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Brief Reviews

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PANoptosis: A Unique Innate Immune Inflammatory Cell Death Modality

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Innate immunity is the first response to protect against pathogens and cellular insults. Pattern recognition receptors sense pathogen- and damage-associated molecular patterns and induce an innate immune response characterized by inflammation and programmed cell death (PCD). In-depth characterization of innate immune PCD pathways has highlighted significant cross-talk. Recent advances led to the identification of a unique inflammatory PCD modality called PANoptosis, which is regulated by multifaceted PANoptosome complexes that are assembled by integrating components from other PCD pathways. The totality of biological effects observed in PANoptosis cannot be accounted for by any other PCD pathway alone. In this review, we briefly describe mechanisms of innate immune cell death, including molecular mechanisms of PANoptosis activation and regulation. We also highlight the PANoptosomes identified to date and provide an overview of the implications of PANoptosis in disease and therapeutic targeting. Improved understanding of innate immune-mediated cell death, PANoptosis, is critical to inform the next generation of treatment strategies. ***The Journal of Immunology*****, 2022, 209: 1625–1633.**

Innate immunity provides the body's first line of defense against infectious and noninfectious cellular insults. This defense mechanism uses an array of host sensors called pattern recognition receptors (PRRs), which recognize components of pathogenic microbes (pathogen-associated molecular patterns [PAMPs]) or host molecules generated by damaged or dying cells (damage/danger-associated molecular patterns [DAMPs]). Sensing of PAMPs and DAMPs by the PRRs can occur at the membrane level, mainly through TLRs and C-type lectin receptors, or in the cytosol, primarily through nucleotide-binding oligomerization domain-like receptors (NLRs), absent in melanoma 2 (AIM2)–like receptors, and retinoic acid–inducible gene-I–like receptors (1). Identifying the innate sensors that specifically detect a particular PAMP or DAMP, and understanding how this interaction elicits an immune reaction, have been a major focus of the innate immunity field.

Sensing of PAMPs and DAMPs by PRRs initiates a wide range of responses, including the transcriptional activation of inflammatory cytokines and IFNs, thereby modulating the innate and adaptive immune responses, and induction of diverse programmed cell death (PCD) pathways, including pyroptosis, apoptosis, and necroptosis (2, 3) (Fig. 1). Although pyroptosis and necroptosis are lytic forms of cell death and are inflammatory in nature, apoptosis is traditionally considered silent in eliciting an immune response (4). However, there exists an intricate cross-talk between PCD pathways (5). Studies focused on this extensive cross-talk led to the identification of an additional PCD pathway called PANoptosis (6–18) (Fig. 1). PANoptosis is a unique form of innate immune inflammatory cell death that is regulated by multifaceted PANoptosome complexes, which are triggered by innate immunity and assembled by integrating components from other PCD pathways. The totality of biological effects in PANoptosis cannot be accounted for by pyroptosis, apoptosis, or necroptosis alone. Multidisciplinary genetic, molecular, and biochemical studies to analyze this totality of effects have bridged historically divided research areas, such as pathogens (microbiology), innate immunity, and cell death, and facilitated a growing, integrated understanding of innate immunity and infection-induced cell death at a fundamental level.

In this review, we discuss the molecular mechanisms of cell death, including PANoptosis, and describe the PANoptosome complexes that have been identified to date. We also provide an overview of what is known about the regulatory mechanisms controlling PANoptosis. We then discuss examples of how PANoptosis is implicated across the disease spectrum and highlight avenues for future investigation. Continued study of innate immune inflammatory cell death, PANoptosis, will be important to define molecular mechanisms of

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Abbreviations used in this article: AIM2, absent in melanoma 2; ASC, apoptosis-associated speck-like protein containing a caspase activation and recruitment domain; BAK, B cell lymphoma 2–antagonist killer; BAX, B cell lymphoma 2–associated X protein; BCL-2, B cell lymphoma 2; BID, BH3-interacting domain death agonist; CARD, caspase activation and recruitment domain; DAMP, damage/danger-associated molecular pattern; FADD, Fas-associated death domain; GSDMD, gasdermin D; GSDME, gasdermin E; IAV, influenza A virus; IRF1, IFN regulatory factor 1; MHV, murine hepatitis virus; MLKL, mixed lineage kinase domain-like protein; MOMP, mitochondrial outer membrane permeabilization; NLR, nucleotide-binding oligomerization domain-like receptor; NLRP3, nucleotide-binding oligomerization domain-like receptor family pyrin domain containing 3; PAMP, pathogen-associated molecular pattern; PCD, programmed cell death; PRR, pattern recognition receptor; RHIM, RIP homotypic interaction motif; RIPK, receptor-interacting protein kinase; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TAK, TGF-β–activated kinase; ZBP1, Z-DNA–binding protein 1.

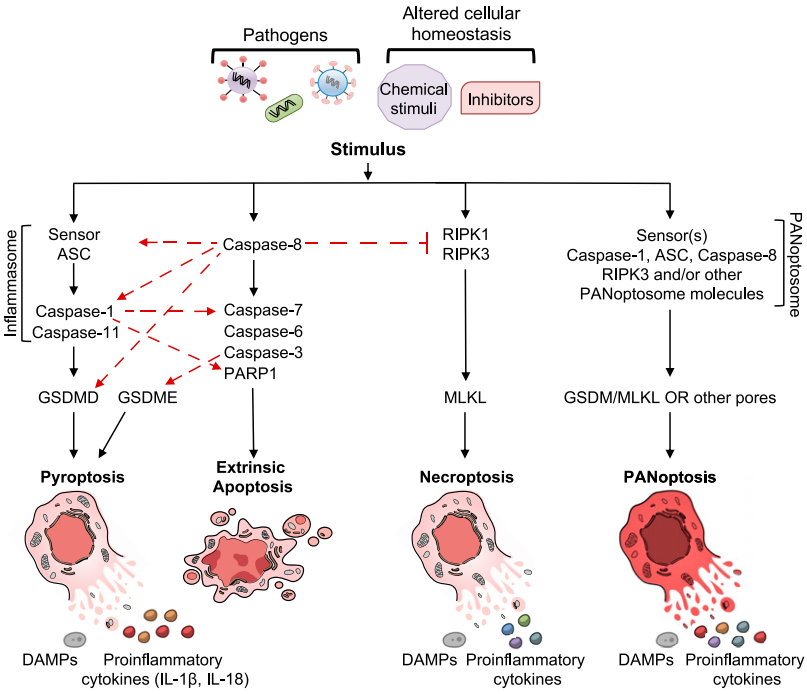

FIGURE 1. PCD pathways. Exposure to cellular insults, such as microbial infection or altered cellular homeostasis, can lead to the activation of different PCD pathways. Pyroptosis, extrinsic apoptosis, necroptosis, and PANoptosis are four distinct PCD pathways. Each pathway's sequential activation is indicated with black connectors, and context-dependent cross-talk between the pathways is indicated in red. PARP1, poly(ADP-ribose) polymerase 1.

disease and identify strategies for therapeutic interventions for infectious and inflammatory diseases, cancers, and beyond.

Canonical PCD pathways

Conventionally, PCD pathways have been categorized into lytic and nonlytic forms, with pyroptosis, necroptosis, and PANoptosis characterized as lytic modalities, whereas apoptosis is nonlytic (19–21) (Fig. 1). Pyroptosis is an inflammatory PCD pathway with distinct morphological characteristics, such as cell swelling, DNA fragmentation, and plasma membrane rupture. Pyroptotic cell death is mediated through the assembly of a multiprotein signaling complex called an inflammasome (22, 23). A variety of inflammasomes are assembled in response to different triggers, and the inflammasomes are named based on their cognate PRR sensor. Among the inflammasome sensors, NLR family pyrin domain containing 3 (NLRP3) is the most widely studied. Other well-characterized inflammasome sensors include NLRP1, NLR family caspase activation and recruitment domain (CARD)–containing 4 (NLRC4), Pyrin, and AIM2 (23–32). In response to the sensing of a pathogen or danger signal, the sensor PRR undergoes a conformational change and associates with the adaptor protein apoptosis-associated speck-like protein containing a CARD (ASC) through pyrin domain or CARD homotypic interactions (33–35). Caspase-1 is then recruited through CARD–CARD interactions to this PRR–ASC oligomeric complex. This recruitment promotes caspase-1 activation, resulting in proteolytic maturation of interleukins IL-1β and IL-18 (36). Caspase-1 also cleaves the pore-forming protein gasdermin D (GSDMD) to generate C-terminal and N-terminal fragments (37). The N-terminal GSDMD fragments translocate to the plasma membrane to form oligomeric pores. NINJ1 is then recruited to facilitate plasma membrane rupture (38). As a result of pore formation and plasma membrane rupture, cytokines, including IL-1β and IL-18, and other DAMPs are released. This process also leads to cell lysis through water influx (2, 39–42). In addition to this "canonical" inflammasome activation pathway, direct sensing of Gram-negative bacterial LPS by human caspase-4/5 and its murine ortholog caspase-11 can also cleave GSDMD to induce noncanonical NLRP3 inflammasome activation, pyroptosis, and inflammation (37, 39, 40, 42, 43).

Apoptosis has historically been considered an immunologically silent PCD pathway, but recent evidence suggests that apoptotic molecules can directly or indirectly impact the inflammatory response (44, 45). Apoptosis is mediated through a hierarchical activation of caspases: initiator caspases, such as caspase-8, -9, and -10, proteolytically cleave effector caspases, caspase-3 and -7, to execute cell death (46, 47). Apoptosis is classified into intrinsic and extrinsic pathways and has morphological features, including cell shrinkage, nuclear condensation, DNA fragmentation, and membrane blebbing (48). Loss of mitochondrial integrity forms the central component of intrinsic apoptosis, and this is mediated by the proapoptotic B cell lymphoma 2 (BCL-2) family proteins, BCL-2–associated X protein (BAX), and BCL-2–antagonist killer (BAK). Intrinsic apoptotic triggers include DNA damage, cell cycle arrest, growth factor deprivation, UV radiation, and oxidative stress; these triggers can induce oligomerization of BAX and BAK (49). This BAX/BAK complex translocates to mitochondria to cause mitochondrial outer membrane permeabilization (MOMP), resulting in cytochrome *c* efflux to the cytosol. The initiator caspase caspase-9 forms a cytosolic complex with apoptotic protease activating factor 1 and cytochrome *c*, leading to its activation (49). Active caspase-9 further proteolytically activates the effector caspases, such as caspase-3 and -7, which in turn cause proteolytic cleavage of downstream substrates to execute apoptosis (46, 47). In contrast, extrinsic apoptosis results from the engagement of death receptors, such as TNFR1 (CD120a) and Fas receptor (CD95/FAS), leading to the recruitment and activation of caspase-8. Active caspase-8 can directly cleave caspases-3 and -7 to execute cell death (50, 51). Caspase-8 can also induce intrinsic apoptosis through proteolytic cleavage of BH3-interacting domain death agonist (BID)

to form truncated BID, which promotes BAX/BAK-mediated MOMP and cytochrome *c* release to initiate an amplifying apoptotic loop (52, 53).

Necroptosis is a lytic form of PCD that is activated in caspase-8–deficient cells or under conditions in which apoptosis is inhibited by pathogens or chemical mediators (21, 54–56). Morphologically, necroptosis is characterized by organelle swelling, loss of plasma membrane integrity, and cell lysis (57). Necroptosis can be induced by TNF-α, Fas ligand, TRAIL, and other TLR ligands under conditions in which caspases are inhibited (58–60). Upon TNF-α binding to TNFR1, a series of proteins is recruited to the cytoplasmic domain of the receptor to form complex I; these proteins include TNFR-associated death domain, TNFR-associated factor 2, receptor-interacting protein kinase 1 (RIPK1), cylindromatosis, cellular inhibitor of apoptosis protein 1, and NF-κB essential modulator (58, 61). Complex I activates the NF-κB prosurvival signaling pathway through IκBα phosphorylation (62). However, when NF-κB signaling is dysregulated, RIPK1, TNFR-associated death domain, Fas-associated death domain (FADD), and caspase-8 form complex II to trigger apoptotic cell death (61). In this context, the apoptotic caspase-8 suppresses necroptosis through proteolytic cleavage of necroptotic mediators RIPK1, RIPK3, and cylindromatosis (63–65). However, when caspase-8 is deleted or dysfunctional due to pathogen-mediated or pharmacological inhibition, RIPK1 interacts with RIPK3 through their shared RIP homotypic interaction motif (RHIM) domain, leading to the formation of the necrosome (66). This cytosolic complex promotes the activation of mixed lineage kinase domain-like protein (MLKL) by RIPK3-dependent phosphorylation. Phosphorylated MLKL oligomerizes, translocates to the plasma membrane, and lyses the cell (61, 67–69).

Cross-talk among PCD pathways

Though considered mechanistically distinct, extensive cross-talk among the three PCDs described above has been widely recognized (5, 6, 8, 10, 44, 63) (Fig. 1). For example, caspase-1 can cleave and activate caspase-7, a canonical component of apoptosis, during *Salmonella* Typhimurium infection– and LPS plus ATP treatment–induced NLRC4 and NLRP3 inflammasome activation, respectively (70). Moreover, the apoptotic substrate poly(ADP-ribose) polymerase 1 can also be cleaved by caspase-1 downstream of inflammasome activation, indicating an intricate cross-talk between pyroptotic and apoptotic molecules (71). Inflammasome-mediated caspase-1 activation can also induce activation of apoptotic molecules through mitochondrial damage. This is mediated by the pyroptotic executioner GSDMD, which acts as a mitochondrial pore-forming protein to induce cytochrome *c* release (72). Caspase-1 can also induce activation of components of intrinsic apoptosis in the absence of GSDMD through direct proteolytic activation of the BCL-2 family protein BID, resulting in the activation of intrinsic apoptotic mechanisms via MOMP, cytochrome *c* release, and caspase-9 activation (73). Caspase-1–deficient cells are resistant to mitochondrial damage downstream of NLRP3 or AIM2 inflammasome activation (74). In contrast, in some circumstances, components of pyroptosis can also induce activation of apoptotic components during caspase-1 deficiency. In response to AIM2-activating stimuli, such as dsDNA electroporation or *Francisella novicida* infection, or in response to LPS plus nigericin–induced NLRP3 inflammasome activation, ASC can associate with caspase-8, a component of apoptosis, to induce cell death in the absence of caspase-1 (75, 76).

Apoptotic components can also regulate pyroptotic processes. The apoptotic protein caspase-8 contributes to priming and activation of both canonical and noncanonical inflammasomes, and it can proteolytically cleave caspase-1, as shown in an in vitro recombinant assay system (77). Caspase-8, along with FADD, can be recruited to the NLRP3 inflammasome complex in response to LPS plus ATP stimulation or infection with *Citrobacter rodentium* (77–79). Similarly, caspase-8 can also be recruited to the NLRC4 inflammasome in response to *Salmonella* and contributes to the subsequent transcription of IL-1β; however, caspase-8 is dispensable for cell death induction under these circumstances (78). Caspase-8 is also important for the activation of pyroptotic effectors in response to TGF-β–activated kinase 1 (TAK1) inhibition (8). During *Yersinia* infection–induced TAK1 inhibition, caspase-8 activates GSDMD to drive cell death (80–82).

There are several additional connections between apoptotic caspases and gasdermin family members to modulate pyroptotic activation. Caspase-3 has been shown to both activate and halt inflammatory cell death through its cleavage of gasdermins (Fig. 1). Caspase-3 can cleave and activate gasdermin E (GSDME) in response to several apoptotic triggers, including TNF-α, chemotherapeutic drugs, and iron-activated reactive oxygen species; this activation induces membrane pore formation and cell death (44, 45, 83). Additionally, caspase-3 can also cleave GSDMD. However, this caspase-3–mediated proteolysis of the pore-forming N-terminal GSDMD fragment renders it inactive and inhibits pyroptotic activation (84). Caspase-8 can also act on other members of the gasdermin family; gasdermin C was shown to be cleaved by caspase-8 in response to TNF-α treatment to drive pyroptotic molecule activation (85). However, caspase-8 can also be responsible for limiting GSDMD-mediated pyroptotic activation through caspase-3–induced GSDMD inactivation during influenza A virus (IAV) infection (86). Furthermore, in addition to its proteolytic function, caspase-8 can act as a scaffold, facilitating the recruitment of caspase-1 and ASC to induce pyroptotic molecule activation during development (87).

Besides its roles in regulating activation of apoptotic and pyroptotic molecules, caspase-8 has a regulatory role for necroptotic molecules. Inhibition of caspase-8 drives necroptosis by stabilizing the necrosome complex. Indeed, the embryonic lethality of *Casp8*$^{-/-}$ mice can only be rescued by deletion of necroptotic components RIPK3 or MLKL (88–90). Similarly, because FADD is required for the recruitment of caspase-8, FADD-deficient embryos undergo massive necrosis; however, deletion of necroptotic proteins such as RIPK3 can rescue them (91–94).

Necroptotic molecules can also influence pyroptotic activation. Efflux of potassium is a well-known inducer of NLRP3 inflammasome activation. Plasma membrane rupture due to MLKL-mediated necroptosis induces potassium ion efflux, resulting in NLRP3 inflammasome activation (95, 96). Also, ASC oligomerization is MLKL-dependent in response to combined treatment of a TLR3 agonist and zVAD (97). In some cases, necroptotic components are activated as a consequence of pyroptotic activation. For instance, in response to AIM2 inflammasome activation in macrophages with a gain-of-function mutation of *Lrrk2*^{G2019S} (leucine-rich repeat kinase 2), GSDMD mediates mitochondrial pore formation and triggers cell death that is dependent on the RIPK1-RIPK3-MLKL axis (98). Together, these findings support the

extensive interconnectedness of pyroptotic, apoptotic, and necroptotic molecules. Many of these cross-talk examples have been observed in context-specific manners, and additional studies are needed to determine other circumstances in which they occur.

Cross-talk or redundancies among the PCD pathways can have significant biological impacts. In the context of the innate immune response, cross-talk between PCDs can benefit the host by assisting in pathogen detection. For example, several viruses encode caspase-8 inhibitors, like CrmA from the cowpox virus or B13R from the vaccinia virus (99), which aid in evasion of apoptosis induction; however, RIPK1-mediated necroptosis acts as a backup mechanism to kill infected cells and ensure host survival (61). Also, a recent report showed that necroptosis induced in response to pan-caspase inhibition in macrophages could be used as an immunotherapy against community-acquired bacterial infections, including methicillin-resistant *Staphylococcus aureus* (100). In contrast, there are cases in which PCD cross-talk contributes to disease progression or aberrant immune responses (101, 102). Given the importance of PCD in health and disease, it is critical to determine whether the cross-talks observed represent an intersection of two pathways that are independently regulated or whether this is evidence of a separate, distinct pathway. Considering a comprehensive view of PCD and understanding these regulatory connections will provide a more complete picture of disease processes and allow the identification of new therapeutic strategies.

PANoptosis: a unique innate immune inflammatory cell death modality bridging gaps in biology

Based on the above physiologically relevant observations highlighting the extensive cross-talk between PCD pathways, the conceptualization of an integrated cell death modality called "PANoptosis" was formed. Building on the initial observations, extensive mechanistic studies and substantial genetic evidence have now shown that this PCD cannot be accounted for by pyroptosis, apoptotis, or necroptosis alone. For example, in the *Pstpip2*^{cmo} disease model of osteomyelitis-like bone inflammation, inflammation in the mice is not rescued by deletion of pyroptotic, apoptotic, or necroptotic machineries alone; protection requires combined deletion of NLRP3 or caspase-1 with caspase-8 and RIPK3 (101, 102). Similarly, in the contexts of IAV infection or TAK1 inhibition, deletion of pyroptotic, apoptotic, or necroptotic machineries alone is not sufficient to prevent cell death; combined deficiencies are required (6, 8, 10–12, 103). This genetic evidence has established PANoptosis as a unique innate immune inflammatory PCD pathway that is mechanistically regulated by multifaceted PANoptosome complexes are assembled by integrating components from other PCD pathways (Fig. 1) (8, 9, 11–13, 103, 104).

The most well-characterized examples of PANoptosis are in the context of infections, specifically IAV, HSV1, or *F. novicida* infections. IAV induces PANoptosis by activating pyroptotic markers caspase-1 and GSDMD, apoptotic markers caspase-8, -3, and -7, and necroptotic markers, such as MLKL. Deletion of molecular components of pyroptosis, apoptosis, or necroptosis individually fails to protect cells against IAV-induced cell death; however, deletion of the cytosolic sensor Z-DNA–binding protein 1 (ZBP1) rescues the cells from IAV-induced PANoptosis. Mechanistically, ZBP1 initiates PANoptosis through the formation of the ZBP1-PANoptosome, a multiprotein complex comprised of NLRP3 inflammasome components along with RIPK3, RIPK1, caspase-8, and caspase-6 (10–12). The ZBP1-PANoptosome has also been implicated in cancer treatment, with combination therapy with IFN and nuclear export inhibitors inducing its formation and subsequent cell death in cancer cells (9). Similarly, the innate immune sensors ZBP1 and Pyrin have also been shown to be molecular components of the AIM2-PANoptosome. In response to *F. novicida* and HSV1 infections, the cytosolic dsDNA sensor AIM2 forms the AIM2-PANoptosome comprised of ZBP1, Pyrin, ASC, caspase-1, caspase-8, FADD, RIPK1, and RIPK3 (13). Together, these data suggest that the cell death–inducing PANoptosome complexes typically consist of sensors (e.g., ZBP1, NLRP3, AIM2, Pyrin), adaptors (e.g., ASC, FADD), and effectors (e.g., RIPK1, RIPK3, caspase-8, caspase-1). Additionally, the evidence suggests that PANoptosomes with differing compositions are likely to form in response to different infections or stimuli, similar to the diversity observed in inflammasomes.

In addition to the relatively well-characterized ZBP1- and AIM2-PANoptosomes, PANoptosis has also been observed under several other physiological conditions, though the molecular identity of those PANoptosomes remains to be elucidated. Infection with murine hepatitis virus (MHV), a betacoronavirus, induces PANoptotic cell death; absence of inflammasome or pyroptotic components, including NLRP3, caspase-1, or GSDMD, exacerbates cell death by enhancing the activation of apoptotic caspase-3, -7, and -8 along with necroptotic MLKL (105). Furthermore, PANoptosis can also play a key role in cytokine storm–related clinical pathology in COVID-19. TNF-α in combination with IFN-γ mirrors the clinical symptoms of COVID-19 and drives PANoptosis. The TNF-α plus IFN-γ–induced PANoptosis can be abrogated completely in *Ripk3*$^{-/-}$*Casp8*$^{-/-}$ or *Ripk3*$^{-/-}$*Fadd*$^{-/-}$ macrophages, but not in *Casp1*$^{-/-}$, *Gsdmd*$^{-/-}$, *Gsdme*$^{-/-}$, *Casp3*$^{-/-}$, *Casp7*$^{-/-}$, *Ripk3*$^{-/-}$, or *Mlkl*$^{-/-}$ cells (7). This cytokine mixture can also induce PANoptosis in multiple human cancer lineages, including cells derived from melanoma, leukemia, colon, and lung cancers (106). Likewise, PANoptosis can also be induced by TAK1 inhibition through *Yersinia* infection, genetic mutation of TAK1, or treatment with TAK1 inhibitors (8, 80, 81, 103). RIPK1 governs the PANoptotic cell death program after TAK1 inhibition, and RIPK1 forms a PANoptosome complex with NLRP3 inflammasome components, caspase-3, caspase-8, FADD, and RIPK3 (103). This RIPK1-mediated PANoptosome requires further characterization.

Regulating PANoptosis

Due to the critical role of PANoptosis in activating inflammatory cell death and cytokine and DAMP release, its regulation is essential. IFN regulatory factor 1 (IRF1) has been identified as a key upstream regulator of PANoptosis in many conditions. IRF1 drives PANoptosis to limit colorectal tumorigenesis in mice; *Irf1*$^{-/-}$ mice exhibit higher tumor burden, which correlates with reduced PANoptosis in the colon (107). In line with this report, HCT116 human colon cancer cells deficient in IRF1 are resistant to TNF-α plus IFN-γ–induced PANoptosis (106). Mechanistically, TNF-α plus IFN-γ–induced PANoptosis is regulated through the JAK/STAT1 pathway, which relays its downstream signaling through IRF1 (7). In murine macrophages, IRF1 controls the expression of *Nos2* and thereby regulates the consequent NO production to trigger PANoptosis. Although the role of NO in cell death is debated (108),

TNF-α plus IFN-γ–induced PANoptosis in murine macrophages can be fully rescued by *Nos2* deletion or by addition of NO inhibitors (7). However, human cancer cells undergo PANoptosis in an NO-independent, IRF1-dependent manner (106), suggesting there may be cell type– or species-specific differences in regulation.

Additionally, the PANoptosome sensor ZBP1 can be transcriptionally regulated by IRF1. In response to IAV infection, *Irf1*$^{-/-}$ macrophages exhibit lower induction of ZBP1 protein expression compared with wild-type cells, which is correlated with reduced activation of PANoptotic markers (109). IFN signaling has been further implicated in ZBP1-mediated PANoptosis, as IFN treatment during severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and MHV infections in macrophages upregulates ZBP1 to drive robust PANoptosis and cytokine release (14). Similarly, in response to *F. novicida* infection, IRF1 has also been shown to regulate the AIM2 inflammasome through the induction of guanylate-binding proteins (110), indicating that IRF1 could have a key regulatory role in AIM2-mediated PANoptosis; however, this remains to be confirmed.

Several additional points of regulation have been identified in PANoptosis. The apoptotic executioner caspase caspase-6 was found to have an important role in this process. Caspase-6 is a key ZBP1-PANoptosome component that facilitates the RHIM-dependent interaction of ZBP1 with RIPK3 (12). Additionally, the Zα domain of ZBP1 is essential for its activation and the subsequent interaction with RIPK3 and downstream cell death signaling. Indeed, perinatal lethality caused by mutation in the RHIM domain of RIPK1 can be rescued by deletion of ZBP1 or its Zα domain. When the RIPK1–RIPK3 interaction is interrupted, ZBP1 can interact with RIPK3 to drive cell death (111, 112). Similarly, the Zα domain of ZBP1 was shown to be crucial to induce PANoptosis in response to fungal pathogens *Aspergillus fumigatus* and *Candida albicans* (113) and in response to coronavirus infections (14). More recently, another layer of regulation of ZBP1-mediated PANoptosis was discovered. Adenosine deaminase acting on RNA 1, the only mammalian protein in addition to ZBP1 that contains a Zα domain, interacts with ZBP1 to inhibit ZBP1-dependent PANoptosis. However, when adenosine deaminase acting on RNA 1 is restricted to the nuclear compartment, through treatment with nuclear export inhibitors (KPT-330 or leptomycin B), ZBP1 interacts with RIPK3 to induce PANoptosis (9). This regulation has been shown to have therapeutic implications for treating cancers (9).

Caspases: viewed with new glasses in an old frame

The molecular characterization of PCD pathways highlights the critical role of caspases within these processes (Table I). Apart from inducing inflammation and cell death, caspases are also involved in many nonlethal processes, including cell proliferation, differentiation, and remodeling (114). Based primarily on their cell death functions, the caspases have historically been classified as either pyroptotic/inflammatory (caspase-1, -4, -5, and -11), apoptotic (caspase-3, -6, -7, -8, -9, and -10), and other (caspase-2, -12, and -14) (115). However, the recent evidence showing extensive cross-talk among the PCD pathways and the critical role of caspases in this cross-talk have suggested that the classical grouping of caspases may be misleading. Indeed, many caspases that had been classified as apoptotic have now been shown to drive lytic cell death or inflammatory cytokine production directly or indirectly (Fig. 1). For example, caspase-8 can also cause direct cleavage of GSDMD to drive the formation of membrane pores (80). In addition, caspase-8 cleaves IL-1β at the same cleavage site as caspase-1, producing the mature form of the cytokine (116). This shows that caspase-8, which was previously categorized as apoptotic, can cleave the pore-forming protein GSDMD as well as release inflammatory cytokines. In contrast, caspase-7, which was categorized previously as an apoptotic caspase, counteracts the activation of pyroptotic molecules to facilitate activation of apoptotic components. Caspase-7 antagonizes GSDMD pores, facilitating the completion of intestinal epithelial cell extrusion in response to *Salmonella* infection. Also, caspase-7 activates acid sphingomyelinase by proteolytic cleavage to generate ceramide, which in turn enhances membrane repair (117). Moreover, the process of PANoptosis, in which caspase-1, -8, -3, and -7 are activated together, suggests significant additional connections for caspases (9–14, 104, 105). As a particular example, in the bone inflammation observed in *Pstpip2*^{cmo} mice, combined deletion of both caspase-1 and caspase-8, along with RIPK3, can prevent the inflammation, whereas single deletions of caspase-1 or caspase-8 do not rescue mice from disease. This suggests redundant roles for these caspases in the disease (101). Together, these observations lead us to propose that caspases like caspase-1, -3, -6, -7, and -8 should be classified as PANoptotic caspases or apoptotic/innate immune cell death molecules. It is possible that other caspases might also have such redundant roles and are involved in the PANoptotic process; this requires further investigation and characterization.

Significance of PANoptosis for innate immunity and therapeutics

The innate immune system has evolved to respond to different types of stresses the body encounters, from infection to tumorigenesis. Although the nature of the triggers may vary, the immune compartment engages its diverse PRRs to protect the host (22). Pathogens, in contrast, have developed strategies to escape the surveillance of the innate immune system to replicate inside the host. An example of this strategy is the encoding of caspase inhibitors by various viruses (61). Similarly, bacteria like *Shigella flexneri* carry molecules that allow them to block both apoptosis and necroptosis simultaneously; *S. flexneri* produces OspC1, which blocks caspase-8, and OspD3, which degrades RIPK1 and RIPK3 (118).

As a result of this evolutionary tug of war between hosts and pathogens, the innate immune system must develop alternative approaches to clear the pathogen and protect the host. In this context, an integrated cell death modality would be beneficial to counteract the invading infectious agent (13). PANoptosis is one such unique mode of integrated cell death with features of pyroptosis, apoptosis, and necroptosis that could allow for activation of an innate immune response despite pathogen-evasion strategies (11, 119, 120). Indeed, PANoptosis is activated in response to diverse triggers, ranging from viruses to fungi. In response to fungi, specifically *C. albicans* and *A. fumigatus* infections, ZBP1 functions as the apical sensor to induce an immune response by activating PANoptosis (113). Notably, ZBP1 also senses IAV to induce PANoptosis and NLRP3 inflammasome activation (10, 121), and ZBP1 also can form a

Table I. Caspases and their currently known roles in cell death

Caspase	Host	Historic Classification in PCD	Current Known Functions	Proposed Reclassification in PCD	First Author, Reference
Caspase-1	H/M	Inflammatory (pyroptotic)	Pyroptosis, PANoptosis: cleaves and activates GSDMD, IL-1β, IL-18, caspase-7, and PARP1	Innate immune cell death molecule	Kesavardhana et al. (5), Shi et al. (37), Lamkanfi et al. (70), Malireddi et al. (71), Tsuchiya et al. (73), Kostura et al. (122), Thornberry et al. (123)
Caspase-2	H/M	Apoptotic initiator	Apoptosis: cleaves and activates caspase-3 and caspase-7 from PIDDosome	Apoptotic initiator	Kesavardhana et al. (5), Tinel and Tschopp (124)
Caspase-3	H/M	Apoptotic executioner	Pyroptosis, apoptosis, PANoptosis: cleaves and inactivates GSDMD; cleaves and activates GSDME; executes apoptosis through cleavage of other substrates	Apoptotic/innate immune cell death molecule	Kesavardhana et al. (5), Wang et al. (45), Orning et al. (81), Zhou et al. (83), Chen et al. (84)
Caspase-4	H	Inflammatory (pyroptotic)	Pyroptosis: cleaves and activates GSDMD	Inflammatory (pyroptotic)	Kesavardhana et al. (5), Shi et al. (37)
Caspase-5	H	Inflammatory (pyroptotic)	Pyroptosis: cleaves and activates GSDMD	Inflammatory (pyroptotic)	Kesavardhana et al. (5), Shi et al. (37)
Caspase-6	H/M	Apoptotic executioner	Apoptosis, PANoptosis: cleaves and activates caspase-3, caspase-7, and lamin A; stabilizes PANoptosome complex	Apoptotic/innate immune cell death molecule	Kesavardhana et al. (5), Zheng et al. (12), Ruchaud et al. (125)
Caspase-7	H/M	Apoptotic executioner	Pyroptosis, apoptosis, PANoptosis: cleaves and inactivates GSDMD; cleaves and activates GSDME; executes apoptosis through cleavage of other substrates	Apoptotic/innate immune cell death molecule	Kesavardhana et al. (5), Lee et al. (13), Nozaki et al. (117)
Caspase-8	H/M	Apoptotic initiator	Pyroptosis, apoptosis, necroptosis, PANoptosis: cleaves and activates GSDMD, GSDME, IL-1β, IL-18, caspase-3, caspase-7, caspase-9, RIPK1, and RIPK3	Apoptotic/innate immune cell death molecule	Kesavardhana et al. (5), Boldin et al. (50), Muzio et al. (51), Orning et al. (81), Demarco et al. (82), Maelfait et al. (116)
Caspase-9	H/M	Apoptotic initiator	Apoptosis: cleaves and activates caspase-3, caspase-7, and caspase-8	Apoptotic initiator	Kesavardhana et al. (5), Zou et al. (49)
Caspase-10	H	Apoptotic initiator	Apoptosis: cleaves and activates caspase-3 and caspase-7; suggested to negatively regulate caspase-8	Apoptotic initiator	Kesavardhana et al. (5), Horn et al. (126)
Caspase-11	M	Inflammatory (pyroptotic)	Pyroptosis: cleaves and activates GSDMD	Inflammatory (pyroptotic)	Kesavardhana et al. (5), Shi et al. (37), Kayagaki et al. (43), Shi et al. (127)
Caspase-12	H/M	Inflammatory (pyroptotic)	Pyroptosis: conflicting reports of inhibiting caspase-1 activity	Inflammatory (pyroptotic)	Kesavardhana et al. (5), Saleh et al. (128), Salvamoser et al. (129), Vande Walle et al. (130)

H, human; M, mouse; PARP1, poly(ADP-ribose) polymerase 1; PIDD, P53-induced protein with a death domain.

PANoptosome complex with other inflammasome sensors, AIM2 and Pyrin, to drive PANoptosis in response to HSV1 and *F. novicida* infections (13). This suggests that inflammasomes can act as integral components of PANoptosomes in a trigger-specific manner.

Together, these observations indicate that activation of PANoptosis is a common host immune response to fight infections. Furthermore, these results suggest that PANoptosis could be induced by multiple sensors in response to various triggers. However, the identity of triggers and their PANoptosis-engaging PRRs needs further investigation. The composition of PANoptosomes and the mechanisms involved in the execution of PANoptosis may exhibit cell type-specific, or species-specific, nuances that have yet to be discovered.

Continued characterization of the molecular mechanisms of PANoptosis has proven to be informative for the development of treatment strategies. For example, although it was known that the serum of patients infected with SARS-CoV-2 contained elevated levels of proinflammatory cytokines, the functional consequence of this phenomenon in terms of inflammation and pathology was not well understood. The identification of PANoptosis downstream of cytokine storm, specifically in the context of the synergistic action of TNF-α and IFN-γ, led to the characterization of this regulatory pathway (7). Understanding the underlying molecular mechanism highlights many potential therapeutic targets and provides an avenue to test pharmaceutical candidates that modulate this pathway. Indeed, the administration of neutralizing Abs against TNF-α and IFN-γ improves the survival of mice infected with SARS-CoV-2 (7). Similarly, PANoptosis has been implicated in the failure of IFN therapy in SARS-CoV-2 treatment (14). IFN treatment strategies can be used to reduce the viral load in patients and were expected to improve patient outcomes; however, the upregulation of the IFN-inducible gene *ZBP1* compromises the therapeutic benefits by driving PANoptosis in response to IFN treatment during SARS-CoV-2 infection and MHV infection in human and murine macrophages, respectively (14). These results suggest that inhibiting ZBP1 could improve the efficacy of IFN-based therapies and pave the way for development of novel therapeutic approaches.

Alternatively, although PANoptosis has negative effects during cytokine storms and some infections, it can be beneficial in other disease processes, such as cancer. For instance, by leveraging the discovery of TNF-α plus IFN-γ–induced PANoptosis, an effective antitumor strategy can be developed. Indeed, intratumoral administration of TNF-α plus IFN-γ suppresses tumor growth in mice (106). Similarly, the combination of IFN and a nuclear export inhibitor, such as KPT-330, can upregulate ZBP1-mediated PANoptosis; this combination regresses tumors in a murine model of melanoma (9). These examples provide clear evidence that modulating PANoptosis or its components is a promising strategy for therapeutic innovation.

Conclusions

The existence of different cell death modalities has diverse, critical implications in the innate immune system and its impacts on health and disease. However, characterizing the cross-talk among the PCDs is necessary to understand the mechanisms of innate immunity in terms of pathogen or danger sensing and develop novel therapeutics. Employing genetic and biochemical approaches in conjunction with organismal phenotypic characterization to inform an integrated, multidisciplinary understanding of PCD has led to the discovery of PANoptosis. Continuing to use these multifaceted approaches that integrate diverse areas of biology, such as microbiology, innate immunity, and cell death, provides a foundation for continued discovery that builds on initial characterizations of the innate immune system that focused on a specific PRR recognizing and responding to a specific PAMP or DAMP.

Although the characterization of different PANoptosome complexes, including the ZBP1- and AIM2-PANoptosomes, and their downstream effectors has now been achieved, there is still much to learn regarding the regulators upstream of PANoptosome assembly and execution. Additionally, understanding the cell type–specific involvement of specific molecules and analyzing potential differences between murine and human cells will provide key insights. A fresh assessment of previous models of innate immune responses and PCD is warranted to better understand the full picture of cell death and its implications in health and disease.

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Disclosures

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