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Antimicrobial inflammasomes: unified signalling against diverse bacterial pathogens

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Inflammasomes — molecular platforms for caspase-1 activation — have emerged as common hubs for a number of pathways that detect and respond to bacterial pathogens. Caspase-1 activation results in the secretion of bioactive IL-1β and IL-18 and pyroptosis, and thus launches a systemic immune and inflammatory response. In this review we discuss signal transduction leading to 'canonical' and 'non-canonical' activation of caspase-1 through the involvement of upstream caspases. Recent studies have identified a growing number of regulatory networks involving guanylate binding proteins, protein kinases, ubiquitylation and necroptosis related pathways that modulate inflammasome responses and immunity to bacterial infection. By being able to respond to extracellular, vacuolar and cytosolic bacteria, their cytosolic toxins or ligands for cell surface receptors, inflammasomes have emerged as important sentinels of infection.

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Introduction

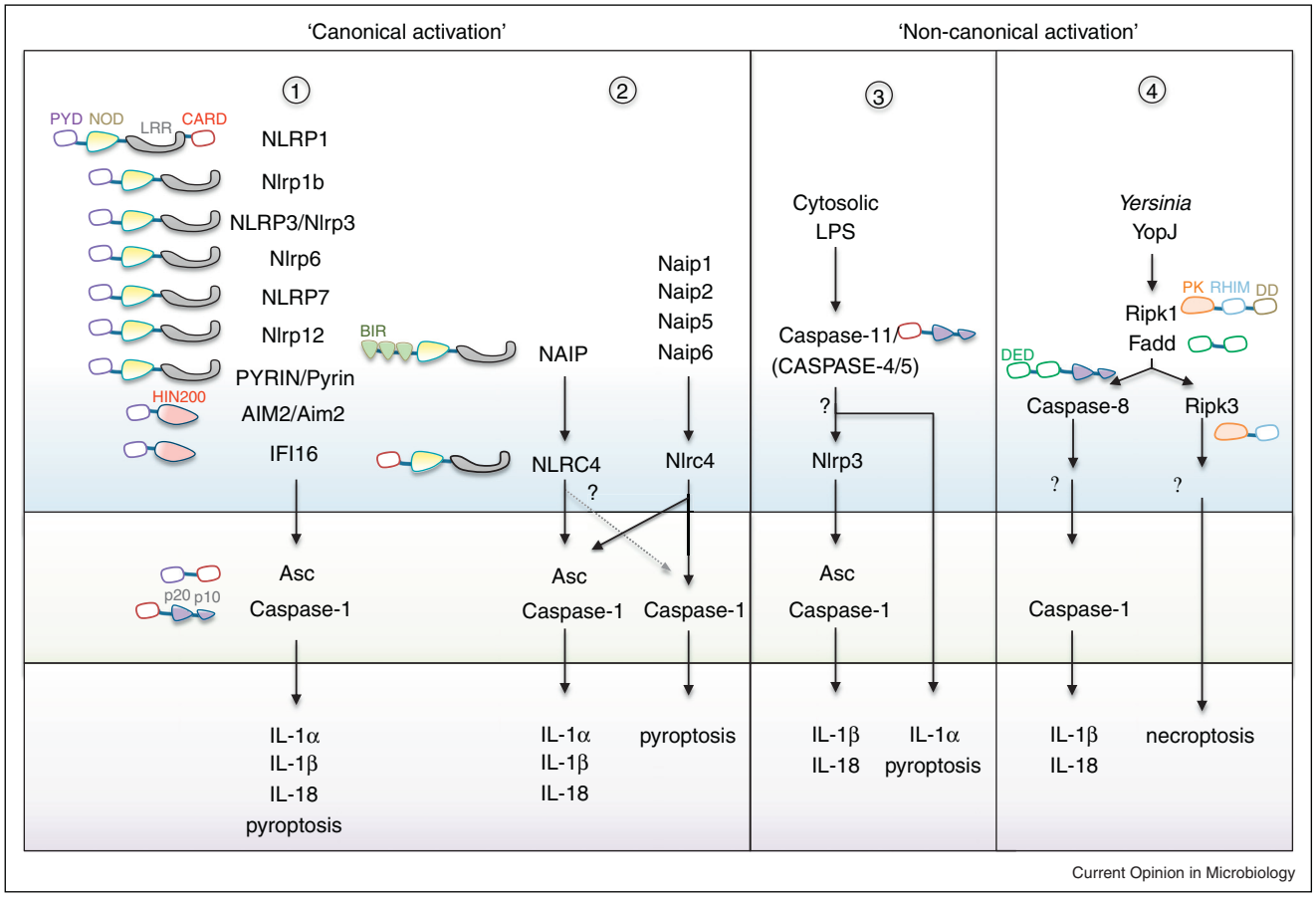
Mammalian innate immunity has evolved a diverse repertoire of sensors that respond to microbial infection, such as the Toll-like receptors (TLRs), RIG-I-like receptors/helicases (RLRs/RLHs), C-type lectin receptors (CLRs), NOD-leucine-rich repeat proteins (NLRs) and AIM2-like receptors (ALRs) [1]. Collectively, these proteins orchestrate appropriate responses to bacteria in extracellular or intracellular (including subcellular organellar, vacuolar or cytoplasmic) milieus. In this review we discuss new developments in mechanisms by which the NLR and ALR family of cytosolic proteins sense bacterial infection and assemble a large, multimeric signalling complex called the inflammasome. The inflammasome is a molecular scaffold that catalyses the auto-proteolytic activation of pro-caspase-1 into its active p20 and p10 subunits [2]. The convergence of pathogen sensing mechanisms on a post-translational event, *i.e.* caspase-1 activation, sets inflammasome signalling apart from other innate immune networks that control gene expression programmes in the host.

Active caspase-1 controls three key events, first, proteolytic processing of pro-IL-1β and pro-IL-18 into their bioactive forms, second, unconventional secretion of mature IL-1β/IL-18, and in most cases also that of mature or pro-IL-1α, and third, cell death by pyroptosis. These cytokines, as well as cell death, promote robust antimicrobial immunity to bacterial infection. Inflammasomes also play key roles in antiviral immunity, microbiome maintenance and autoinflammation, which have been reviewed recently [3,4]. Here we discuss the increasing complexity in inflammasome signalling since the identification of additional caspases, such as murine caspase-11 (represented by two genes, caspase-4 and caspase-5 in humans) and caspase-8, as indispensable upstream mediators of caspase-1 activation in a limited, but notable, number of settings. We also discuss the growing set of accessory signalling networks that modulate inflammasome activation and antimicrobial responses to bacterial pathogens.

Activation of caspase-1 by *'canonical'* inflammasomes by prion-like polymerization

Activation of NLR/ALRs results in their assembly into a single inflammasome 'speck' which may act as a signalling hub containing multiple NLR/ALRs and caspases [2,5••,6•]. NLR/ALR oligomerization has emerged as a common mechanism for caspase-1 activation. Thus, NLRP3 oligomerises in response to K^+ efflux, AIM2 by direct binding to double stranded DNA and NLRC4 through oligomeric NAIP (neuronal apoptosis inhibitor protein) proteins (Figure 1). Cutting-edge structural studies recently elucidated a 'prion-like' polymerization process nucleated by NLR/ALRs to generate star-like fibres of ASC (Apoptotic speck-associate protein) that form inflammasomes [7••,8••]. Clustering of pro-caspase-1 within these fibres leads to its activation. Interestingly, assembly driven activation of inflammasomes is analogous to polymerization of proteins that also contain domains of the death domain superfamily such as those present in NLRs/ALRs (Figure 1), for example the MyDDosomes, PIDDosomes, Fas/FADD-DISC and MAVS [9].

Figure 1



Canonical and non-canonical routes of activation of caspase-1 (1) & (2) From among 22 NLRs and 4 ALRs in the human and 34 NLRs and 6 ALRs in the mouse, a handful can activate caspase-1 as shown in the schematic above [2]. Names of human proteins appear in capital letters; only the first letter of mouse proteins are capitalised. Canonical inflammasomes can be reconstituted *in vitro* (for example HEK293 cells) however, non-canonical signalling, as shown in (3) & (4), requires additional as yet unknown proteins. ALRs have HIN200 domains that bind cytosolic DNA and assemble inflammasomes whereas NLRs shown are not receptors of microbial ligands [2]. Mouse Nlrp1b is activated by proteolysis and can induce cytokine maturation and pyroptosis by caspase-1 independently of Asc [58•]. (2) NLRC4/Nlrc4 activation in human and mouse cells requires the NAIP proteins. A single NAIP in human (which detects the type 3 secretion system (T3SS) needle protein) and Naip1-7 in mouse (which detect cytosolic flagellins, T3SS rod or needle proteins) act upstream of NLRC4/Nlrc4. Ligand binding promotes activation and oligomeric assembly of NAIPs [59,60•,61,62•]. In mouse cells, Asc-independent caspase-1 activation is sufficient for pyroptosis and whether this is also true in human cells has not been tested (dotted line with question mark) [63]. (3) Detection of LPS in the cytosol activates caspase-11, 4 or 5 [14••,15••,16••]. Caspase-11 promotes the assembly of Asc *via* Nlrp3 and this activates caspase-1. In the non-canonical pathway, caspase-11 controls pyroptosis and IL-1α release independently of Nlrp3, Asc and caspase-1. A lack of understanding of how caspase-11/4/5 activate Nlrp3 is indicated by (?). (4) *Yersinia* infection triggers caspase-1 activation *via* caspase-8, which itself is activated through proteins in necroptosis associated pathways — Ripk1 (receptor-interacting protein kinase-1), Ripk3 and Fadd (Fas associated protein with death domain) [17•,18•]. The mechanism of caspase-8-dependent caspase-1 activation and the role of Ripk3-dependent necroptosis are unclear and indicated by (?) marks. Domain compositions are colour coded and abbreviated as follows: BIR — baculovirus inhibitor of apoptosis domain; CARD — caspase-activation and recruitment domain; DD — death domain; DED — death effector domain, HIN200 — haematopoietic expression, interferon inducible, nuclear localized (HIN) DNA binding domain of ~200 residues; NOD, nucleotide binding and oligomerization domain; LRR — leucine rich repeat, p20 & p10 — large and small catalytic subunits; PK — protein kinase; PYD — pyrin domain, RHIM — Receptor-interacting protein (RIP) homotypic interaction domain. CARD, PYD, DED and DD are related in structure but less so in sequence.

'Non canonical' activation of caspase-1 and the involvement of upstream caspases

An indispensable upstream role for capsase-11 in activating Nlrp3-Asc-caspase-1 was first identified in cells infected with non-pathogenic *E. coli* or treated with a combination of LPS and cholera toxin B (which delivers LPS into the cytosol; Figure 1) [10••,11•,12]. How caspase-11 controls the assembly of Asc specks by Nlrp3 in this scenario is not yet understood. LPS is detected independently of Tlr4 when present in the cytosol by the activation of caspase-11 or human caspase-4 and caspase-5 [13•,14••,15••]. However, all other Nlrp3 activating