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Minireview **Open Access**

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New insights in caspase-11 functions in noncanonical inflammasome signalling

Abstract: Inflammasomes are multi-protein complexes that play a crucial role in innate immunity. They are assembled by cytosolic sensors of the Nucleotide-binding domain and Leucine-rich repeat containing Receptor (NLR) and PYrin and HIN (PYHIN) domain-containing protein families upon sensing various pathogens and danger signals. Inflammasome formation culminates in caspase-1 activation, which causes the cleavage of pro-IL-1β and pro-IL-18 into active cytokines; this eventually results in the induction of an inflammatory cell death called pyroptosis. Recent data using Gram-negative bacteria suggests a role for caspase-11 not only in NLRP3 inflammasome activation but also in a caspase-1- and inflammasome-independent cell death. This novel caspase-11-dependent pathway is critical to control infection by Gram-negative bacteria and has been named the noncanonical inflammasome.

Keywords: caspase-1, cell death, cytosolic LPS, IL-1β, inflammasome

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Introduction

An efficient immune response depends on the inflammatory cascade that is orchestrated by the innate immune system. Innate immunity relies on the activity of germline-encoded Pathogen Recognition Receptors (PRRs) in surveying the extracellular and intracellular space for any signs of pathogen invasion or tissue injury. These sensors detect highly conserved motifs in pathogens, known as Pathogen Associated Molecular Patterns (PAMPs) and Danger Associated Molecular Patterns (DAMPs), which are released after cellular stress or damage. PRRs trigger different cellular signalling pathways, resulting in inflammation. Key actors in this immune surveillance are cytosolic protein complexes termed inflammasomes. Inflammasomes regulate the activity of caspase-1, which subsequently controls the production of pro-inflammatory cytokines and cell death. Although most of the research has focused on the prototype inflammatory caspase, caspase-1, recent data has highlighted major roles for caspase-11 in innate immunity through its ability to modulate inflammasome activation and cell death.

The inflammatory caspases in humans and mice

Caspases are cysteine proteases synthesized as inactive zymogens requiring proteolytic processing for activation. They can be subdivided into two groups, apoptotic caspases and inflammatory caspases [1]. Whereas apoptotic caspases are well conserved throughout evolution, inflammatory caspases are less conserved as they appear in the vertebrate lineage [2]. Inflammatory caspases play a prominent role in innate immunity. In *Homo sapiens* (*Hs*), the main inflammatory caspases consist of caspase-1, -4, and -5 (h*caspase-12* carries mutation giving rise to a non-functional enzyme), while in *Mus musculus* (*Mm*) there are caspase-1, -11 and -12 (Figure 1) [3,4]. In both species these caspases are located within the same locus, chromosome 11q22 for *Hs* and chromosome 9A1 for *Mm*. Genetic analysis suggested that human and mouse caspase-1 are orthologues whereas caspase-4 and -5 could originate from the duplication of a caspase-11-like ancient gene [5].

The major substrates of the inflammatory caspase-1 are pro-Interleukin-1β (pro-IL-1β) and pro-IL-18, two important pro-inflammatory cytokines. Inflammatory caspases are mainly initiator caspases. Like apoptotic initiator caspases, they exhibit a death fold-containing CARD prodomain (Caspase Activation and Recruitment Domain) suggesting their recruitment and activation

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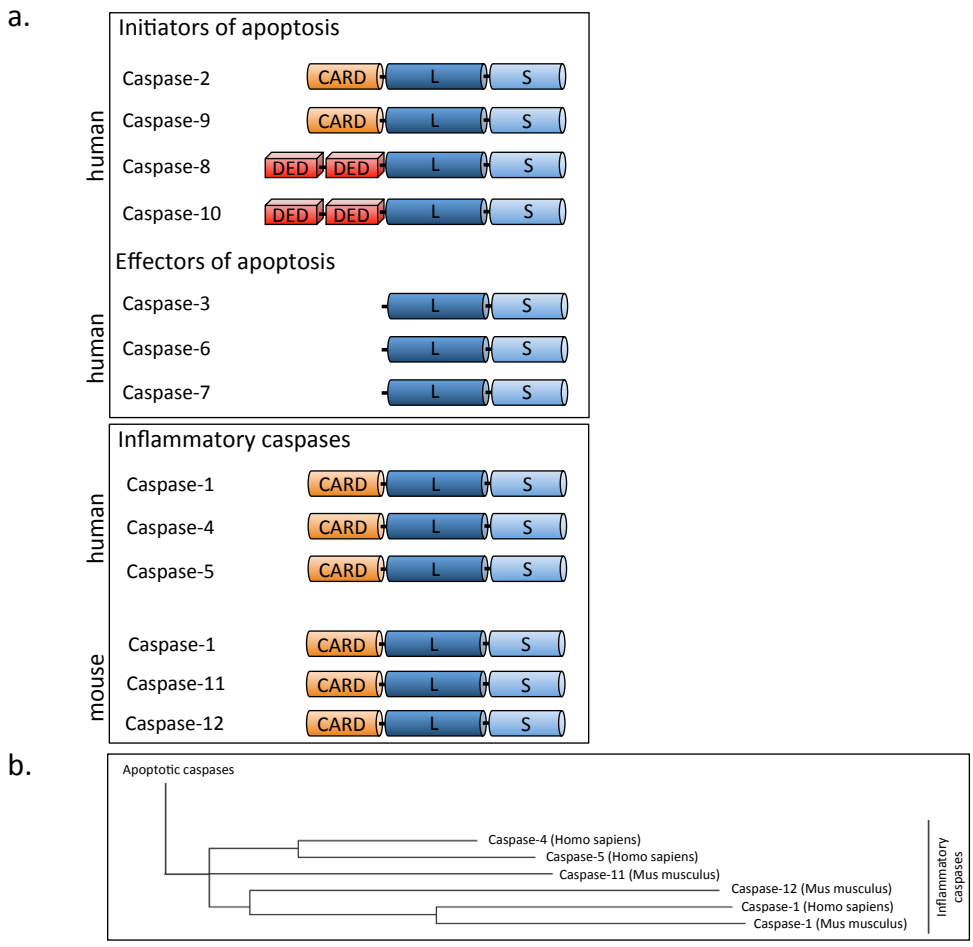

Figure 1: Overview of apoptotic and inflammatory caspases. (a) Schematic view of the structural organisation of human apoptotic and inflammatory caspases; L, large subunit, S, short subunit. CARD, Caspase Activation and Recruitment Domain, DED, Death Effector Domain. * non functional in human. (b) Phylogenic analysis of mouse and human inflammatory caspases based on full sequences.

within multiprotein complexes. Among inflammatory caspases, caspase-1 is the only member whose activation within a molecular platform, the inflammasome, has been well-documented [6]. Little is known about the modes of activation, functions, and substrates of caspase-4, -5, -11 and -12. Caspase-5 was proposed to be part of the inflammasome, but little work has corroborated this early observation [6]. Recent studies using different *caspase-12*-deficient mouse models led to conflicting observations. Although some data suggested that caspase-12 may participate in endoplasmic reticulum stress-induced apoptosis, other studies suggested it acts as a negative regulator of inflammation by impairing caspase-1 function [7,8]. Before 2011, little was known about caspase-11 function in inflammation except that it participates in the inflammatory response by controlling caspase-1 activation upon lipopolysaccharide (LPS) stimulation [9]. Since then, caspase-11 has emerged as a new focus in the inflammation field with new functions, which will be described below.

General overview of the inflammasomes

The term inflammasome was first proposed in 2002 by Martinon and Tschopp to describe a caspase-1-activating platform resulting from the assembly of a protein complex that includes the PRR NLRP1 [6]. Since then, different NLR (e.g. NLRP3, NLRC4, NLRP6, NLRP12) and PYHIN (AIM2) family members have been shown to form inflammasomes [10-15]. The human NLR family is composed of twenty-two members sharing a similar structural organisation: a N-terminal interacting domain, followed by a central Nucleotide Oligomerization Domain (NOD) and a C-terminus Leucine-Rich Repeat (LRR) motif. The LRRs behave as a

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sensing module and interact with NOD to keep the receptor in an inactive monomeric state [16,17]. Most PRRs involved in inflammasome formation contain at their N-terminus a PYD (in the case of NLRPs and AIM2) or a CARD domain (in the case of NLRC4). Once oligomerized, the scaffolding receptors recruit the adaptor protein, Apoptosis-associated Speck-like protein containing a CARD (ASC), which recruits caspase-1 molecules, resulting in a local increase in caspase-1 concentration and activation. NLRC4 contains a CARD domain that can directly interact with caspase-1 to induce cell death. However, ASC is required for efficient NLRC4-dependent caspase-1 auto-processing and IL-1β secretion [11,18-20].

Inflammasomes assemble in the cytosol in a stimulus-specific manner. The NLRP3 inflammasome is assembled in response to a plethora of pathogens, including bacteria such as *Staphylococcus aureus*, viruses such as Influenza virus, and fungi *Candida albicans* [21-23]. In addition, DAMPs such as extracellular ATP, MonoSodium Urate (MSU) and cholesterol crystals, as well as airborne pollutants, such as silica or asbestos, were shown to induce NLRP3 inflammasome activation [23-26]. The hNLRP1 inflammasome senses Muramyl Di-Peptide (MDP), while murine NLRP1b is activated by *Bacillus anthracis* lethal toxin [27,28]. NLRP12 recognizes *Yersinia pestis* bacteria, the causative agent of the plague, and NLRP6 is implicated in the maintenance of the commensal microbiota [12,13]. AIM2 senses cytosolic double-stranded DNA, while NLRC4 senses cytosolic bacterial flagellin and type III secretion system components [14,19,29,30]. After integration of activating signals, inflammasomes are involved in the activation and release of mature IL-1β and IL-18, inducing the recruitment of immune cells at the site of infection or damage. In addition, inflammasome activation can result in a caspase-1-dependent cell death called pyroptosis, crucial to pathogen clearance and characterized by cell swelling and the release of inflammatory factors such as IL-1α and IL-1β [31].

Caspase-11 and the discovery of the noncanonical inflammasome

Two key observations led to the recent breakthroughs in caspase-11 biology. First, mice genetically engineered to inactivate caspase-1 expression were also found to be deficient for caspase-11 expression [32,33]. The second observation, made by Kayagaki and Dixit, was that murine macrophages isolated from 129 strains were insensitive to Cholera Toxin B (CTB) and LPS stimulation, a treatment they demonstrated to specifically engage caspase-11 in sensitive strains such as C57BL/6. Although many research laboratories work with C57BL/6 *caspase-1* knockout (KO) colonies, the ES cells used in the past to generate knockout mice originate from 129 strains. These strains appear to carry inactivating mutations in the *caspase-11* locus resulting in the absence of caspase-11 protein. As *caspase-1* and *caspase-11* are adjacent on the mouse chromosome 9, it is unlikely that these genes could segregate by recombination upon backcrossing. Therefore, the *caspase-1* KO mice used thus far in all studies are *casp1/11* double KO [34,35].

The use of macrophages isolated from the C57BL/6 *caspase-11*- or *caspase-1/11*-deficient mice complemented with a *caspase-11* transgene (*caspase-1*$^{-/-}$*caspase-11*^{tg}) revealed that upon Gram-negative bacterial infection, caspase-11 is critical for both caspase-1 dependent cytokine maturation and caspase-1 independent pyroptosis. Upon stimulation with CTB and LPS or Gram-negative bacteria, such as *Vibrio cholera (Vc), Escherichia coli (Ec)* or *Citrobacter rodentium (Cr)*, caspase-11 activation contributes to the production of mature IL-1β and IL-18 through the NLRP3 inflammasome [32,36,37]. However, the NLRP3 inflammasome activity is not required for bacterial-mediated caspase-11 cell death associated with IL-1α, HMGB1, and LDH release (Figure 2). Furthermore, caspase-11 is not involved in inflammasome formation in response to the well-characterized NLRP3 agonists or Gram-positive bacteria. These observations led the Dixit laboratory to employ the term "noncanonical inflammasome" to designate an unknown caspase-11 activating platform that, on one hand, controls caspase-1 activation and cytokine processing, and on the other hand, induces cell death independently of caspase-1. Since then, other groups have supported and extended this concept to other Gram-negative bacterial strains such as *Salmonella typhimurium (St), Legionella pneumophila (Lp)* or *Yersinia pseudotuberculosis (Yp)* [39-42]. *St* differs from *Vc*, *Ec* and *Cr* in that IL-1β and IL-18 production (through both NLRP3 and NLRC4 inflammasomes) is only partially dependent on caspase-11.

Novel activators of caspase-11

Caspase-11 is activated by most Gram-negative bacteria as well as by the combination of CTB and LPS. Gram-negative bacteria share in common the presence of LPS on their outer membranes, a well-known ligand of the Toll-Like Receptor 4 (TLR4) [43]. Recent investigations revealed

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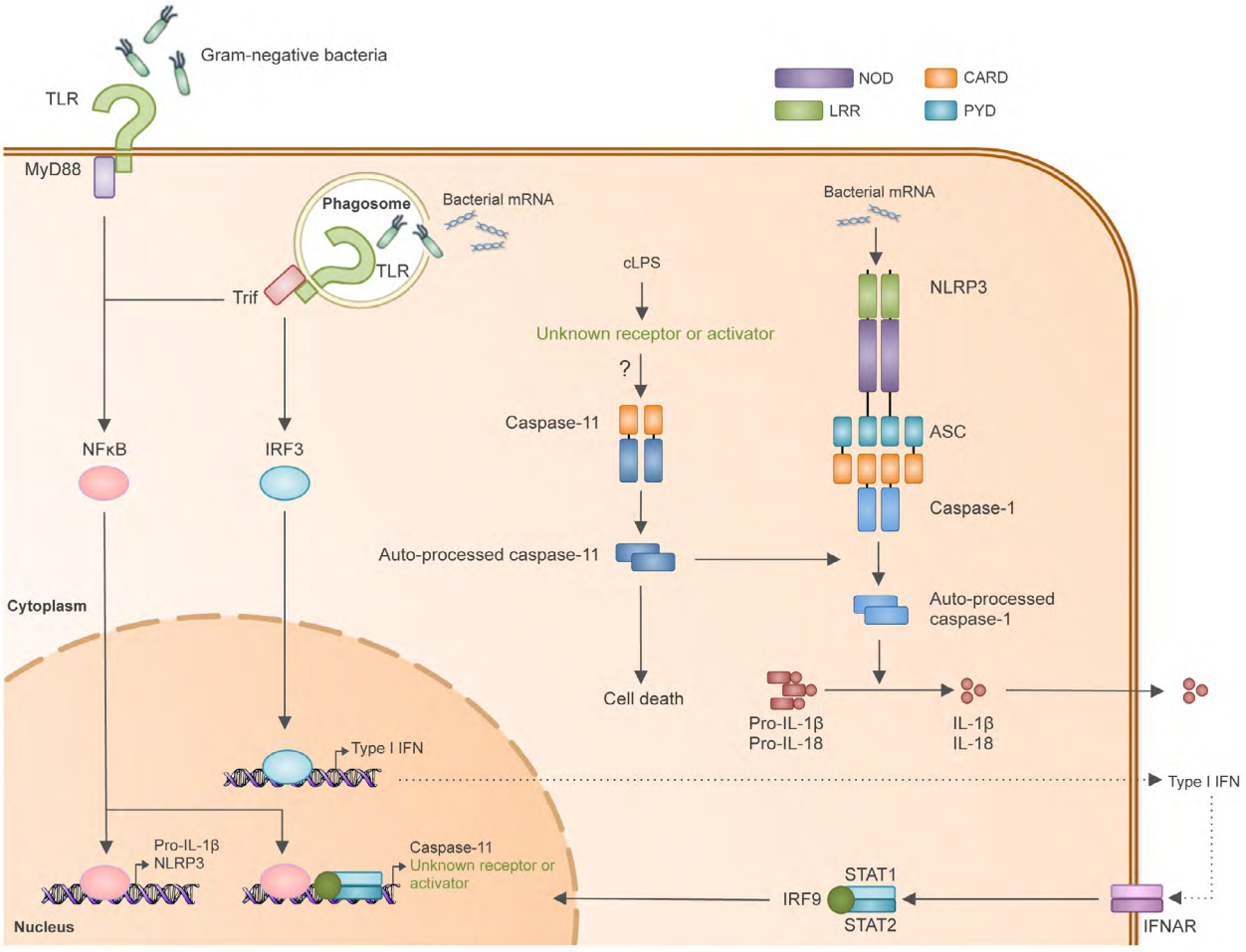

Figure 2: Pathways under caspase-11 control in response to Gram-negative bacteria. Sensing of Gram-negative bacteria by TLRs results in the activation of NFκB and IRF3 transcription factors through the TLR-adaptor proteins MyD88 and Trif. NFκB induces the transcription of pro-IL-1β, NLRP3, caspase-11 and a putative unknown receptor, whereas IRF3 transcriptional activity leads to the production of Type I IFN. Type I IFN signals through IFNAR pathway, which participates in caspase-11 production and leads to the transcription of an unknown caspase-11 activator. Detection of cytosolic LPS by a putative receptor or the production of an unknown activator leads to the processing and activation of caspase-11. Once active, caspase-11 induces cell-death associated with IL-1α and HMGB1 release; active caspase-11 also contributes to caspase-1 activation, within the NLRP3 inflammasome, resulting in IL-1β and IL-18 maturation and release.

that the caspase-11 noncanonical inflammasome is triggered by cytosolic LPS (cLPS) in a TLR4-independent manner [44,45]. Transfection or electroporation of LPS in murine macrophages, including *TLR4*$^{-/-}$ macrophages, resulted in caspase-11-dependent caspase-1 activation and IL-1β processing as well as caspase-1-independent pyroptosis. Detailed biochemical analysis demonstrated that the LPS moiety lipid A is a potent caspase-11 activator. In fact, only penta-acylated or hexa-acylated lipid A triggers the caspase-11 pathway, whereas tetra-acylated lipid A does not. This structural modification of lipid A is a strategy employed by specific bacterial strains, such as *Francisella novicida* and *Helicobacter pylori*, to evade the immune system in order to hinder caspase-11 activation.

Mechanisms leading to caspase-11 activation

Until recently, few studies addressed the regulation and activation of caspase-11. Unlike caspase-1 and apoptotic caspases, caspase-11 expression is inducible. Although caspase-11 is difficult to detect in resting macrophages, its expression was originally shown to be inducible upon exposure to LPS [9]. Recently, it was observed that the TLR pathway adaptors TRIF and MyD88 are required for full caspase-11 expression, suggesting that its induction is regulated by upstream TLR pathways [32,40-42,44]. The molecular pathways involved in caspase-11 activation are not yet fully understood and

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different mechanisms may underlie its response to different pathogens.

Using *Ec* or *Cr* enteropathogens, Rathinam *et al.* described that caspase-11 expression is sufficient to trigger its autoactivation. In macrophages, the sensing of these enteropathogens by the NLRP3 inflammasome and the noncanonical inflammasome is dependent on the TLR4/TRIF pathway. In mouse macrophages, caspase-11 is upregulated by type I IFN (Figure 2). The absence of IFNARI or STAT1 results in impaired levels of caspase-11 and as a consequence absence of IL-1β and IL-18 maturation and secretion, and caspase-11 dependent pyroptosis [37,46]; this defect can be circumvented by the addition of recombinant IFN-β.

However, other studies reported that up-regulation of caspase-11 is not sufficient to induce its processing. *Trif*$^{-/-}$ macrophages present a defective caspase-11 activation upon *St* infection, despite consistent levels of caspase-11 [42]. Furthermore, caspase-11-dependent pyroptosis and IL-1β processing are also impaired in *Irf3*$^{-/-}$, *Ifnr1*$^{-/-}$ and *Stat1*$^{-/-}$ macrophages, despite capase-11 is expressed in the cells. Intriguingly, addition of exogenous type I IFN during *St* infection restored caspase-11 activation in the *Trif*-deficient cells. These data suggest the existence of an interferon-inducible activator of caspase-11 (Figure 2). This mechanism was also described in response to flagellin-deficient *Lp* infection. Thus, according to these observations, caspase-11 activation is not triggered by its expression but requires a second signal, for instance IFN type I signal, for licensing. Of note, cLPS or WT *Lp* activate the noncanonical inflammasome in Bone-Marrow Derived Macrophages (BMDM) lacking either *Tlr4*, *Trif* or *Ifnar*. cLPS induces IL-1β release and cell death in the absence of any priming signal, though the levels of IL-1β are lower than in primed cells and the kinetics are slower than infection by live bacteria [43]. Thus, it is likely that efficient caspase-11 activation relies on an unknown activator or receptor. Finally, it is not fully understood how caspase-11 activates the NLRP3 inflammasome and why it is specific to the NLRP3 inflammasome. It was described in the absence of caspase-11, and in response to *Ec* or *Cr*, that ASC molecules were still able to oligomerize and recruit caspase-1 [36]. In response to LPS and CTB or to infection, caspase-1 and caspase-11 were shown to physically interact, therefore it is possible that caspase-11 catalyses caspase-1 activation within the inflammasome complex [9,32,33]. However, mutant *St*, which exclusively engages caspase-11 for cell toxicity, could not induce ASC oligomerization in absence of caspase-11 [41]. Therefore, more experiments are required to clarify how caspase-11 contributes to caspase-1 activation and to understand the implications for NLRP3 inflammasome activity.

In vivo functions of caspase-11

Caspase-11 is proposed to protect the host from bacteria escaping the phagosome and accessing and replicating in the cytosol [38]. Moreover, *in vivo* experiments performed using both *caspase-11*-deficient mice and *caspase-1*$^{-/-}$*caspase-11*^{tg} mice revealed that caspase-11, and not caspase-1, is the main effector of endotoxic (LPS) shock lethality [32]. In fact, *TLR4*-deficient mice primed with a TLR3 ligand succumb to secondary LPS challenge, whereas *caspase-11*-deficient mice are less sensitive to LPS treatment [43,44]. These findings suggest that the past interpretations made using the *caspase-1/11*$^{-/-}$ mice in different sepsis models should be revisited. Nonetheless, *ASC*$^{-/-}$ and *NLRP3*$^{-/-}$ mice were shown to be protected from LPS treatment (Mariathasan et al., 2004, 2006). Thus, it remains to be determined if NLRP3, ASC and caspase-11 work together in the same pathway *in vivo*. Surprisingly, in response to oral *St* infection, caspase-11 activation in absence of caspase-1 is detrimental to the host as more bacterial load was found in the spleen, liver and mesenteric lymph nodes of *caspase-1*$^{-/-}$*caspase-11*^{tg} compared with WT or *caspase-11*$^{-/-}$ mice. This increased burden was most likely due to impaired neutrophil function in *caspase-1*$^{-/-}$*caspase-11*^{tg} [41]. Thus, caspase-11 activation in absence of caspase-1 could represent a breach used by some pathogens to cause host disease.

Concluding remarks

During bacterial infection, different sensing systems cooperate to detect and control infections. TLR and NLR recognize specific PAMPs located in different cellular compartments. Bacteria or PAMPs reaching the cytosol are detected by different inflammasomes. Recent data unravel a new role for caspase-11 in the control of Gram-negative bacterial infection and inflammasome activation. Through sensing of cLPS, caspase-11 engages a noncanonical inflammasome that controls caspase-1 activation, and a caspase-1 independent cell death [43,46]. The caspase-11 pathway appears to constitute an ingenious cellular mechanism allowing the detection by the host of intracellular pathogens that escape sensing by the canonical inflammasomes. Indeed, caspase-11 activation results in IL-1β processing by caspase-1 and cell death upon infection by Gram-negative pathogens including mutant strains that are deficient in PAMPs, such as flagellin. The mechanisms whereby caspase-11 is activated are still not fully understood. Whether caspase-11 is auto-processed when present in the cells at a threshold concentration

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or whether it requires an activator or a platform remains to be elucidated. Several data support a two-step model. Caspase-11 is structurally related to initiator caspases and it is likely that molecular scaffolds would similarly control its activity. It remains to be determined whether such a pathway is conserved in humans and whether caspase-4 or -5, that both arose from a caspase-11-like ancient gene, would participate in a similar cLPS sensing. Such findings could create new therapeutic opportunities for sepsis treatment. More practically, these new observations may significantly change the data interpretation of the Gram-negative bacterium infection literature, not only in *casp1/11* KO mouse studies, but also for many KO studies that were carried out using C57BL/6 and 129 mixed backgrounds.

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