REVIEW ARTICLE

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PANoptosis: A Coordinated Response in the Diversity of Cell Death

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Abstract

The recently introduced concept of PANoptosis describes a highly regulated mechanism involving the coordinated action of pyroptosis, apoptosis, and necroptosis. However, none of these three types of cell death can explain this concept alone. PANoptosis is mediated by a structure called the PANoptosome. PANoptosome components can be formed in different ways according to triggers and receptor interactions. Therefore, stimulators and regulators become central to understanding the mechanism of PANoptosis. In this review, the mechanism of PANoptosis was summarized in general, and PANoptosome regulators in the literature were discussed collectively. We aimed to contribute to the possible therapeutic approaches.

Keywords: PANoptosis, pyroptosis, apoptosis, necroptosis, cell death

Introduction

Programmed cell death (PCD) mechanisms are an inherent part of protection against pathogens and cellular stress. Pyroptosis, apoptosis, and necroptosis are the best-known PCD pathways that protect the body against both internal and external risk factors (1, 2). The observation that all three cell death pathways can be activated in response to certain stimuli, such as influenza virus (IAV) infection, has raised the question of whether they are triggered independently or work in concert. In 2019, PANoptosis (P, pyroptosis; A, apoptosis; N, necroptosis), a concept that encompasses the interplay of pyroptosis, apoptosis, and necroptosis, was defined by realizing that the three PCD mechanisms are linked (3). With the discovery of the regulators of the PANoptosis mechanism, it became evident in 2020 that these three death pathways are controlled through the PANoptosome complex

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(4). PANoptosis is an inflammatory PCD mechanism that highlights the important cross-talk and coordination between the three death pathways regulated by the formation of PANoptosome complexes as a result of complex interactions of different receptors and molecular signaling. It has been associated with many diseases, including infectious, neurodegenerative, autoinflammatory, cancer, and metabolic (5, 6). In particular, inflammasome elements, which act as constituents of the PANoptosome, have a pivotal function in the regulation of inflammatory responses and cell death pathways. Components such as the NOD-like receptor family and pyrin domain-containing 12 (NLRP12) also contribute to the activation of PANoptosomes, as well as the inflammasome, shaping inflammatory outcomes and cell death (7).

PANoptosome production and PANoptosis activation begin with sensing pathogen-associated molecular patterns (PAMP), damage-associated molecular patterns (DAMPs), or other risk factors. Almost all PANoptosomes share common structural components of pyroptosis, apoptosis, and necroptosis. In essence, a PANoptosome consists of three types of structures: the sensor protein, which is important for sensing and determining the type of PANoptosome; the adaptor protein region with the caspase (CASP) recruitment domain (CARD); and the effector protein, which is required for subsequent catalytic activity. In general, the initiation of PANoptosis involves sensing endogenous or exogenous danger signals by specific sensors, such as absent in melanoma 2 (AIM2), Z-DNA binding protein 1 (ZBP1), NLRP12, followed by the transduction of signals recognized by downstream adapter proteins to effector proteins. These effectors, gasdermin D (GSDMD), Casp3, Casp7, and mixed lineage kinase domain-like protein (MLKL), are activated in response to PANoptosome formation and drive PANoptosis. These are followed by pyroptosis, which is mediated by GSDMD, Casp8-dependent apoptosis, and necroptosis, which is mediated by MLKL. Amongst them, GSDMD is cleaved by Casp1 and certain other caspases. Casp3 and Casp7 are activated by Casp8, while receptor-interacting protein kinase 1 (RIPK1) interacts with RIPK3 for activation. MLKL is then phosphorylated, and PANoptosis is induced through the three death pathways (8). However, this generalization is not valid for every stimulus. The components and interactions that make up the PANoptosome vary depending on the triggers. Therefore, the PANoptosome has become a central focus for the study of the mechanism of PANoptosis (5).

An important point to consider in understanding PANoptosis is the coactivation of the three death pathways (pyroptosis, apoptosis, and necroptosis). However, this does not mean all three cell death forms occur simultaneously. In some cases, when one type of cell death in PANoptosis is inhibited, other types of cell death can be promoted (9). For example, in *Salmonella* infection, a PANoptosis mechanism can be observed in which pyroptosis and apoptosis are inhibited, and necroptosis is promoted by the down-regulation of Casp8 (10).

Awareness of the basic mechanisms of types of PCD is important for understanding the mechanism of PANoptosis and its relationship with diseases, as these processes are interconnected in PANoptosis through common regulatory proteins and signaling pathways.

Pyroptosis, Apoptosis, Necroptosis

Each multicellular organism has a number of processes that kill its own cells. Physiologically, the reasons for this are related to defense, development, homeostasis,

Highlights

- PANoptosis provides an integrated cell death mechanism that responds to a wide range of triggers, from viruses to fungi, supporting the immune response against invading pathogens.
- The composition of the PANoptosome varies depending on specific triggers and disease contexts; this review compiles PANoptosis regulators that have previously been discussed separately in the literature.
- Reviewing the molecular interactions among pyroptosis, apoptosis, and necroptosis, draws attention to the context-dependent roles of caspases, contributing to a better understanding of PANoptosis.
- Recent findings on macrophage polarization, dendritic cell activation, and immunogenic cell death have begun to shape our understanding of the role of PANoptosis in tumor immunity.
- The coordinated activation of pyroptosis, apoptosis, and necroptosis in PANoptosis does not necessarily indicate that all three cell death pathways occur simultaneously.

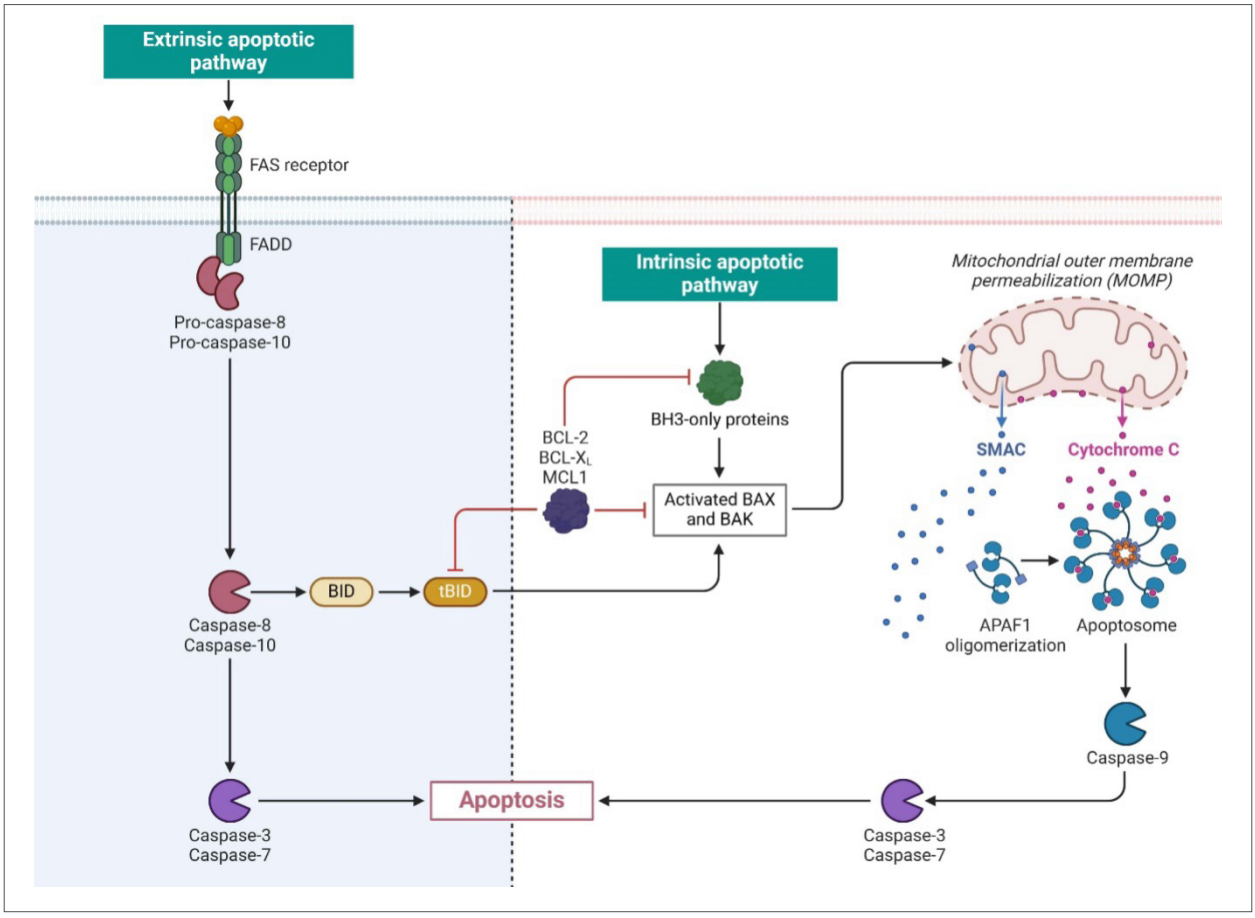

Figure 1. General representation of signaling molecules involved in endogenous and exogenous apoptosis pathways. While signaling molecules basically mediate apoptosis, they also play a role in the PANoptosis mechanism by cross-talking with molecules involved in pyroptosis and necroptosis. *(Modified and created with BioRender.com by Karaca, M. Adapted from "Apoptosis Extrinsic and Intrinsic Pathways" by BioRender.com, 2025. Retrieved from https://app.biorender.com/biorender-templates)*

and aging. Apoptosis is a morphologically recognizable form of cell death that can occur through multiple mechanisms (11). Apoptosis, one of the first defined PCD pathways, can occur through three pathways. Endogenous (intrinsic) apoptosis, exogenous (extrinsic) apoptosis, and the later identified endoplasmic reticulum (ER) stress pathway. Intrinsic and extrinsic pathways are summarised in Figure 1. In the endogenous apoptosis pathway, mitochondrial damage or dysfunction causes the outer membrane to become permeable, releasing several molecules, including cytochrome C (cyto-C). Subsequently, cytosolic cyto-C is recognized by Apaf-1. Casp9, an intrinsic apoptosis pathway initiator, is activated by cyto-C to mediate apoptosome formation (12). Afterward, Casp3, Casp6, and Casp7 are activated, and apoptosis occurs (13). The Bcl-2 gene family regulates this pathway (14). Binding extracellular death ligands to death receptors on the cell surface initiates the extrinsic apoptosis pathway and triggers apoptosis. Casp8 has been identified as the initiator of this pathway (15). These ligands can be secreted by immune cells (T lymphocytes, natural killers [NKs], macrophages, and dendritic cells [DCs]). The subsequent signaling pathway differs depending on the activated ligand (16). In the stress-induced apoptosis pathway of the ER, a response termed the unfolded protein response (UPR) is triggered when the stress of the ER is experienced due to various factors. The UPR is activated by three major ER stress-integrated proteins: inositol requiring enzyme-1 (IRE1), protein kinase RNA-like endoplasmic reticulum kinase (PERK), and activating transcription factor 6 (ATF6). This is followed by a process in which the pro-apoptotic proteins Bcl-2 associated X protein (BAX), Bcl-2 associated agonist of cell death (BAD), and Bcl-2 antagonist/killer (BAK) are activated (17). Killer caspases have the ability to initiate apopto-

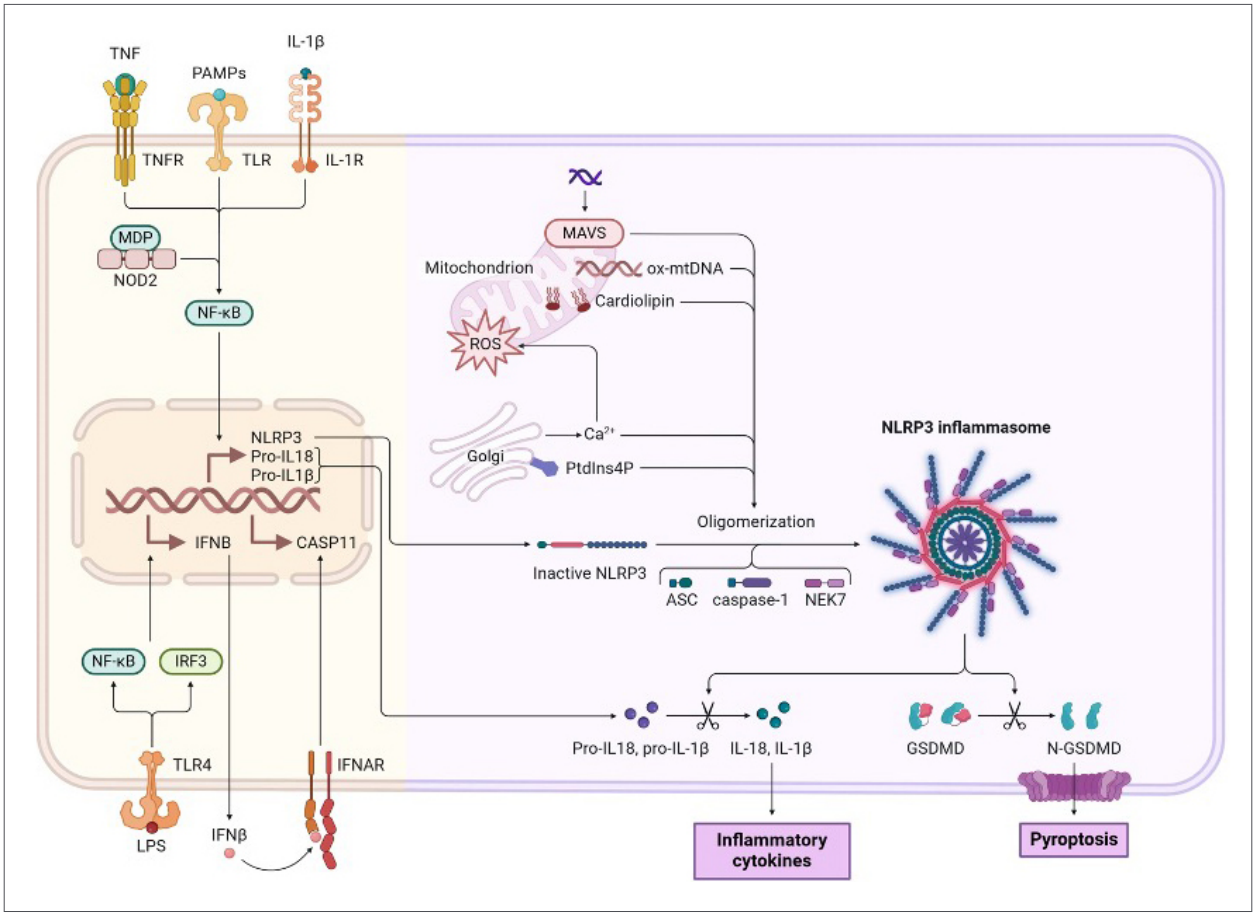

Figure 2. Structures involved in NLRP3 inflammasome-mediated pyroptosis mechanism. *(Modified and created with BioRender.com by Karaca, M. Adapted from "NLRP3 Inflammasome Activation" by BioRender.com, 2025. Retrieved from https://app.biorender.com/biorender-templates)*

sis by acting on chaperones and approximately a thousand substrates. The morphological characterization of apoptotic cells is also well-known (18).

Pyroptosis was first reported in 1992 as Casp1-mediated cell death (19). However, its mechanism was elucidated in the following years with the realization that GSDMD is a target for cleavage by different caspases (20, 21). Thus, pyroptosis was identified as a GSDMD-driven lytic and inflammatory-driven cell death program. GSDMD is a lethal protein that is proteolytically cleaved and activated by pro-inflammatory caspases (Casp1/4/5/11), forming cytoplasmic membrane pores (19). Pro-inflammatory caspases are localized in inflammasomes, which are large cytosolic protein complexes that can cleave and activate protein substrates. Inflammasomes are a complex that executes pyroptosis of multimeric protein structures formed in a cell to regulate host defense mechanisms against infectious agents and physiological perturbations (22). Some NOD-like receptors (NLRs) and other sensors, such as AIM2, act as sensors for assembling inflammasomes. Inflammasomes often contain the apoptosis-associated speck-like (ASC) adaptor protein, which has both the pyrin domain (PYD) and CARD. Following the formation of the inflammasome, inactive pro-IL-1ß, and pro-IL-18 cytokines are cleaved and released in their mature and bioactive form as IL-1ß and IL-18, similar to GSDMD, and pyroptosis is initiated (23), summarised in Figure 2. According to distinct molecular mechanisms, it can occur in four ways: canonical, non-canonical, Casp3/8-mediated, and granzyme-mediated (24). Pyroptosis occurs mainly in professional phagocytes of the myeloid lineage but is also seen in some other cell types, such as $CD4^+$ T lymphocytes and neurons (25). Furthermore, while GSDMD is the most well-known executioner protein of pyroptosis, it is not the only gasdermin capable of inducing pyroptotic cell death (26).

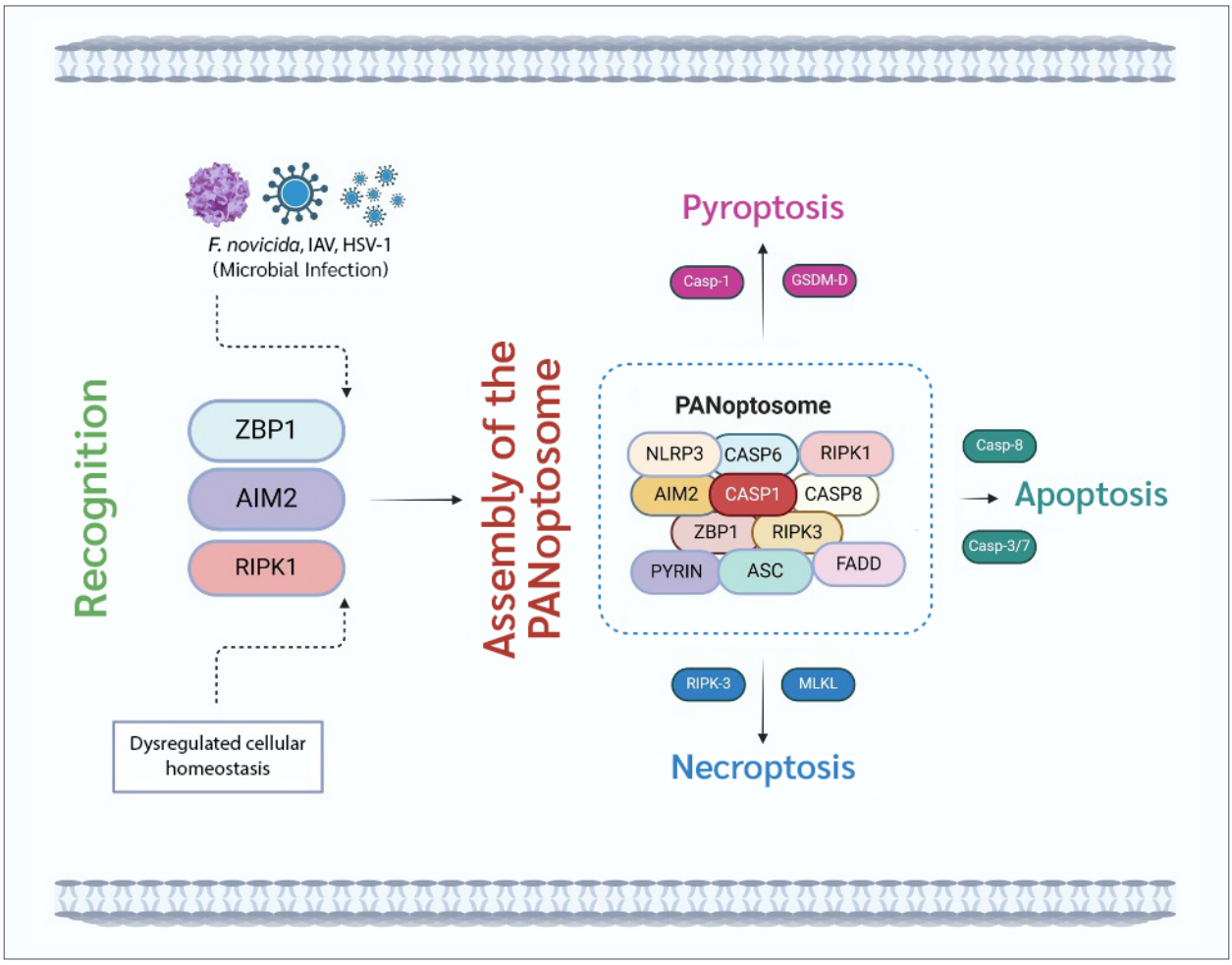

Figure 3. Components involved in PANoptosome formation. The components depicted in the figure do not coexist in this exact arrangement during PANoptosome formation. Variations in formation are seen according to the type of PANoptosome. Therefore, both sensor molecules and stimulus diversity are essential. PANoptosome structure should be evaluated specific to the pathogen and should not be generalised. (*Created with BioRender.com by Karaca, M., 2025*)

Although necroptosis is activated by MLKL phosphorylation mediated by RIPK1 and RIPK3 oligomerization rather than caspase cleavage, its initiation requires Casp-8 inhibition. Nevertheless, unlike apoptosis and pyroptosis, it is generally considered caspase-independent (27). It is a regulated form of necrosis in which the dying cell releases its intracellular components, which can trigger an innate immune response (28). Necroptosis is typically caused by tumor necrosis factor (TNF), Fas, or lipopolysaccharide (LPS) activating RIPK3 kinase, allowing the subsequent phosphorylation of the pseudokinase MLKL. It is triggered by Casp8-mediated disruption of apoptosis and depends on receptor-interacting protein kinases (RIPK1/3) and the mixed lineage kinase domain to form the necroptosome. The release of cytosolic contents and cell death-associated molecular patterns (CDAMPs) can trigger innate immune responses and promote acquired immune responses (29).

These three death pathways have a more complex mechanism than outlined above and are regulated by many additional factors not mentioned here (1, 18). The focus of this review is PANoptosis, which arises from the interactions among these three death pathways that act together, as well as the connections between the PANoptosome and diseases and the associated regulatory molecules.

PANoptosome Component

The PANoptosome serves as an integrative platform for the simultaneous interaction of the active elements of

the three death pathways. This flexible, multiprotein complex consists of several proteins, including serine/threonine kinases, caspases, and specific death domains. Various stimuli such as IAV, vesicular stomatitis virus, *Listeria monocytogenes*, and *Salmonella enterica* serovar Typhimurium activate sensors such as ZBP1 that trigger the formation of PANoptosome. Once the PANoptosome is formed, it promotes the activation of executors in each death pathway, including apoptosis mediated by Casp3/7, pyroptosis via GSDMD/E, and necroptosis driven by RIPK1/MLKL (4, 30-38). (Figure 3 summarises the structures mainly involved in PANoptosome formation.) Sensors encountering stimuli interact with various molecules to form PANoptosomes. The components of PANoptosomes vary depending on the stimulus and the sensor. The known types of PANoptosomes are summarized in Figure 4.

It was initially shown that the PANoptosome is composed of RIPK1, CARD, NLRP3, and caspases (39). Further studies showed that RIPK3, Casp6, ZBP1, and Casp1 are also involved in the PANoptosome formation triggered by IAV infection (32). Understanding the diversity of these molecules and how they interact reveals that the three types of PCD are interconnected, constituting PANoptosis. Rather than being activated separately, they are regulated together by the PANoptosome complex, inducing cell death (3, 4, 39). In some cases, inhibition of pyroptosis allows Casp8 to activate the inflammasome, which may trigger both apoptosis and a Casp8-dependent form of cell death known as secondary pyroptosis (4, 40, 41). Moreover, the inhibition of Casp-8 results in the formation of complex IIb via the TNF or Toll-like receptor (TLR) pathway, which ultimately culminates in necroptosis (42). These analogous mechanisms permit us to comprehend the reasons behind the non-standardized structure of the PANoptosome, the potential for

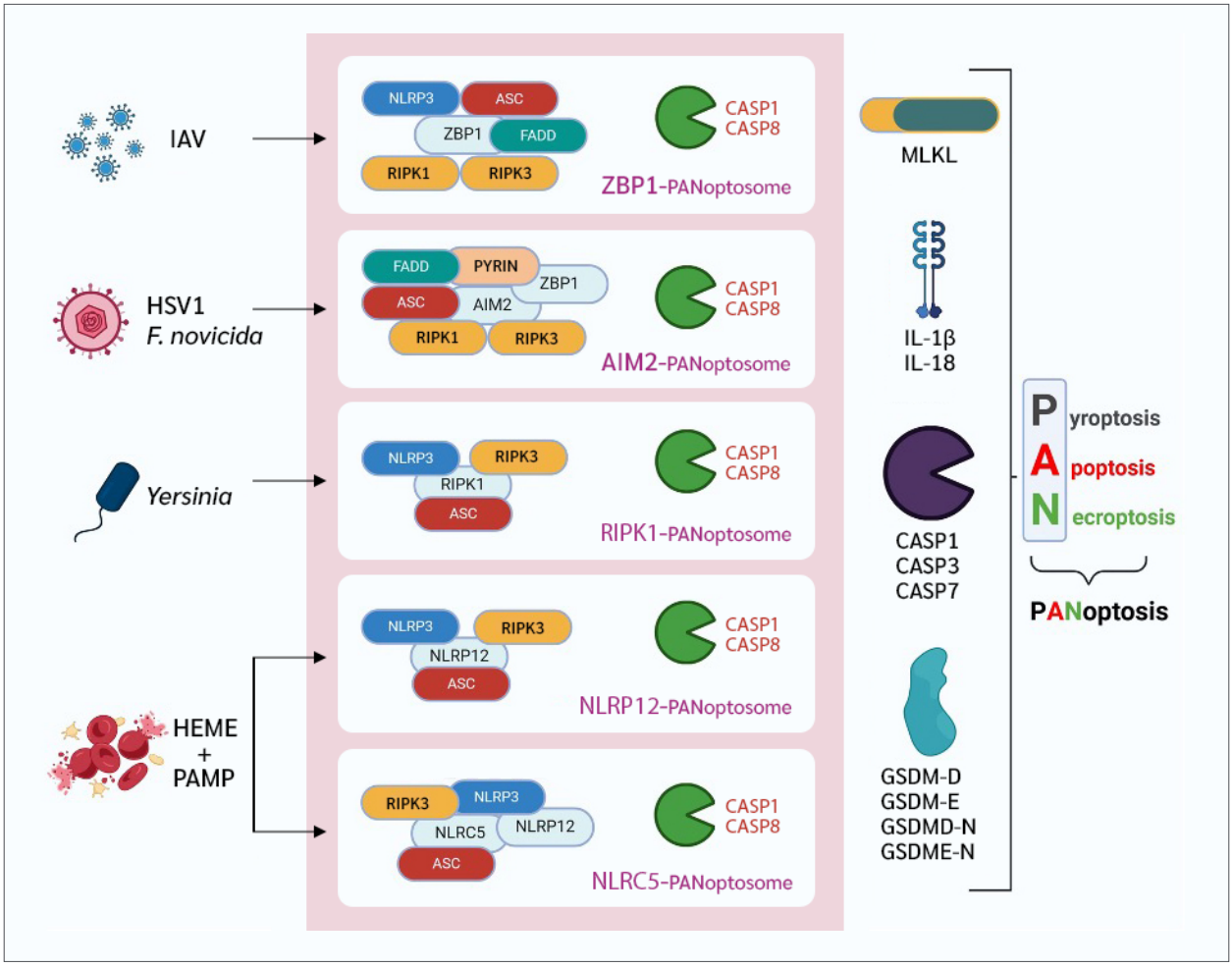

Figure 4. Types of PANoptosome defined for different stimuli. *(Created with BioRender.com by Karaca, M., 2025)*

it to comprise disparate components and the necessity for a PANoptosome in which the three death pathways operate in concert.

The components of the PANoptosome vary between different diseases. Therefore, the main phenotypic members can vary depending on the type of stimulus applied. Single cell analysis of PANoptosome complexes has led to a better understanding of PANoptosomes under specific conditions (30, 43). In addition to the first described PANoptosomes, RIPK1-PANoptosome and NLRP12-PANoptosome were identified (7, 44). Most recently, it was reported that NLR family, CARD domain containing 5 (NLRC5) similarly mediates PANoptosome formation (45).

In the mechanism of PANoptosome formation, the structures that give the aforementioned PANoptosome types their names (ZBP1, AIM2, RIPK1, NLRP12) act as sensors for triggers such as various microbial infections and altered cellular homeostasis. Sensor interactions then initiate the assembly of other components to form the PANoptosome. In necroptosis-associated structures, homotypic actions among receptor-interacting protein homotypic interaction motifs (RHIMs) domains and in the assembly of pyroptotic and apoptotic structures, heterotypic actions between the PYD and the death effector domain are realized (46-49). The PANoptosome is thought to be formed by similar interactions. Furthermore, intrinsically disordered regions (IDRs) have alternatively been reported to be involved in PANoptosome formation (30). The known identified PANoptosome types; ZBP1-PANoptosome (ZBP1, NLRP3, ASC, Casp1, Casp6, Casp8, RIPK1 and RIPK3) (4, 50), AIM2-PANoptosome (AIM2, Pyrin, ZBP1, ASC, Casp1, Casp8, Fas-associated death domain [FADD], RIPK1 and RIPK3) (51), RIPK1-PANoptosome (RIPK1, RIPK3, NLRP3, ASC, Casp1 and Casp8) (44) and NLRP12-PANoptosome (NLRP12, ASC, Casp8 and RIPK3) (7). These PANoptosomes then induce Casp3/7 activation, GSDMD / E cleavage, and phosphorylation of MLKL, leading to membrane pore formation and PANoptosis progression (52). A systematic examination of the established molecular constituents of pyroptosis, apoptosis, and necroptosis, as analyzed through STRING, indicates that these three forms of cell death are not independent processes. This observation supports the hypothesis that they are part of a larger, interconnected PCD network (46, 53).

Furthermore, the formation of PANoptosomes can be regulated by interferon regulatory factor 1 (IRF1) in specific circumstances (54). This topic has been elaborated in the section on 'Regulatory Factors and Diseases.'

ZBP1-PANoptosome

ZBP1 is also known as a DNA-dependent activator of interferon-regulatory factors (DAI) or a DNA-dependent activator of DLM1. ZBP1 consists of three parts: N-terminal Z-DNA binding domain (ZBD), RHIM, and C-terminal signal domain (SD) (55-57). The N terminal contains two Z-form nucleic acid binding domains (Zα1 and Zα2) and a protein homotypic interaction motif (RHIM1 and RHIM2) in the middle that interacts with two receptors. It is inducible by interferon (IFN) and interacts with the RHIM domain and other proteins. The Zα2 domain plays a critical role in the activation of PCDs (51, 58).

Activation of ZBP1 results in its interaction with RIPK3 and recruitment of Casp8, thereby forming cell death signaling scaffolds. The resulting ternary complex has the capacity to activate all three death pathways. Furthermore, ZBP1 induces NF-κB signaling during influenza infection (59, 60).

In addition to its ability to recruit cell death elements such as RIPK3 and Casp8, which are required for the formation of PANoptosomes, ZBP1 can activate cell death signals. A lack of Zα domains has been demonstrated to restrict infection-induced ZBP1 mediated inflammatory cell death (55, 56, 58). ZBP1 deletion prevents IAV-induced activation of the NLRP3 inflammasome. Additionally, RIPK1 plays an active role in preventing ZBP1/RIPK3/MLKL-dependent necroptosis during the development of RHIM (61, 62).

Recently, a novel cell death complex known as TRIFosome, which is triggered by TRIF signaling and involves FADD, RIPK1, and Casp8, has been reported. This complex has a critical role in LPS-induced cell death in the context of transforming growth factor-β (TGF-β)-activated kinase 1 (TAK1) inhibition (63). The regulatory importance of TAK1 for PANoptosis has been mentioned in the "Regulatory Factors and Diseases" section. Despite the absence of evidence indicating a direct interaction between TRIF and other death mediators, it is plausible that TRIF may facilitate the assembly of the PANoptosome complex through its RHIM domain.

PANoptosis caused by ZBP1-PANoptosome is bidirectional. It promotes the elimination of invading pathogens and dysregulated cancer cells, but aberrantly, it

may trigger severe infectious and non-infectious inflammatory responses (64).

AIM2-PANoptosome

The inflammasome is an oligomeric multiprotein complex located in the cytosol. It is not a fixed cell structure but only forms when stimulated by specific DAMPs and PAMPs. Inflammasomes are classified according to the structure of the sensor molecule (64-68). AIM2 is one of these sensor molecules, characterized by a hematopoietic, interferon-induced, and nuclear localization (HIN) region at the carboxyl site and a PYD at the amino-terminal. The AIM2 inflammasome is activated in response to the presence of dsDNA in the cytoplasm and mediates pyroptosis (69). DNA can be of microbial origin (from pathogens) or host DNA released during cellular stress or damage.

Inflammasome formation is initiated following AIM2 detection of dsDNA produced by pathogens, nucleus, and mitochondria. ASC establishes homotypic domain-based connections with AIM2 and pro-Casp1 through PYD-PYD and CARD-CARD. The components of AIM2-ASC-pro-Casp1 bind to the pseudo-axis of double-stranded DNA, forming a large oligomeric complex. Casp1 is the mature form of pro-Casp1 that converts pro-IL-1β, pro-IL-18, and GSDMD into their active forms. IL-1β and IL-18 elicit a cascade of inflammatory responses, while GSDMD-N binds to the cell membrane and induces pyroptosis (70,71).

The inflammasome is a crucial component in the process of PANoptosis as a part of PANoptosomes (7). The interaction of pyrin and ZBP1 facilitates the formation of the AIM2-PANoptosome. However, current knowledge shows this is limited to infections such as herpes simplex virus 1 and *Francisella novicida* and does not occur upon exposure to pure dsDNA. Zα domains of ZBP1 are activated by detecting nucleic acids. AIM2 can also be controlled by activating the IFN signaling pathway. The AIM2-PANoptosome complex includes AIM2, pyrin and ZBP1 as well as ASC, Casp1, Casp8, RIPK3, RIPK1 and FADD (51). These additional components play an important role in facilitating the PANoptosis process. Targeting AIM2 or other components of the PANoptosome may show therapeutic efficacy in the treatment of inflammatory cell death molecules, as well as various viral and inflammatory diseases.

RIPK1-PANoptosome

RIPK1 regulation of PANoptosis is crucial for maintaining cell homeostasis and mediating both PCD and inflammatory reactions. The scaffolding role of RIPK1 facilitates survival signaling by assembling complex I that inhibits cell death, thereby maintaining TNF receptor-1 (TNFR-1) activity (30, 72-76). Complex I activate the NF-κB prosurvival pathway, yet should this signal be disrupted, complex II will then initiate cell death (77, 78). In this context, Casp8 can suppress necroptosis through proteolytic cleavage of RIPK, which are necroptotic mediators. Conversely, the deletion of Casp8 results in the formation of the necrosome (79-82). Deletion of RIPK1 in mice is embryonically lethal and has been shown to cause systemic inflammation through activation of PANoptosis-like cell death regulated by RIPK3, with the involvement of Casp8 and FADD (83-85). PAMPs, via TLRs or death receptor signaling, can promote RIPK1-dependent PANoptosome formation when regulatory proteins such as TAK1 are inhibited (39). Moreover, mutations that inactivate Casp8 catalytic activity can lead to death in embryonic mice by activating RIPK1, RIPK3-MLKL, and Casp1 (86, 87). This situation could be considered as PANoptosis-relation death with the involvement of other effectors. However, it should be noted that MLKL has not been identified in the RIPK1-PANoptosome core scaffold. More specifically, these studies collectively contribute to understanding the regulation of PANoptosis by RIPK1 and Casp8 (30).

NLRP12-PANoptosome

NLRs belong to a group of cytoplasmic pattern recognition receptors (PRRs) that play a role in detecting pathogens or damage, regulating inflammatory signaling, and controlling the transcription of specific genes. NLRP12 is one of the first members identified in the NLR family to contain an N-terminal PYD, nucleotide-binding domain (NBD), and C-terminal leucine-rich repeat (LRR) domain (88). Furthermore, NLRP12 is the first identified to interact with the adaptor protein ASC, leading to the formation of an active inflammasome capable of releasing IL-1β (89). Following the introduction of the PANoptosis concept, it was recognized that NLRP12 not only activates the inflammasome in response to specific PAMPs or TNF but also drives PANoptosome activation, cell death, and inflammation. TLR2/4-mediated signaling through IRF1 leads to inflammasome formation. NLRP12 acts as an integral component of an NLRP12-PANoptosome that drives inflammatory cell death via Casp8 / RIPK3. PAMPs containing ‘heme’ groups can trigger cell death (90). Under certain conditions, these heme-containing PAMPs can also activate the NLRP3 inflammasome (91, 92). In addition to the inflammasome, Casp8 has also been shown to play an essential role in directing NLRP12-mediated inflammatory cell death in response to

exposure to PAMP carrying the heme domain. With this, a multiprotein PANoptosome complex is formed that specifically contains ASC, RIPK3, Casp8, and NLRP3. PANoptosomes can form against heme-positive PAMPs even in the absence of NLRP3, demonstrating that NLRP12 is the main actor (7).

PAMPs and DAMPs released as a result of hemolysis-inducing events can induce activation of TLR-2 and TLR4 by a combination of 'heme.' Therefore, Myd88 signaling is also seen with NLRP12 activity. Mitochondrial reactive oxygen species (ROS) also contribute to NLRP12 induction. Activated NLRP12 triggers the formation of an NLRP12-PANoptosome protein complex involving RIPK3, ASC, and Casp8. This complex promotes the well-characterized mechanism of gasdermins (D and E) cleavage in pyroptosis and pore formation in the plasma membrane, leading to PANoptotic cell death (93). During some infections, ZBP1 can be stimulated simultaneously with AIM2. This shows that it is possible to create PANoptosomes containing different sensors (51).

Molecular Mechanisms and Involvement of the Three Types of Cell Death in PANoptosis

In PANoptosis, the apoptosis, pyroptosis, and necroptosis pathways act together within the same cell, with the components of the three death pathways interacting with each other. This interaction has been described in the literature as cross-talk. The emerging understanding of the connections between cell death pathways has guided the conceptualization of PANoptosis as an inflammatory cell death mechanism. The caspase and RIPK families play the most prominent roles in cross-talk (36).

Caspases are members of the cysteine protease family, proteolytic enzymes that are particularly well characterized in apoptosis. They can be classified according to their role, mechanism of action, and the organism in which they are found. In addition to apoptosis, caspases are also involved in the nonapoptotic cell death processes of necroptosis and autophagy. They also have central roles in pyroptosis (94). In mammals, caspases are classified into three functional groups according to their role: inducers (Casp2, Casp8, Casp9, Casp10), effectors (Casp3, Casp6, Casp7), and inflammatory caspases (Casp1, Casp4, Casp5, Casp11, Casp12, Casp13, Casp14). Aside from some exceptional caspases, the roles of almost all known caspases in apoptosis, necroptosis, and pyroptosis have been described in detail (95, 96). Casp1, which is known to mediate pyroptosis, can function through the Bid-Casp9-Casp3 axis to initiate apoptosis in cells lacking GSDMD (94). Casp3, which is also involved in apoptosis, can initiate secondary necrosis and pyroptosis after cutting the GSDMD-related protein DFNA5 (97). Furthermore, GSDMD / DFNA5 redirects Casp3-mediated apoptosis to pyroptosis upon stimuli such as TNF or chemotherapy drugs (98, 99).

During PANaptosis, Casp1, Casp8, and Casp3 are activated simultaneously to induce cell death through a complex interaction. Casp8 has emerged as a pioneer regulator that links the apoptotic and necrotic pathways. NLRP3 induces pyroptosis in inflammasome activation. Therefore, Casp8 plays a central role in PANoptosis, regulating the delicate balance between the three pathways and ultimately influencing cell fate by activating specific death signals (100, 101).

Apaf-1, one of the leading players in apoptosis, has been shown to cause Casp4-mediated pyroptosis (102). Looking at the close interaction between apoptosis and necroptosis at the signaling level, the double knockout assays FADD / RIPK3 and FLIP / RIPK3 reveal a complex cross-regulation of apoptosis and necrosis. FLIP (an important modulator of apoptosis) prevents the association of FADD-bound Casp8 homodimers that mediate apoptosis. Instead, Casp8-FLIP heterodimers form, preventing the activation of necrosis-mediating RIPK3. In the absence of this heterocomplex, RIPK3 promotes necrosis; however, when FADD is present without FLIP, Casp8-mediated apoptosis is favored (103). In other words, when RIPK3 expression is high, cells undergo necroptosis, whereas when RIPK3 expression is low, they tend toward apoptosis (104).

The binding of TNF-α to TNFR1 results in the formation of complex II also referred to as the cytosolic death-inducing signaling complex (DISC), which is capable of mediating necroptosis. Polyubiquitination of RIPK1 also affects the transition from complex I to complex II. Casp8 has the capacity to inactivate complex II and RIPK1-3 through proteolytic cleavage, thereby initiating the pro-apoptotic caspase cascade. On the contrary, when Casp8 undergoes deletion, depleted or inhibited complex II does not initiate the apoptotic program, and binding of TNFR1 causes necroptosis (105).

Table 1. The key regulators of PANoptosis identified so far in various diseases and conditions.

Regulator	Role	Condition/Pathogen	Mechanisms
M2, NS1, PB1-F2	Regulates ZBP1-NLRP3	Influenza	Viral proteins act as regulators for PANoptosis
Casp6	Facilitates PANoptosis through the ZBP1-RIPK3 interaction	IAV infection Thyroid cancer	Bridges sensor-effector interaction, diagnostic marker in cancer
RDX	Prognostic marker	Breast cancer	Associated with molecular clustering in PANoptosis-based survival prediction
Certain lncRNAs linked to PANoptosis	Associated with metastasis	Colon adenocarcinoma	Linked to immune infiltration and tumor microenvironment
RIPK1, RIPK3, Casp8, NLRP3, ASC, Casp1	Forms RIPK-PANoptosome	*Yersinia* infection	Induces PANoptosis in macrophages independent of ZBP1
TAK1	Inhibits RIPK1 activation, prevents spontaneous PANoptosis	*Yersinia* infection	TAK1-RIPK1 phosphorylation restricts PANoptosis; TAK1 inhibitors allow the formation of RIPK-PANoptosomes
ADAR1	Negative regulator of ZBP1-mediated PANoptosis	Cancer	Tumor suppressor through PANoptosis induction when inhibited
Caspase-1 (Casp1)	Inhibits PANoptosis	*E. faecalis infection*	Suppresses osteoblast PANoptosis through regulation of the NLRP3 inflammasome
IRF1	It promotes PANoptosome assembly by various mechanisms. (such as the JAK/STAT pathway)	COVID-19 Cancer IAV infection	NLRP12 and RIPK1 activate PANoptosomes and inhibit tumor progression
ZBP1	Sensor for PANoptosis	SLE Fungal infections	Activates immune response and links to immune cells through type I interferon signaling
S100A8/A9^{hi} neutrophils	ZBP1-mediated PANoptosis inducer	Lung tissues of septic mice	Mitochondrial dysfunctions and mtDNA-mediated PANoptosis
SopF	Regulates PANoptosis in epithelial cells	*Salmonella* infection	PDK1-RSK phosphorylation downregulates Caspase-8
AIM2	Activates the IL-23 / IL-7 axis, sensor for PANoptosis	Psoriasis	Inflammasome activation increases pro-inflammatory cytokine release
NLRC5	Regulates PANoptosome formation	Colitis Hemophagocytic lymphohistiocytosis	Activated by TLR2/4 signals and NAD^+ levels
Melatonin, Dickkopf-1	Inhibits PANoptosis	Ocular hypertension Diabetic retinopathy	Suppress cell death and retinal ganglion cell loss

M2: Matrix protein 2, **NS1:** Nonstructural protein 1, **PB1-F2:** Polymerase basic protein 1-F2, **Casp6:** Caspase-6, **RDX:** Radixin, **RIPK1:** Receptor-interacting protein kinase 1, **RIPK3:** Receptor-interacting protein kinase 3, **Casp8:** Caspase-8, **NLRP3:** NOD-like receptor pyrin domain containing 3, **ASC:** Apoptosis-associated speck-like protein containing a CARD, **Casp1:** Caspase-1, **TAK1:** TGF-β activated kinase 1, **ADAR1:** Adenosine deaminase acting on RNA 1, **IRF1:** Interferon regulatory factor 1, **ZBP1:** Z-DNA binding protein 1, **S100A8/A9^{hi}:** High expression of S100A8/A9, **SopF:** *Salmonella* outer protein F, **AIM2:** Absent in melanoma 2, **NLRC5:** NLR family, CARD domain containing 5, **TLR2/4:** Toll-like receptor 2/4, **PDK1:** 3-phosphoinositide dependent protein kinase-1, **RSK:** Ribosomal S6 kinase, **IL-23:** Interleukin 23, **IL-7:** Interleukin 7, **SLE:** Systemic lupus erythematosus, **mtDNA:** Mitochondrial DNA, **IAV:** Influenza A virus, **COVID-19:** Coronavirus disease 2019, **SLE:** Systemic lupus erythematosus, **TGF-β**: Transforming growth factor-beta, **TLR2/4:** Toll-like receptor 2/4.

The first genetic argument for a relationship between pyroptosis and apoptosis was the ability of Casp1 to dissociate Casp7 from its activation site in macrophages (106).

Casp8 can act on NLRP3 inflammasome-induced pyroptosis interactions, interact with other inflammasomes, and mediate their activation (46).

In the absence of GSDMD, Casp1 has been shown to induce apoptosis by activating Casp3 and Casp7 in monocytes and macrophages. In contrast, during apoptosis, Casp3 and Casp7 can specifically inhibit pyroptosis by interrupting GSDMD at a different point from inflammatory caspases that inactivate the protein (107, 108).

Inflammasome-activated Casp1 can cleave Bid, leading to the release of mitochondrial SMAC (the second mitochondria-derived activator of caspases) and triggering subsequent necrosis (109). In apoptotic Casp3, it cleaves GSDMD at a cytotoxic N-terminal cleavage point, forming an inactive fragment. This may potentially limit GSDMD-mediated pore formation and pyroptosis (46).

Programmed cell death pathways are nonlinear, including interactions not mentioned here. They are interconnected and have complex signaling cascades and interactions. These interactions between death pathways facilitate the fight against pathogenic agents, including preventing some of the escape strategies of cells generated by pathogens. For this reason, PANoptosis is important for the control of infections and host defense.

PANoptosis and Its Relationship with Different Modes of Cell Death

Available evidence of the relationship between PANoptosis and other pathways of PCD is still limited. Unlike PANoptosis, autophagy was traditionally thought to be regulated primarily through lysosomal pathways rather than caspase enzymes or RIPKs. In time, with the understanding that autophagy and apoptosis are in extensive cross-talk with each other, it is not surprising that many ATGs are recognized and cleaved by caspases (110-114). For instance, hATG3 can be cut down by Casp3, Casp6, and Casp8 (115). While recent research has yet to establish a definitive connection between ER stress, autophagy, and PANoptosis, their involvement in managing cellular stress and orchestrating PCD remains significant. In central gene analyses performed in ulcerative colitis, the TIMP1, TIMP2, TIMP3, IL6, and CCL2 genes were identified as associated with PANoptosis and autophagy (116). Some of the central genes associated with PANoptosis and autophagy have been reported to be correlated with certain immune system cell infiltrations (116). Another study reported that mitochondrial damage mediated by S100A8/A9^{hi} (high expression of S100A8/A9) neutrophils in lung tissues of septic mice causes mtDNA-mediated ZBP1 PANoptozome formation. The same study also reported that S100a8/a9 increased the expression of LC3B, a marker of autophagosomes (117). Furthermore, the impaired autophagy mechanism is known to lead to abnormal activation of inflammasomes by cross-talk (118).

In the metabolic-associated fatty liver disease (MAFLD) mice model, it has been reported that the ferroptosis inhibitor LPT1 can act as a PANoptosis blocker and may protect against steatosis (119). Screening for PANoptosis-related genes identified ten genes associated with colorectal adenocarcinoma (120). Among these, CAV1 has regulatory roles for apoptosis, pyroptosis, and ferroptosis (121-123). The GPX3, IGFBP6, and TIMP1 genes, which are known to be associated with ferroptosis, were also identified among these ten genes (124-126). These results raise an important question of whether ferroptosis can be induced simultaneously with PANoptosis and draw attention to the possible relationship between ferroptosis and PANoptosis. It is suggested that anoikis, a type of apoptosis occurring within tissues, may be associated with PANoptosis due to caspase and signaling molecule interactions such as PI3K/Akt and Smad (101).

The elaboration of these interactions and a better understanding of the relationships linking PANoptosis and other types of PCD are still crucial for the development of clinical and therapeutic approaches. Current studies focus on gene analyses for different diseases to understand the relationship between the death complex PANoptosome and PANoptosis, which can differ from disease to disease.

Regulatory Factors and Diseases

The most important factor affecting PANoptosis and the formation of PANoptosomes with different cellular components is the diversity of the pathogen. Different diseases, such as bacterial, viral, fungal infections, tumors, and autoimmune disorders, can lead to differences in PANoptosome types and regulators. An overview of the summarized regulators is provided in Table 1. For example, influenza viral proteins such as matrix protein 2 (M2), nonstructural protein 1(NS1), and polymerase basic protein 1-F2 (PB1-F2) may play a regulatory role for ZBP1-NLRP (31).

Casp6 also promotes IAV-induced PANoptosis and facilitates the connection between ZBP1 and RIPK3 after infection (32). This is surprising for Casp6, which is characterized as an executioner caspase due to its role as a bridge between a sensor and an effector. Casp6 has also been identified as an important regulator of the cross-talk signaling pathway for PANoptosis in cancer. When

scanning for PANoptosis-related genes as prognostic indicators of thyroid cancer, Casp6 was found to be highly diagnostic and abundant in tumor tissue (127, 128). Casp6 can also promote the differentiation of M2 macrophages and activation of inflammasomes and PANoptosis (32). Despite these, we still have limited knowledge about the role of Casp6 in PANoptosis induced by other pathogens or stimuli (4). Radixin (RDX) was found to be the most relevant gene in investigating the potential of PANoptosis-based molecular profiling and prognostic factors to predict survival in breast cancer patients (129). Nine lncRNAs associated with PANoptosis and colon adenocarcinoma metastasis have been identified and are significantly associated with immune infiltration. This suggests that PANoptosis plays an important role in the tumor immune microenvironment (130).

Yersinia infection triggers PANoptosis in macrophages by promoting the formation of a RIPK-PANoptosome complex that includes RIPK1, RIPK3, Casp8, NLRP3, ASC, and Casp1 (independent of ZBP1) (44). TAK1 is pivotal for cell survival and cellular homeostasis in innate immunity (131). This is significant, as it was among the first regulators to identify PANoptosis. The TAK1-RIPK1 relationship is a good demonstration that phosphorylation does not always lead to activation. TAK1 inhibits RIPK1, limiting its activation and preventing spontaneous activation of PANoptosis (3). *Yersinia* can inhibit TAK1 through YopJ mediation, acting as a handbrake for PANoptosis (39, 132, 133). In fact, the effects of TAK1 on cell death were recognized and investigated prior to the identification of PANoptosis (20, 21, 134). Many pathogens produce inhibitors of TAK1 (TAK1i). Inhibition or deletion of TAK1 results in the induction of PANoptosis in the host through the RIPK1-PANoptosome complex. PANoptosis also promotes pathological inflammation. Therefore, it is important to understand the molecular mechanisms that regulate TAK1i-induced cell death. Recently, it was reported that TAK1i-induced RIPK1-mediated activation of PANoptosis requires the phosphatase PP6 complex (131). PTBP1 and RAVER1 are also functional regulators involved in activating TAK1i-induced PANoptosis (135).

Since deletion of components of the linear-ubiquitin assembly complex (LUBAC) associated with cell death signaling and other complex-I molecules such as ubiquitin effector protein A20 can lead to embryonic death and autoinflammatory diseases, it is thought that they may contribute to the regulation of PANoptosis in a similar way to TAK inhibitors (30, 136).

Another regulator of PANoptosis is adenosine deaminase acting on RNA1 (ADAR1). Acting as an RNA regulator to maintain homeostasis, ADAR1 is a negative regulator of ZBP1-mediated PANoptosis. Inhibition of ADAR1 activity triggers ZBP1-mediated PANoptosis to inhibit tumor formation (137).

Casp1 inhibition in macrophages infected with *Enterococcus faecalis* OG1RF prevents PANoptosis formation (138). *E. faecalis* can also induce PANoptosis of osteoblasts, which is detrimental to the regeneration of periapical bone tissue. The regulation is provided by the NLRP3 inflammasome (139).

IRF1 is known to regulate cell death (140-142). TLR2/4 can induce NLRP12 expression through IRF1-mediated signaling, resulting in inflammasome formation to trigger IL-1β/-18 maturation. In addition, the generated inflammasome acts as an integral element of an NLRP12-PANoptosome that drives PANoptosis via Casp8 / RPK3 (94). Studies indicate that pro-inflammatory cytokines are significantly overexpressed during COVID-19 infection (143). However, only the combination of TNF-α and interferon-gamma (IFN-γ) has been reported to trigger PANoptosis. Collectively, TNF-α and IFN-γ trigger nitric oxide (NO) formation by activating JAK/STAT1/IRF1 signaling. This is followed by Casp8/FADD-based PANoptosis (144). The synergistic effect of these two cytokines can also inhibit PANoptosis-mediated growth of various types of tumors (145). Although other cytokine associations are not clear for PANoptosis, the signaling of IL6-JAK-STAT3, the IFN-γ response, and IL-2-STAT5 signaling in cancer positively correlate with the PANoptosis scoring. This scoring shows that PANoptosis is significantly correlated with the tumor microenvironment and infiltration levels of many types of immune cells, including NK cells, $CD4^+$ and $CD8^+$ T cells, and DCs (146). The discovery of gain-of-function mutations in STAT1 and STAT3 has expanded immunological research aimed at understanding both signaling pathways and associated disorders (147). In this respect, their relationship with the realization of PANoptosis is open to further investigation. In a different study, IRF1 was identified as a master regulator of PANoptosis in myeloid and epithelial cells to protect against colorectal cancer formation (148). Furthermore, IRF1 acts as an up-regulator of RIPK1-PANoptosis when co-stimulated with TAKi and LPS (54). In IAV infection, IRF1 contributes to the formation of the ZBP1-PANoptosome and drives PANoptotic cell death during infection (60).

ZBP1, MEFV, LCN2, IFI27, and HSP90AB1 have been identified as PANoptosis-associated genes in systemic lupus erythematosus (SLE) and are associated with memory B cells, neutrophils, and $CD8^+$ T cells. These genes play a role in SLE by regulating type I interferon responses and IL-6-JAK-STAT3 signaling-mediated regulation of immune cells (149).

In response to fungus, particularly infections by *Candida albicans* and *Aspergillus fumigatus*, ZBP1 acts as an apical sensor to induce an immune response by activating PANoptosis (150).

Salmonella outer protein F (SopF) acts as an effector in *Salmonella* infection, regulating PANoptosis of intestinal epithelial cells to aggravate infection systemically. Phosphoinositide-dependent protein kinase-1 (PDK1) activated by SopF phosphorylates the p90 ribosomal S6 kinase (RSK). Phosphorylation of RSK leads to the downregulation of Casp8. Thus, PANoptosis in intestinal epithelial cells contributes to the severity of systemic infection (10).

The IL-23/IL-7 axis plays an important role in psoriasis and is strongly associated with PANoptosis. AIM2, one of the important sensors of the PANoptosome complex, is elevated in keratinocytes of psoriatic lesions and shows a pro-inflammatory effect by increasing the release of IL-1B and IL-18 and activating the IL-23/IL-7 axis after stimulation (151, 152).

NLRC5, which functions as an innate immune sensor, acts as a regulator for PANoptosome formation by regulating TLR 2/4 signaling and NAD^+ levels. NLRC5 deletion also protects against colitis and hemophagocytic lymphohistiocytosis in mice (45).

PANoptosis is also involved in the death of retinal ganglion cells (RGCs) induced by acute ocular hypertension and diabetic retinopathy. Melatonin and Dickkopf-1 may inhibit PANoptosis and prevent cell death (153, 154).

PANoptosome interactions vary according to the pathogenesis of the disease. Therefore, our molecular understanding of PANoptosis is not yet as well established as that of apoptosis or other cell death mechanisms. Disease- or inducer-specific regulatory mechanisms continue to be investigated. Various PANoptosome components, such as NLRP3 and RIPK3, were known to be associated with different diseases even before PANoptosis was identified (30). Reassessing these diseases with PANoptosis mechanisms can contribute to improve our further understanding of PANoptosis regulation.

The classification of many autoimmune diseases, for which there are still no effective treatments, may vary for related reasons, including environmental, biological, and genetic factors (155). The regulatory mechanisms of PANoptosis in autoimmune diseases have been investigated (156). Mechanisms such as the secretion of significant amounts of IFNs by regulating upstream pathways such as GAS/STING influence PANoptosome formation (156).

Other Interactions of PANoptosis with the Immune System

As a result of the conflict between the host and pathogens, pathogens can develop escape strategies from the immune system and death mechanisms. The innate immune system also has different mechanisms to eliminate pathogens and protect the host. PANoptosis also allows the activation of an innate immune response, giving host cell immunity an advantage as an integrated cell death mechanism that can be particularly effective against invading infectious agents. With different sensors, it can be activated in response to pathogenic triggers ranging from viruses to fungi (157). Cross-talk mechanisms between death pathways are important to overcome bacterial and viral escape strategies. This is because the escape strategies of pathogens are well understood and are generally focused on bypassing a single death pathway; some bacterial species can perform Casp1, Casp4 activations, NLRC4, and NLRP3 inhibition to avoid pyroptosis (158-160).

Furthermore, they can develop different strategies to keep pyrin inactive, such as activating PRK1/2 (161). Both viruses and bacteria carry out this and similar evasion strategies through some specific proteins. For example, HPV from the papillomavirus family can regulate the degradation of the IFI16 inflammasome through the E7 protein (162). Both bacteria and viruses can try to avoid death by similar mechanisms to escape apoptosis and necroptosis (18). PANoptosis offers a strategy to block immune evasion and infections. In addition, it may promote immune activation to combat immune resistance in certain cancer types.

Interactions between innate immune system cells and PANoptosis in cancer studies have been examined according to PAN scoring, a risk-scoring system based on PANoptosis models. M2 macrophage infiltration and cancer-associated fibroblasts were significantly associated with high TGF-β expression. A negative correlation exists between M1 macrophages and PAN score (163). Casp6, which plays an important role in inflammasome activation and PANoptosis, promotes differentiation into M2 macrophages. The PAN score is notably correlated with the tumor microenvironment, immune-related genes, and infiltration levels of most immune cells, such as NKs, $CD4^+$/$CD8^+$ lymphocytes, and DCs (146).

A study with specifically created extracellular vesicles (EVs) and ultrasound (US) technique, which has been suggested to improve the efficacy of cancer immunotherapy, showed that immunogenic PANoptotic cell death promotes dendritic cell maturation and macrophage polarization and subsequent presentation of antigens to T cells by activating the STING pathway STING is an interferon stimulator (164). IFN-γ produced by DC cells promotes PANoptosis in mice. IFN-γ deficiency affects the activation of the PANoptosis-specific markers Casp3, GSDMD, and MLKL and decreases IL-1β expression. Furthermore, dendritic cells express ZBP1, AIM2, and RIPK1, which are also PANoptosome sensors (165). The role of the STING pathway in immunity against intracellular pathogens and its possible direct effects on T-cells are well known (166). Additional studies are required to understand the contribution of these effects to PANoptosis.

A pro-tumoral group of tumor-associated neutrophils has been identified, with HMGB1 overexpression that reduces anti-tumor immunity and contributes to immune escape through the GATA2 / HMGB1 / TIM-3 axis (167). However, we still have limited knowledge about the direct function of neutrophils, NK cells, and other innate immune system cells in the mechanism of PANoptosis.

Future perspectives

Our knowledge of the concept of PANoptosis in the literature remains limited. Currently, research conducted primarily by the groups that defined this concept has contributed to its development. In this review, we provide an overview of the basic mechanisms of PANoptosis based on these studies; however, our main goal is to present the regulators identified in the literature in a comprehensive manner.

The diversity of these regulators across different triggers and disease pathogenesis makes PANoptosomes particularly interesting. Each of the identified sensors mediating the formation of PANoptosomes responds to different pathogens and endogenous danger signals, various PAMPs and DAMPs, to induce PANoptosis. To better understand the mechanisms of PANoptosis and develop therapeutic approaches, it is important to identify downstream molecules and different sensor compositions that activate phenotypic outcomes. The most stunning example of this is that PANoptosis has been implicated in the failure of IFN treatment for SARS-CoV-2 (64). SARS-COV-2 is able to escape the immune system by inhibiting IFN-I production and reducing its activity (168). IFN therapy can be used to reduce viral load. It was also thought that patients would improve when administered; however, IFN-induced upregulation of ZBP1 activated PANoptosis in response to IFN treatment, compromising therapeutic benefits (64). This suggests that inhibition of ZBP1 may improve the efficacy of IFN-based therapies, suggesting the importance of PANoptosis inhibitors and PANoptosome components in the development of novel therapeutic approaches. Research in this area has shown promising results. A study targeting the inhibition of PANoptosis demonstrated that this approach protects the kidney from reperfusion injury (169).

For therapeutic approaches targeting cancer, infection, and inflammatory diseases, it is important to investigate not only PANoptosome components and regulators but also to consider triggers. For example, as a strategy for escape from bacterial death, *Shigella flexneri* prevents necroptosis by targeting RIPK1 and RIPK3 with the protease effector Ospd3. Similarly, OspC1 can inhibit CASP8 apoptotic signaling (170). *Shigella*'s ability to block two death pathways is noteworthy, but its connection to PANoptosis remains unexplored. There are many triggers that have not been investigated in relation to PANoptosis, and this gap is rapidly being filled in the literature. Accumulated knowledge will improve our understanding of the mechanisms, sensors, and regulators of PANoptosis, paving the way for the development of potentially significant new therapeutic strategies.

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