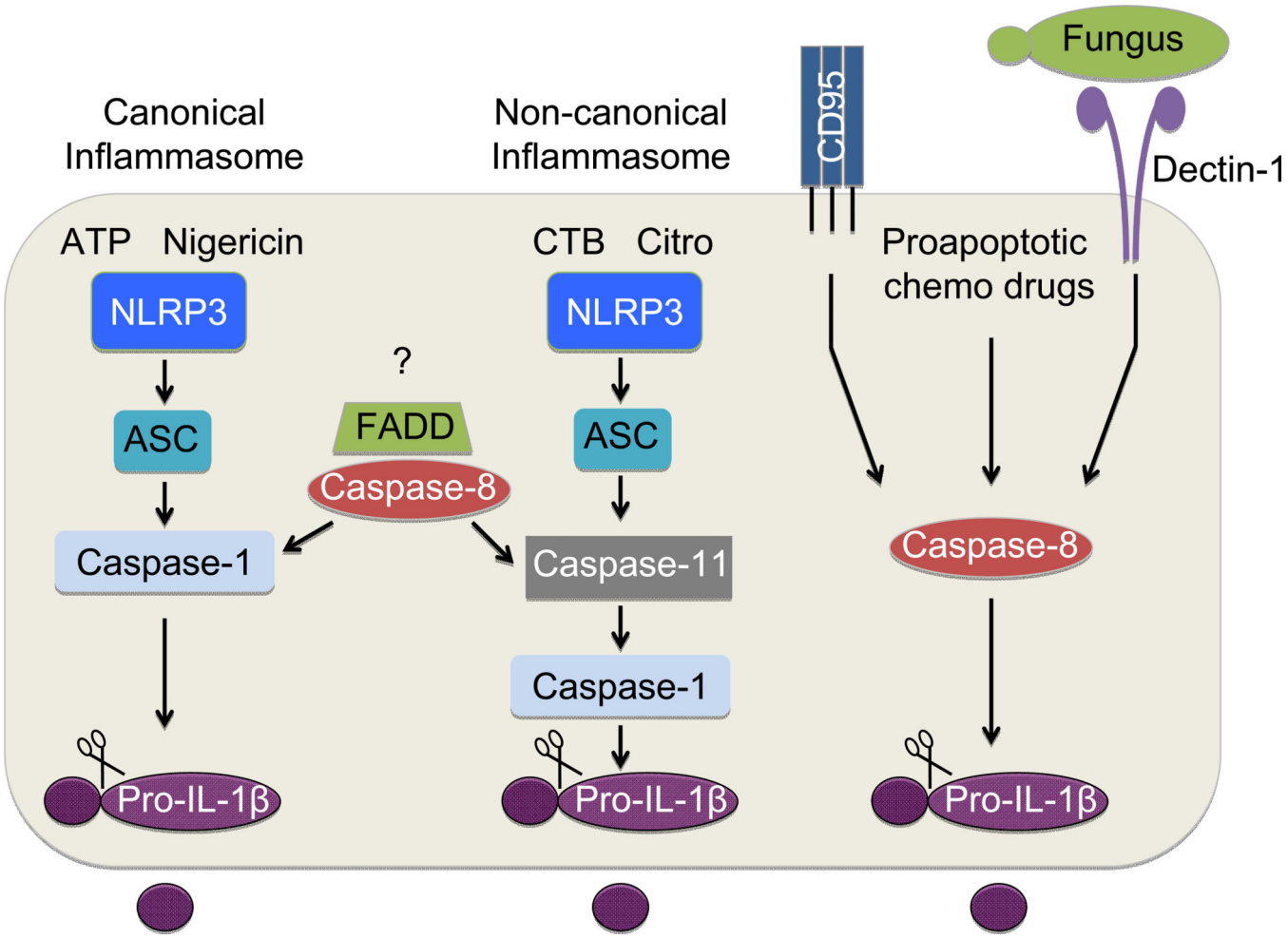

Figure 2. Pathways involved in caspase-mediated IL-1β maturation

IL-1β requires cleavage to elicit its biological activity and to promote its secretion. Multiple caspase-dependent pathways have been identified to promote IL-1β maturation. The best characterized of these pathways involves caspase-1 activation in inflammasome complexes. Recognition of pathogen- or danger-associated molecular patterns (PAMPs and DAMPs, respectively) by NOD-like receptors (NLRs) or AIM2-like receptors (ALRs) promotes the recruitment of caspase-1 into a multiprotein complex with the help of the adaptor protein ASC. Inflammasome complex formation orchestrates the self-cleavage and activation of caspase-1. Active caspase-1 subsequently cleaves the pro-form of IL-1β. Inflammasomes were originally thought to only require participation from a cytosolic sensor molecule, the adaptor protein ASC and caspase-1. However recent studies suggest that additional caspases and signaling molecules can directly impinge on pathways that coordinate IL-1β maturation. For instance, caspase-11 is required for efficient downstream caspase-1 and IL-1β activation in complexes that are now referred to as non-canonical inflammasomes. Caspase-11 is essential for inflammasome-induced IL-1β production in response to cholera toxin B and *citrobacter rodentium*. In contrast, other activators of inflammasome-dependent IL-1β maturation such as ATP and nigericin can trigger IL-1β cleavage via canonical inflammasomes in a fashion that is NLR/ASC/caspase-1 dependent and caspase-11

independent. The traditional cell death molecules, caspase-8 and FADD, have also been established to play major regulatory roles in both canonical and non-canonical inflammasome activation. However the upstream regulators of FADD and caspase-8 in these pathways still remain to be identified. Caspase-8 can also cleave IL-1β independently of caspase-1/11, and this has been suggested to contribute to IL-1β production that occurs in response to engagement of the death receptor CD95 (also known as FAS), fungal infection, and following treatment of cells with proapoptotic chemotherapeutic drugs.