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Inflammasome-mediated pyroptotic and apoptotic cell death, and defense against infection

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Cell death is an effective strategy to limit intracellular infections. Canonical inflammasomes, including NLRP3, NLRC4, and AIM2, recruit and activate caspase-1 in response to a range of microbial stimuli and endogenous danger signals. Caspase-1 then promotes the secretion of IL-1β and IL-18 and a rapid form of lytic programmed cell death termed pyroptosis. A second inflammatory caspase, mouse caspase-11, mediates pyroptotic death through an unknown non-canonical inflammasome system in response to cytosolic bacteria. In addition, recent work shows that inflammasomes can also recruit procaspase-8, initiating apoptosis. The induction of multiple pathways of cell death has probably evolved to counteract microbial evasion of cell death pathways.

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Introduction

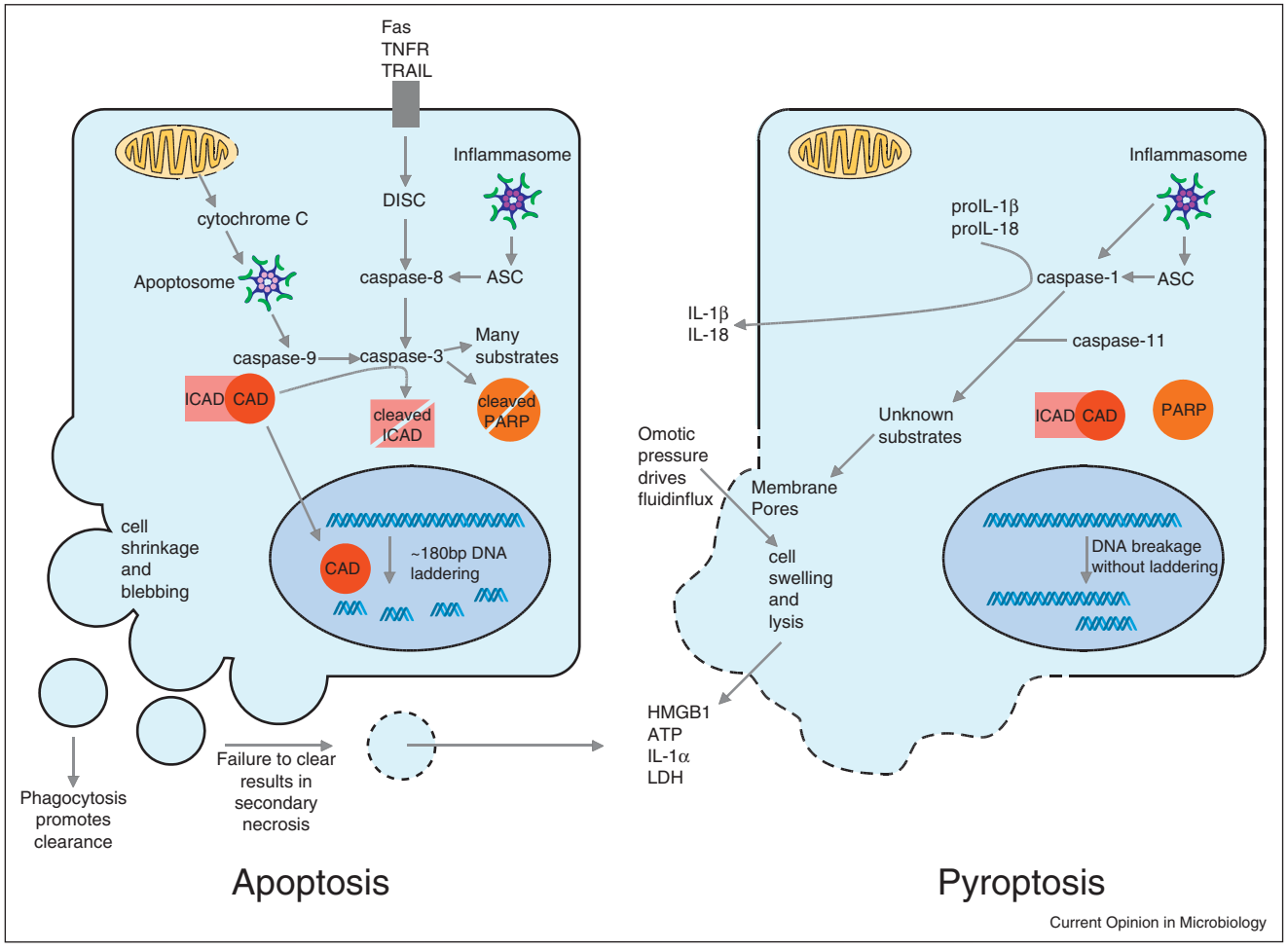
While viral infection is necessarily intracellular, many bacteria also find a replicative or survival niche within cells, evading immune cell attack. In such cases, death of the infected cell can benefit the host by cutting short the replicative cycle, and releasing the invader for killing by neutrophils [1]. Alternatively, cell death could be co-opted by pathogens to deplete immune cells, or to release replicated organisms, enhancing pathogen spread. An emerging mechanism for microbe-induced cell death involves formation of inflammasome complexes. Inflammasomes are well known as the route to activation of caspase-1, which cleaves the precursors of the inflammatory cytokines IL-1β and IL-18 [2]. These cytokines are of great importance in clearance of a number of infections. The induction of cell death by inflammasomes is less studied, but analysis in fish suggests that the inflammasome system evolved as part of a cell death program, and that cytokine processing was a later development [3]. In this review we examine the pathways of inflammasome-induced cell death, and what is known of the contribution of this process to host defense. The role of non-inflammasome cell death pathways in bacterial infection has been reviewed elsewhere [4].

Caspases in apoptosis and pyroptosis

For many years programmed cell death was synonymous with apoptosis. Apoptosis is described as 'immunologically silent', as cell membrane integrity is normally maintained until cells are engulfed by phagocytes (Figure 1). A lack of inflammatory consequence of apoptosis is important during development and homeostasis. Apoptosis can also be induced by infection, and in that case, immunologically silent death is undesirable and unlikely, since the dying cell contains microbial products that should activate the engulfing macrophage. Cell death by necrosis, involving cell swelling and lysis, was long seen as the passive response to overwhelming environmental stress or injury, independent of signaling pathways. However, programmed necrosis ('necroptosis') involving RIP1/RIP3 signaling has now been described, and is reviewed elsewhere [5]. Pyroptosis is another form of programmed lytic cell death, frequently induced by infection. Pyroptotic death elicits inflammation due to release of cytosolic contents such as ATP, HMGB1 and IL-1α, and is commonly accompanied by processing of inflammatory cytokines IL-1β and IL-18 (Figure 1) [1,2].

Both pyroptosis and apoptosis involve activation of members of the caspase family of proteases. Pyroptosis is established as inflammasome-dependent cell death, executed following activation of inflammatory caspases (caspase-1 or mouse caspase-11). In contrast, apoptotic initiator caspases (caspase-2, caspase-8 and caspase-9) subsequently cleave effector caspases (caspase-3, caspase-6 and caspase-7). Caspases then cleave target proteins to trigger programmed pyroptotic or apoptotic cell death. The critical step in commitment to both pathways is the recruitment of initiator caspases into a protein complex where they are activated by dimerization, generally followed by

Figure 1



The cellular events during pyroptosis and apoptosis. Both pyroptosis and apoptosis require activation of caspases, caspase-1/11 or caspase-2/3/7/8/9, respectively, but differ morphologically. Pyroptosis is characterized by formation of membrane pores between 1.1 and 2.4 nm in diameter. These pores likely cause dissipation of cellular ionic gradients leading to osmotic water influx, cell swelling, and plasma membrane lysis, releasing the cytosolic content into the extracellular space. Specific markers for this lysis are useful *in vitro*, for example, lactate dehydrogenase release is readily detected by enzyme assay. Other cytosolic components released have inflammatory biologic functions, for example, HMGB1, IL-1α, and ATP. On the other hand during apoptosis, plasma membrane integrity is maintained and cellular contents are not released. The plasma membrane loses leaflet lipid composition asymmetry as phosphatidyl serine becomes exposed on the outer leaflet, promoting phagocytosis. However, in the absence of phagocytosis, at later timepoints the apoptotic bodies undergo secondary necrosis characterized by rupture of the membrane. Apoptosis is an energy requiring process during which cells shrink and form apoptotic blebs. The DNA repair factor PARP1 is inactivated by cleavage, and nuclear condensation and fragmentation occur. Internucleosomal DNA cleavage, detected as laddering on gel electrophoresis or by TUNEL staining for DNA ends, occurs due to ICAD degradation and activation of CAD (caspase-activated DNase). Weak TUNEL staining is also seen in pyroptosis, but DNA laddering and ICAD degradation are absent [55].

intermolecular cleavage. Caspase-1, caspase-2, caspase-8 and caspase-9 are each recruited into a unique activating complexes via their N terminal pro-domain of the death-fold family (either a caspase recruitment domain (CARD) or death effector domain (DED)). For example, the caspase-1 and caspase-9 activating platforms are the inflammasome and apoptosome, respectively [6].

Inflammasome induction of pyroptosis

Inflammasomes activating caspase-1 are initiated either by a Nod-like receptor (NLRP1, 3, 6, 7, 12, NLRC4), AIM2, or Pyrin, all of which contain a CARD or pyrin domain (PYD) (Figure 2) [2,7]. While NLRP3 responds to a wide array of agonists [2], NLRC4 is specific for cytosolic bacterial flagellin and type III secretion system (T3SS) components [8–11], and AIM2 is specific for cytosolic DNA [12–15]. Many inflammasomes recruit the ASC adaptor, composed of a CARD and a PYD [2], via homotypic interactions. Additional ASC molecules are incorporated via CARD–CARD and PYD–PYD interactions, until all ASC is collected into a single focus (Figure 2). Attraction of procaspase-1 into the ASC focus