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Short Review

Revisiting Caspase-11 Function in Host Defense

Tessie M. Ng[1] and Denise M. Monack[1,*]
[1]Department of Microbiology and Immunology, Stanford School of Medicine, Stanford University, 299 Campus Drive, Stanford, CA 94305, USA
*Correspondence: dmonack@stanford.edu
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Proinflammatory caspases play important roles in innate immunity. Much attention has focused on caspase-1, which acts to eliminate pathogens by obliterating their replicative niches as well as alerting the host to their presence. Now, emerging data have shed light on the lesser-studied proinflammatory caspase-11 in the combat between host and pathogens. Using the new tools available, researchers are further elucidating the mechanisms by which caspase-11 contributes to host defense. Here, we review the emerging understanding of caspase-11 functions and the mechanisms of activation and discuss the implications for human disease.

Paradigms of Caspase Regulation

Caspases are a family of cysteine-dependent proteases that play a major role in various aspects of host physiology, including development, homeostasis, and host defense. The proinflammatory caspases, which constitute a subset of this family of cysteine proteases, have primary functions in innate immune responses and include caspase-1, caspase-11 (also referred to as murine *ich-3* and, in humans, caspase-4 and caspase-5, as discussed later in this review), and caspase-12. Upon activation, these proinflammatory caspases cleave unidentified substrates to induce pore formation in host cell membranes and a specialized form of cell death called pyroptosis (Bergsbaken et al., 2009). Importantly, pyroptotic cell death is distinct from apoptosis, which activates a completely different set of caspases to induce a noninflammatory mode of cell death. In contrast, apoptosis is triggered by the initiator caspases; e.g., caspase-2, caspase-8, caspase-9, and caspase-10, which subsequently activate the executioner caspases: caspase-3, caspase-6, and caspase-7. Then, these executioner caspases cleave cellular proteins directly, prompting the packaging of cellular contents into membrane-bound vesicles, which are then degraded (MacKenzie and Clark, 2012).

Despite their distinct downstream consequences, caspases follow a similar protein structural organization. They are initially expressed as inactive zymogens containing a variable N-terminal prodomain linked to a conserved large and small subdomain. Caspase-1, caspase-2, caspase-4, caspase-9, and caspase-11 have particularly long prodomains that contain either death effector domains (DEDs) or caspase recruitment domains (CARDs), which are thought to confer specificity of activation, given that they mediate interactions with other DED- and CARD-containing adaptor proteins. Association with these adaptor proteins most likely nucleates caspases, increasing their local concentration. This nucleation can favor activation through dimerization, which has been reported for the initiator caspases (Chang et al., 2003; Yang et al., 1998). Upon activation, autoproteolytic cleavage of the prodomain and the linker region between the large (p20) and small (p10) subdomains can occur. However, the executioner caspases must be cleaved directly by the initiator caspases. Then, cleavage enables the formation and stabilization of the active caspase tetramer consisting of two p10 and p20 subunits (MacKenzie and Clark, 2012). It is important to note that cleavage is not absolutely necessary for inducing caspase-1-, caspase-8-, or caspase-9-dependent cell death (Boatright et al., 2003; Broz et al., 2010b). However, autoproteolytic cleavage is required for caspase-1-mediated pro-IL-1β maturation (Broz et al., 2010b). The mechanisms that direct caspase-1-mediated cell death versus cytokine maturation remain to be determined. For a more comprehensive review on the general mechanisms of caspase activation, see Boatright and Salvesen (2003).

Elucidating the mechanisms of the proinflammatory caspases is important because they are absolutely required for the clearance of some pathogens in the host. The proinflammatory caspases serve two main functions: first, these caspases induce a pyroptotic cell death that eliminates the replicative niche of intracellular pathogens, and, second, they process proinflammatory cytokines (e.g., pro-IL-1β and pro-IL-18), which, upon maturation, are released extracellularly along with danger signals (e.g., IL-1α and high-mobility group box 1 [HMGB1]) to alert the host of pathogen invasion (Franchi et al., 2012). Currently, it is unclear whether the release of these cytokines and danger signals is a direct result of pyroptosis-mediated pore formation or whether it occurs through unidentified secretory pathways (Rubartelli et al., 1990; Verhoef et al., 2005; Wewers, 2004).

Proinflammatory caspases must be tightly regulated in order to avoid aberrant activation and host tissue damage. The current model for caspase-1 activation begins upon activation of cytosolic microbial- and danger-associated molecular pattern-recognition receptors that contain CARD and pyrin domains (PYDs), including the neuronal apoptosis inhibitory proteins (NAIPs), nucleotide-binding oligomerization-like receptors (NLRs; e.g., NLRP3 and NLRC4), and the PYHIN (AIM2) families of proteins. Upon detection of their respective agonists, these receptors recruit apoptosis-associated speck-like protein (ASC) through its PYDs and CARDs. The CARD and PYD protein-interacting domains also promote the oligomerization of ASC, leading to the recruitment of caspase-1. Thus, a macromolecular complex called the inflammasome is formed (see Figure 1). Inflammasome formation is believed to provide a platform for promoting the formation and stabilization of the caspase-1 p10/p20 tetramer that is required for proinflammatory cytokine maturation (pro-IL-1β and pro-IL-18). Then, the mature forms of caspase-1

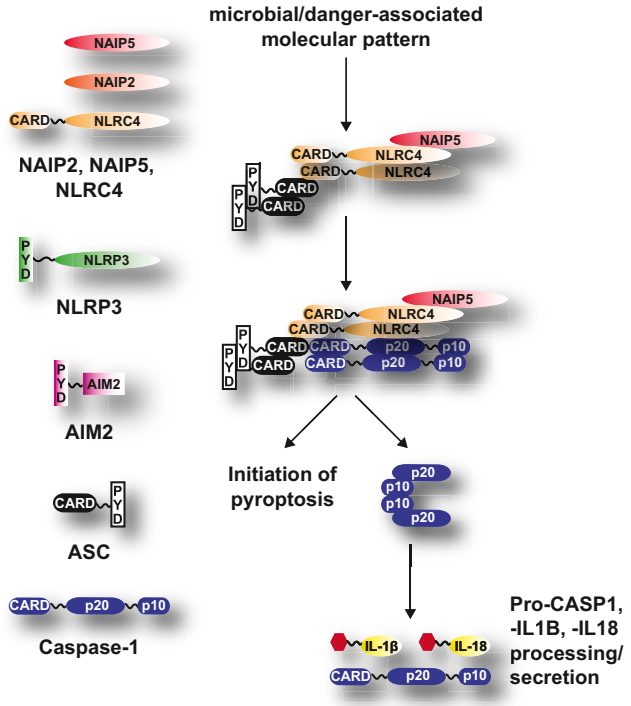

Figure 1. Model for Caspase-1 Activation

Different cytosolic receptors are engaged upon the detection of microbial- and danger-associated molecular patterns. Then, ASC associates with these receptors through its PYDs and CARDs. Recruitment of caspase-1 leads to the formation of the inflammasome. Caspase-1 is activated for the induction of pyroptosis. Further autoproteolytic cleavage of caspase-1 leads to the formation of the catalytic tetramer required for the maturation of other caspase-1 proteins as well as proinflammatory cytokines; e.g., pro-IL-1β and pro-IL-18.

and the cytokines are released outside of the cell in order to engage a systemic inflammatory response (Franchi et al., 2012).

Caspase-11 Contributes to Host Inflammatory Responses

Although most of the work on proinflammatory caspases has focused on caspase-1, recently, caspase-11 has taken center stage. This has stemmed from the availability of mice that are specifically deficient for either *Casp1* or *Casp11* (Kayagaki et al., 2011). Previous studies were performed with mice deficient for both *Casp1* and *Casp11* because the embryonic stem cells used to generate the original *Casp1*$^{-/-}$ mouse strains were isolated from the murine 129 strain that contains a naturally occurring 5 bp deletion within the *Casp11* locus (Kayagaki et al., 2011). Recombination and segregation of the nonfunctional *Casp11* gene away from the *Casp1*$^{-/-}$ locus is nearly impossible, given that *Casp1* and *Casp11* occur only ~1,500 bp apart on chromosome 9 in mice. Now, researchers are actively examining whether the lack of caspase-11 has contributed to any of the previously reported *Casp1*$^{-/-}$ phenotypes.

Caspase-11 was identified almost 17 years ago in a mouse complementary DNA library screen for homologs of human caspase-1, though the mechanisms of caspase-11 in the host response to pathogen invasion remain poorly understood (Wang et al., 1996). Initial characterization of caspase-11 in CV-1 and SV40 (COS) and immortalized embryonic fibroblast cells demonstrated that it plays a direct role in cell death and enhances pro-IL-1β processing in the presence of caspase-1 (Wang et al., 1996; Wang et al., 1998). Additionally, Wang et al. (1996) observed bacterial lipopolysaccharide (LPS) stimulation of caspase-11 expression in several mouse tissues, particularly in the spleen. However, researchers did not observe LPS-stimulated *Casp11* expression in the previous murine 129 *Casp1*$^{-/-}$ mice (detailed above), halting additional studies aimed at elucidating any potential crosstalk between the two proinflammatory caspases. Instead, studies focused on dissecting the independent role of caspase-11 with an LPS-induced septic shock model, given that *Casp11*$^{-/-}$ mice are more resistant to lethal doses of LPS in comparison to wild-type (WT) mice (Wang et al., 1996; Wang et al., 1998). Upon administration of a lethal dose of LPS, caspase-11 activation promotes caspase-3 activity independently of caspase-1 (Kang et al., 2002). However, *Casp3*$^{-/-}$ mice exhibit an LPS-induced mortality that is indistinguishable from that of WT mice. In addition, *Il1b*$^{-/-}$/*Il18*$^{-/-}$ mice are also susceptible to lethal doses of LPS, whereas *Nlrp3*$^{-/-}$ and *Asc*$^{-/-}$ mice are more resistant in comparison to WT mice. This suggests that, although NLRP3 and ASC can engage CASP1 to process pro-IL-1β and pro-IL-18, these cytokines are dispensable in the LPS-induced septic shock model (Lamkanfi et al., 2010; Mariathasan et al., 2004; Mariathasan et al., 2006). Interestingly, the administration of neutralizing antibodies against the HMGB1 alarmin enhances survival in the LPS-induced septic shock model (Lamkanfi et al., 2010). Altogether, these studies suggest that LPS-induced mortality is predominantly due to caspase-11-dependent pyroptotic release of HMGB1 and potentially other sepsis mediators.

More recently, several research groups have examined how caspase-11 contributes to host defenses against pathogen invasion. A variety of known inflammasome activators were added to LPS-primed and -unprimed bone-marrow-derived macrophages (BMDMs), which led to the identification of a specific subset of NLRP3-engaging stimuli that also activate caspase-11-dependent cell death and IL-1β secretion, including cholera toxin B and several Gram-negative bacteria, such as *Escherichia coli*, *Citrobacter rodentium*, *Salmonella typhimurium*, and *Legionella pneumophila* (Aachoui et al., 2013; Broz et al., 2012; Case et al., 2013; Kayagaki et al., 2011; Rathinam et al., 2012). Strikingly, caspase-11-dependent pyroptosis occurs independently of the known inflammasome mediators NLRC4, NLRP3, and ASC (Aachoui et al., 2013; Broz et al., 2012; Case et al., 2013; Kayagaki et al., 2011). This is particularly notable because caspase-1-mediated cell death, in contrast, requires at least one adaptor protein in order to initiate cell death (e.g., NLRC4 and AIM2/ASC) (Broz et al., 2010b). Also, caspase-11 is required for the release of the alarmins IL-1α and HMGB1 (Kayagaki et al., 2011). However, this may not be surprising given that these alarmins do not contain signal peptides and their release from cells appears to be correlated to the loss of cell membrane integrity irrespective of whether caspase-1 or caspase-11 are activated (Lamkanfi et al., 2010; Watanabe and Kobayashi, 1994).

In contrast to cell death, the role of caspase-11 in pro-IL-18 and pro-IL-1β maturation is dependent on NLRP3/ASC/CASP1

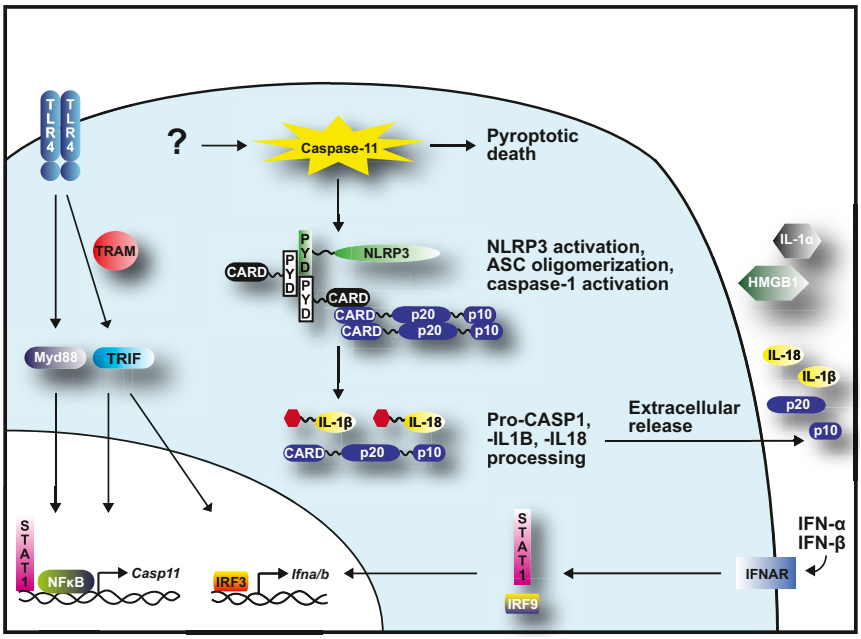

Figure 2. Caspase-11-Activating Pathways
LPS engagement of TLR4 activates Myd88, TRAM, and TRIF signaling pathways that contribute to the transcriptional upregulation of *Casp11* and *Ifna/b*. IFN-α and IFN-β can engage IFNAR, activating signaling pathways that also lead to *Casp11* transcription. Once activated in the cytosol, caspase-11 initiates pyroptosis. Engagement of NLRP3 and ASC promotes caspase-1 inflammasome activity, which leads to the maturation of procaspase-1, pro-IL-1β, and pro-IL-18. This figure was modified from Ng et al. (2013).

inflammasomes. First, upon infection with *S. typhimurium*, the level of pro-IL-1β maturation in BMDMs is reduced in the absence of caspase-11 and completely abrogated in the absence of caspase-1 (Broz et al., 2012). Second, *Casp1*$^{-/-}$ and *Casp11*$^{-/-}$ BMDMs stimulated with LPS in addition to either cholera toxin B or *E. coli* failed to secrete mature IL-1β (Kayagaki et al., 2011). Altogether, it is likely that caspase-11 promotes caspase-1-mediated responses by engaging NLRP3/ASC inflammasomes. Furthermore, upon exposure of BMDMs to stimuli that engage both NLRP3 and NAIP/NLRC4, NAIP/NLRC4/CASP1 inflammasome responses dominate. As a result, caspase-11-dependent cell death and IL-1β secretion can only be detected in vitro in the absence of a NAIP/NLRC4 stimulus; e.g., flagellin (Aachoui et al., 2013; Broz et al., 2012; Case et al., 2013). Thus, it is plausible that caspase-11 functions as a backup measure for macrophages to ensure that cell death and cytokine maturation is initiated, particularly when potent caspase-1 activation and stimulation are abrogated or dampened, which is an immune evasive tactic engaged by many pathogens (Taxman et al., 2010).

Signaling Pathways in Caspase-11 Activation

Recent studies focusing on mechanisms of caspase-11 activation have shed light on the signaling pathways involved. Consistent with previous findings, caspase-11 expression is induced upon TLR4 recognition of LPS (Wang et al., 1996). TLR4 recruits Toll/interleukin 1 (TIR)-domain-containing adaptor-inducing IFN-β (TRIF) and the TRIF-related adaptor molecule (TRAM), resulting in the activation of interferon regulatory transcription factor 3 (IRF3), which leads to type I interferon, IFN-α, and IFN-β, expression (Broz et al., 2012; Gurung et al., 2012; Rathinam et al., 2012). The TLR adaptor Myd88 also appears to contribute to this in some cases (Broz et al., 2012; Case et al., 2013). Then, autocrine or paracrine engagement of interferon-α and interferon-β receptor (IFNAR) stimulates STAT1 and IRF9 signaling pathways, which also contribute to the upregulation of *Casp11* expression and activation (see Figure 2) (Broz et al., 2012; Rathinam et al., 2012).

Although the signaling pathways involved in inducing *Casp11* expression are clear, there are some differences between the proposed models for its activation and function. First, although it is accepted that IFN-β stimulation is necessary for caspase-11-mediated cell death, there is some dispute as to whether this stimulation alone is sufficient (Broz et al., 2012; Rathinam et al., 2012). LPS, IFN-β, and IFN-γ are all certainly capable of inducing *Casp11* expression, given that the *Casp11* promoter contains consensus binding sites for both NFκB and STAT1 transcription factors that are downstream of the Myd88, TRIF, and IFNAR signaling pathways (Schauvliege et al., 2002). Consistent with this, Rathinam et al. (2012) report that the exogenous addition of these stimuli to immortalized BMDMs induces *Casp11* gene expression, and this expression is sufficient for activation, given that exposure to IFN-β and IFN-γ alone leads to caspase-11-dependent cell death. In contrast, Broz et al. (2012) demonstrated that caspase-11-dependent cell death can only occur upon stimulation with IFN-β in conjunction with *S. typhimurium* infection in primary BMDMs. However, this distinction may be attributed to the use of immortalized macrophages, which contain replication-proficient retroviruses used in the immortalization process (data not shown). Still, the issue of sufficiency has broader implications for our understanding of caspase regulation and begs the question of whether a single extrinsic signal can directly induce caspase-mediated cell death or whether cells employ a two-signal model in order to safeguard against unintentional caspase activation.

The second inconsistency centers on whether caspase-11 is required for ASC oligomerization and, thus, for NLRP3/ASC inflammasome assembly. Immunofluorescent microscopy studies have shown that, upon *S. typhimurium* infection of primary BMDMs, ASC oligomerization (through the visualization of the "ASC speck") occurs first and is followed by caspase-1 and pro-IL-1β recruitment (Broz et al., 2010a). Extending this analysis, Broz et al. (2012) recently demonstrated that caspase-11 is required for ASC speck formation in NLRP3 inflammasomes, thus placing caspase-11 early in the sequence of the NLRP3 inflammasome assembly cascade. In contrast, Rathinam et al. (2012) conclude that caspase-11 is not required for ASC

oligomerization upon NLRP3 activation in immortalized BMDMs by using a biochemical assay to measure ASC dimer and oligomer formation. The authors suggest an alternative model in which caspase-1 activation is enhanced through heterodimerization with caspase-11 (Rathinam et al., 2012). It is important to note that the nature of these two assays are starkly different, given that immunofluorescent microscopy examines the spatial organization of proteins within intact cells as opposed to molecular assemblies of proteins isolated from whole-cell lysates. Although both conclusions are consistent with the reported functions of caspase-11 in promoting caspase-1-mediated cell death and pro-IL-1β maturation, they have disparate ramifications on our understanding of NLRP3 inflammasome assembly and function (Case et al., 2013; Kayagaki et al., 2011; Wang et al., 1996; Wang et al., 1998). Thus, additional investigation will be required in order to distinguish between these two models.

What Is the Caspase-11 Activator?

If caspase-11 activation operates on a two-signal model, then the nature of the second signal remains elusive. Interestingly, a recent report demonstrates that the escape of mutant *Legionella* or *Salmonella* from endosomal vacuoles upon the infection of LPS-primed BMDMs specifically triggers caspase-11-dependent cell death and IL-1β secretion, whereas the WT bacteria that remain within vacuoles do not. Although the impact of the absence of these bacterial effectors on host defense is unclear, infection with WT *Burkholderia* exhibited similar phenotypes. Altogether, the authors propose that vacuolar lysis might be a potential source of the second signal (Aachoui et al., 2013). Consistent with this, the endosomal enzyme cathepsin B was previously isolated from lysosomal fractions of murine liver lysates and shown to induce caspase-11 processing and activation (Schotte et al., 1998).

However, the vacuolar lysis hypothesis contradicts two observations. First, many of the other Gram-negative bacteria implicated in caspase-11 activation (*E. coli*, *C. rodentium*, and *S. typhimurium*) do not induce vacuolar lysis (Broz et al., 2012; Kayagaki et al., 2011). Second, the Gram-negative *Francisella tularensis*, which escapes phagosomes in order to replicate in the cytosol of host cells, does not appear to induce caspase-11-dependent IL-1β secretion upon the infection of BMDMs (Kayagaki et al., 2011). Although *F. tularensis* normally engages TLR2, the prestimulation of BMDMs with LPS should have been sufficient for inducing the expression of *Casp11*, which is the first signal for caspase-11 function. It is possible that caspase-11-dependent responses could not be detected during *F. tularensis* infection because of concomitant AIM2/CASP1 inflammasome activation, which may dominate caspase-11 responses in a manner similar to that observed with NAIP/NLRC4/CASP1 inflammasomes (Broz et al., 2012; Case et al., 2013). Considering this, it would be interesting to determine whether the infection of LPS-stimulated BMDMs with *Listeria monocytogenes*, a Gram-positive bacterium that escapes the phagosome, can activate caspase-11. This experiment would not only test the vacuolar lysis hypothesis but would also provide a clue to another possible signal for caspase-11 activation. Intriguingly, in the context of bacterial infections, caspase-11 activation has only been observed in BMDMs infected specifically with Gram-negative bacteria (Aachoui et al., 2013; Broz et al., 2012; Case et al., 2013; Kayagaki et al., 2011; Rathinam et al., 2012). The notion that caspase-11 activation may be due to some component of Gram-negative bacteria is also consistent with a previous report in which caspase-11 did not contribute to the host defense against *L. monocytogenes* (Mueller et al., 2002).

Various toxins have also been tested for caspase-11-activating functions in BMDMs prestimulated with LPS. To date, the only known caspase-11-activating toxin is cholera toxin B (Kayagaki et al., 2011). Although cholera toxin B does not induce endosomal lysis, it reaches the host cytosol by associating with the ganglioside receptor GM1, enabling trafficking from the plasma membrane to the trans-Golgi and endoplasmic reticulum (ER) before retro-translocating across the ER membrane (Reig and van der Goot, 2006). Two other toxins have been tested for the ability to activate caspase-11: the adenylate cyclase and listerolysin O, which, despite their pore-forming capabilities, do not activate caspase-11 (Kayagaki et al., 2011). However, the different modes of action of cholera toxin B, adenylate cyclase, and listerolysin O may provide a hint into the mechanism of caspase-11 activation. Adenylate cyclase penetrates directly through the plasma membrane and, thus, does not involve endosomal acidification (Reig and van der Goot, 2006). In contrast, listerolysin O induces pore formation in vacuolar membranes upon pH reduction. Altogether, these results suggest that the caspase-11 activator may involve a component of membrane trafficking that is disrupted during pathogen invasion rather than vacuolar lysis itself. Furthermore, differences in *S. typhimurium*- and *L. pneumophila*-mediated membrane trafficking may explain why caspase-11 induces cell death within 4 hr of *L. pneumophila* infection in comparison to 8 hr with *S. typhimurium* (Haraga et al., 2008; Hubber and Roy, 2010).

Cell-Death-Independent Functions of Caspase-11

In addition to inducing cell death, caspase-11 has also been implicated in modulating actin dynamics and cell migration (Li et al., 2007). Caspase-11 cooperatively interacts with actin-interacting protein (Aip1) in order to activate cofilin-dependent actin depolymerization, leading to increased splenocyte migration (Li et al., 2007). Caspase-11-mediated actin depolymerization appears to be independent of its enzymatic activity (Li et al., 2007). Thus, LPS, IFN-α, IFN-β, and IFN-γ stimulation of caspase-11 expression may be sufficient for increasing cell migration toward chemokines released at the site of infection as part of the defense against pathogen invasion. Reports of caspase-11 promoting *L. pneumophila* trafficking to the lysosome within BMDMs may also be due to the modulation of actin dynamics (Akhter et al., 2012; Santic et al., 2005). However, it is not clear if these observations can be attributed to the concomitant activation of cell death, given that *L. pneumophila* trafficking in *Casp11-C254G* enzymatic mutant BMDMs was not examined (Akhter et al., 2012). The authors also conclude that caspase-11 is required for cofilin phosphorylation. It is possible that cells induce a compensatory response in order to modulate cofilin levels and cofilin phosphorylation states in order to maintain active actin dynamics (Li et al., 2007).

Caspase-11 Function in Humans

Understanding the mechanisms of caspase-11 activation is critical, particularly given its role in regulating NLRP3, a central

player in many inflammatory diseases in humans (McIlwain et al., 2013). There are two possible human homologs of murine caspase-11: caspase-4 and caspase-5. Murine CASP11 exhibits 60% and 55% identity with human CASP4 and CASP5, respectively. The prodomains of CASP4 and CASP5 exhibit 84%–86% identity to the prodomain of murine CASP11, whereas the catalytic C-terminal p20 and p10 domains of the human homologs exhibit 85%–86% identity to that found in mice. Additionally, CASP4 and CASP5 share 74% identity with each other, although no functional complementation tests have been reported. Analysis of the expression levels in different tissues indicates that human *Casp4* expression is more widely distributed than *Casp5* (Lin et al., 2000). In unstimulated cells, the highest expression levels of murine *Casp11* are observed in spleens, whereas *Casp4* is highly expressed in placental and lung tissues, and *Casp5* is highly expressed in the colon (Lin et al., 2000; Wang et al., 1996). Similar to that of murine *Casp11*, the transcription of *Casp4* and *Casp5* is increased upon stimulation with LPS or IFN-γ, depending on the cell line examined (Lin et al., 2000). Moreover, interactions of both CASP4 and CASP5 with CASP1 have been reported as well as contributions to caspase-1 and pro-IL-1β maturation in vitro in several cell lines (Martinon et al., 2002; Nour et al., 2009; Sollberger et al., 2012). On the basis of these studies, it is not clear which is the functional human homolog of murine CASP11, though this may simply be a matter of tissue specificity and the expression levels therein.

Interestingly, several studies implicate a role for human caspase-4 and murine caspase-12 in ER-stress-induced cell death. These caspases undergo autoproteolytic cleavage in response to tunicamycin and thapsigargin, which inhibit N-linked glycosylation and deplete calcium stores in the ER, respectively (Hitomi et al., 2004; Nakagawa et al., 2000). Furthermore, immunostaining and immunoelectron microscopy reveal caspase-4 localization to the ER, whereas caspase-1 localization to membranes has also been reported (Hitomi et al., 2004; Nour et al., 2009; Singer et al., 1995). However, the role of murine caspase-12 in ER-stress-induced cell death is unclear because the *Casp12*$^{-/-}$ mice used in Nakagawa et al. (2000) were also generated with embryonic cells from the murine 129 strain that is deficient for caspase-11. Because the probability of recombination between the *Casp11* and *Casp12* locus is as low as that between *Casp11* and *Casp1*, the *Casp12*$^{-/-}$ mice are effectively *Casp12*$^{-/-}$ *Casp11*$^{-/-}$ double knockout mice. Finally, given that murine caspase-11 activation potentially involves ER membrane trafficking (see What Is the Caspase-11 Activator?), additional studies are necessary in order to substantiate potential links between ER membranes and caspase-4, caspase-5, and caspase-11 functions.

Concluding Remarks

Innate immune responses are the first line of defense against invasive pathogens, and, as such, the responses must be simultaneously comprehensive and potent. Although the proinflammatory caspase-11 was previously implicated in host defense, researchers did not have the tools to dissect the mechanistic details of the crosstalk between caspase-1 and caspase-11 in mice until recently. Now, emerging data point to a cascade of events during which caspase-11 promotes and corroborates caspase-1 activity through NLRP3 inflammasomes. Caspase-11 is also capable of independently inducing pyroptotic cell death. Future studies will need to be aimed at understanding the precise signals that activate caspase-11, how it synergizes with caspase-1 function, and what downstream targets lead to pyroptosis, given that direct death substrates have not been identified for either caspase-1 or caspase-11. The misregulation of caspase-1 and NLRP3 has also been implicated in cancer and several human inflammatory diseases (McIlwain et al., 2013). Thus, directing treatments aimed at modulating caspase-11-dependent NLRP3 inflammasome assembly and function may prove to be more effective for these relevant diseases.

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