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Review

# An updated view on the functions of caspases in inflammation and immunity

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ABSTRACT

The binary classification of mammalian caspases as either apoptotic or inflammatory is now obsolete. Emerging data indicate that all mammalian caspases are intricately involved in the regulation of inflammation and immunity. They participate in embryonic and adult tissue homeostasis, control leukocyte differentiation, activation and effector functions, and mediate innate and adaptive immunity signaling. Caspases also promote host resistance by regulating anti-oxidant defense and pathogen clearance through regulation of phagosomal maturation, actin dynamics and phagosome-lysosome fusion. Beyond apoptosis, they regulate inflammatory cell death, eliciting rapid pyroptosis of infected cells, while inhibiting necroptosis-mediated tissue destruction and chronic inflammation. In this review, we describe the cellular and molecular mechanisms underlying non-apoptotic functions of caspases in inflammation and immunity and provide an updated view of their functions as central regulators of tissue homeostasis and host defense.



**Contents**



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## 1. Introduction

Caspases are cysteinyl aspartate-specific proteases encoded by 12 genes in humans and 10 in mice (reviewed in [1]). First synthesized as pro-enzymes, consisting of a prodomain and two catalytic subunits, caspases are activated by oligomerization or by processing into an active tetramer of two large and two small catalytic subunits. They are best known for their ability to initiate and execute apoptosis, an evolutionarily conserved form of programmed cell death. However, caspases exert additional functions beyond apoptosis including, most notably, the regulation of inflammation and immunity. Indeed, the first mammalian caspase to be identified, caspase-1, was discovered for its ability to convert pro-interleukin (IL)-1β into its biologically active cytokine form [2,3]. The cloning of caspase-3, a central executioner of apoptosis, followed shortly thereafter [4]. Based on structural and functional similarities to either caspase, other members of the caspase family were classified as either apoptotic or inflammatory. The inflammatory caspase subfamily includes caspases-1, -4, -5 and -12 in humans and caspases-1, -11 and -12 in mice. Except for caspase-12 that has limited enzymatic activity in mice [5] and is inactive in humans [6–8], the inflammatory caspases are activated by proximity within large macromolecular platforms known as the inflammasomes [9]. They enact important functions in inflammation and cell death by directly cleaving their target proteins, notably the pro-inflammatory cytokines pro-IL-1β and pro-IL-18. Apoptotic caspases are further classified into initiator or executioner caspases. The initiator caspases (-2, -8, -9, -10), characterized by long prodomains are activated by 'proximity' in signaling platforms such as the Death-Inducing Signaling Complex (DISC) in the case of caspases-8 and -10 or the apoptosome in the case of caspase-9. According to the insult, specific initiator caspases are engaged, and induce either extrinsic or intrinsic apoptosis. TNF family death ligands including TNF, Fas ligand (FasL) and TRAIL induce extrinsic apoptosis through DISC-mediated activation of caspases-8/-10. In contrast, intracellular insults activate intrinsic (or mitochondrial) apoptosis *via* the apoptosome-caspase-9 pathway. In both instances, the initiators cleave the executioner caspases (-3, -6 and -7) that dismantle the cell by targeting essential structural and housekeeping proteins for proteolysis [10].

Since the description of apoptosis by Kerr in 1972 [11], the field of cell death has seen the emergence of several additional cell death modalities. Here, we focus on two variants of regulated necrosis, termed pyroptosis [12] and necroptosis [13] that are controlled by caspases directly and indirectly, respectively. The identification of the molecular steps governing these cell death pathways has not only enabled the characterization of upstream events leading to necrotic cell death in different pathological contexts, but has also provided the opportunity to target specific effectors for therapeutic benefit. Unlike apoptosis, which is immunologically silent or tolerogenic, pyroptosis and necroptosis are both lytic and inflammatory (reviewed in [14]). Morphologically, cells undergoing apoptosis display blebbing of the plasma membrane, nuclear and cytoplasmic condensation and targeted DNA fragmentation. In contrast, pyroptosis and necroptosis are caused by pore formation at the plasma membrane, which leads to the leakage to the extracellular milieu of cellular content, including danger-associated molecular patterns (DAMPs). Unlike apoptosis and pyroptosis, which are caspase-dependent, necroptosis is mostly caspase-independent (while its execution proceeds independently of caspase activity, caspases-8 and 10 negatively regulate its induction) [13].

## 2. Caspases-1/-4/-5/-11: central effectors of innate immunity

Caspases-1 and -11 (and the human caspase-11 orthologues, caspases-4 and -5) have a Caspase Activation and Recruitment Domain (CARD) in their prodomain. The CARD in caspase-1 enables homotypic protein-protein interactions with CARD-containing partners, most notably the 22 kDa adaptor protein ASC (apoptosis-associated speck-like protein containing C-terminal CARD) [15]. ASC, also known as PYCARD, based on its bi-modular pyrin domain (PYD)-CARD structure links caspase-1 to PYD-containing intracellular innate sensors including Pyrin and members of the nucleotide-binding and oligomerization domain (NOD) leucine-rich repeat containing receptors (NLR) family. The activation of caspase-1 occurs by oligomerization in macromolecular structures called the inflammasomes (reviewed in [9]) (Fig. 1). These complexes are scaffolded by intracellular pattern recognition receptors (PRRs), primarily members of the NLR [16] and PYHIN (pyrin and HIN200 [hematopoietic interferon-inducible nuclear antigens] receptors) [17] families. However, several exceptions to this general model have been described. Most importantly, recent studies have shown that caspases-11/-4/-5 can be activated independently of canonical inflammasomes or of PRRs, by direct interaction with microbial and host-encoded danger motifs such as bacterial lipopolysaccharides (LPS) and oxidized phospholipids (oxPAPC), respectively [18,19]. This discovery pointed to a novel function of these caspases as *de novo* danger sensors.

### 2.1. caspase-1 is the primary driver of canonical inflammasomes

The first inflammasome was described in 2002 by Tschopp and colleagues [20]. Using a cell-free system, the authors showed that a complex scaffolded by a PYD-containing NLR, termed NLRP1, recruited caspase-1 to its N-terminal PYD *via* ASC and caspase-5 to its C-terminus by direct CARD-CARD interaction. Immunodepletion of ASC or expression of a dominant-negative ASC mutant blocked NLRP1-induced caspase-1 activation and pro-IL-1β maturation [20]. Of note, this study did not demonstrate physiological existence of such an NLRP1 inflammasome, and as described below, caspase-5 activation is not thought to occur *via* this inflammasome. Shortly thereafter, the Tschopp group elucidated the molecular basis of three auto-inflammatory diseases, caused by mutations in the *NLRP3*/cryopyrin/*CIAS1* gene and exhibiting spontaneous release of IL-1β, collectively known as cryopyrin-associated periodic syndromes (CAPS) [21,22]. They characterized the NLRP3-ASC-caspase-1 inflammasome and demonstrated its hyper-activation in these conditions [21]. The NLRC4 inflammasome was next described in a study showing that Nlrc4-deficient macrophages failed to activate caspase-1 following infection with *Salmonella typhimurium*, but not in response to other inflamma-

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