Molecular Biology Reports (2024) 51:960
https://doi.org/10.1007/s11033-024-09901-y

REVIEW

PANoptosis: a new insight for oral diseases

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Received: 4 July 2024 / Accepted: 28 August 2024

Abstract
PANoptosis, a burgeoning area of research, is a unique type of programmed cell death typified by pyroptosis, apoptosis, and necroptosis, yet it defies singular classification by any one mode of death. The assembly and activation of PANoptosomes are pivotal processes in PANoptosis, with several PANoptosomes already identified. Linkages between PANoptosis and the pathophysiology of various systemic illnesses are established, with increasing recognition of its association with oral ailments. This paper aims to deepen understanding by conducting a comprehensive analysis of the molecular pathways driving PANoptosis and exploring its potential implications in oral diseases.

Keywords PANoptosis · PANoptosome · Programmed cell death (PCD) · Oral diseases

Introduction

Oral diseases constitute a major global public health challenge. They significantly diminish patients' quality of life by causing pain, difficulties in chewing, and aesthetic concerns, while also heightening the risk of systemic diseases. Moreover, oral diseases exert a considerable negative impact on the economy and healthcare systems worldwide [1–3]. As our understanding of the pathogenesis of common oral diseases deepens, accumulating evidence suggests that cell death plays a crucial role in their onset and progression. For example, in periodontitis, the inflammatory response triggers apoptosis in gingival tissues, accelerating gingival recession and periodontal tissue destruction [4, 5]. In the case of pulpitis, cell death exacerbates inflammation, leading to further tissue damage and intensified pain [6]. The development of oral cancer is associated with dysregulated apoptosis, where uncontrolled cancer cell proliferation and resistance to apoptosis are key factors in tumor development [7]. Therefore, a deeper understanding of the complex role of cell death in oral diseases not only opens new avenues for the development of therapeutic strategies to slow disease progression but also offers novel scientific insights and approaches for the prevention and treatment of clinical oral conditions.

Cell death is a vital process throughout life, essential for embryonic development, maintaining homeostasis, and eliminating damaged cells. It occurs in two distinct forms: accidental cell death (ACD) and regulated cell death (RCD). ACD is unregulated and typically results from mechanical, chemical, or physical insults. In contrast, RCD is a controlled process governed by intracellular signaling cascades that help maintain homeostasis. A subtype of RCD that occurs naturally under physiological conditions is known as programmed cell death (PCD) [8]. The intrinsic immune system can initiate PCD by detecting pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) through pattern recognition receptors (PRRs), thus contributing to the dynamic maintenance of organismal homeostasis [9]. PCD has been extensively studied, with apoptosis, pyroptosis, and necroptosis being the three most commonly recognized mechanisms [10] (Fig. 1).

Apoptosis, the first extensively studied type of PCD, was proposed in 1972 and was long considered the only regulated process of cellular demise [11, 12]. This non-lytic form of cell death is characterized by several features, including intact cell membranes, cellular shrinkage, chromatin condensation, karyorrhexis, and plasma membrane blebbing

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Published online: 05 September 2024

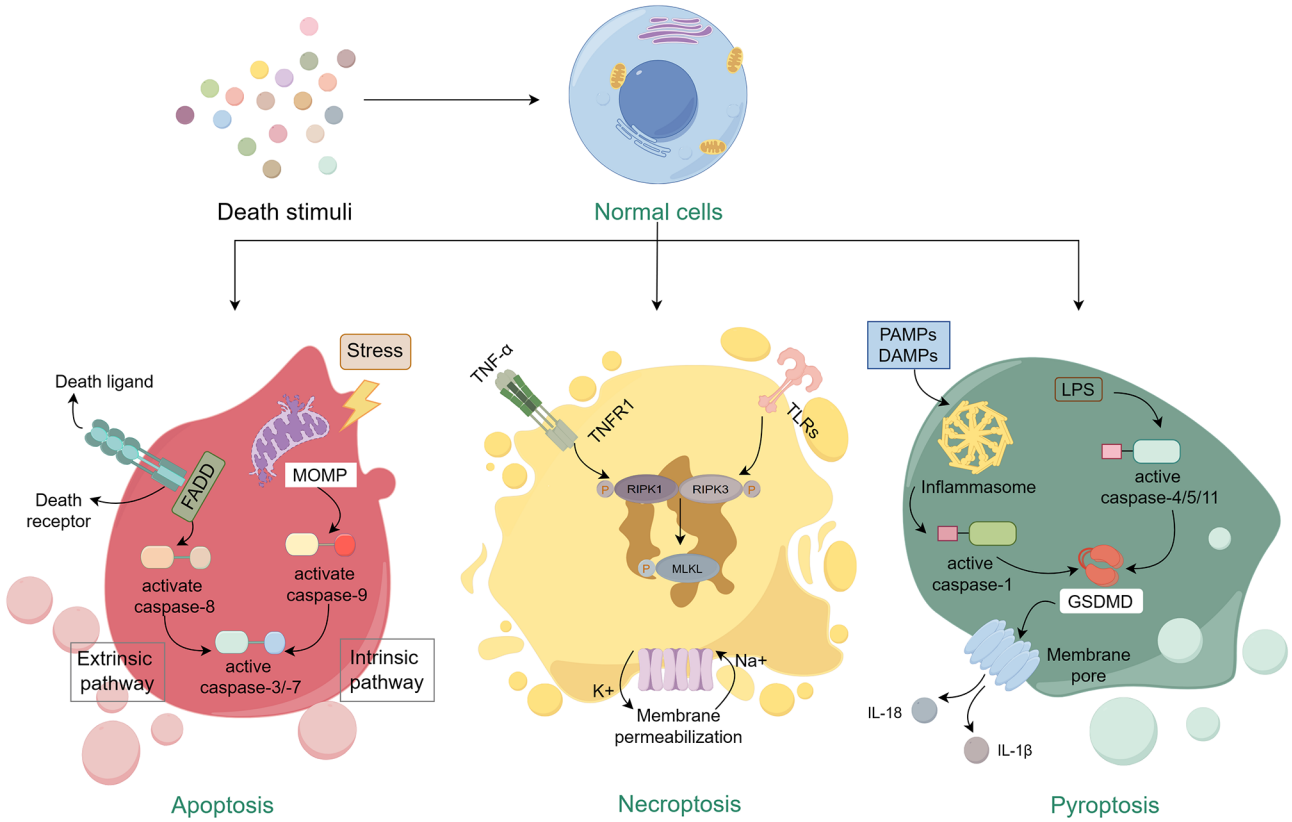

Fig. 1 Programmed cell death. The stimulation of normal cells by specific death stimuli prompts the initiation of programmed cell death, which includes apoptosis, necroptosis and pyroptosis. Two main types of apoptosis are intrinsic pathway and extrinsic pathway. An imbalance in intracellular homeostasis initiates the intrinsic pathway, leading to MOMP, activation of caspase-9, which in turn prompts caspase-3/-7 to carry out its executive function. Conversely, the extrinsic pathway is primarily initiated by the activation of death receptors, which attract death domain-containing adaptor proteins, such as FADD, to activate caspase-8, and then activate caspase-3/-7. Necroptosis is triggered by death receptors when caspase activation is blocked. When TNFR1 activates necroptosis, RIPK1 forms necrosomes with RIPK3, and RIPK3 autophosphorylation initiates MLKL, leading to structural changes and reaching the cell membrane, triggering membrane permeabilisation and necroptosis. Additionally, through the RHIM interaction of TRIF with RIPK, TLR3 or TLR4 can directly initiate necroptosis. Pyroptosis has two pathways. In the traditional pathway, the inflammasome sensor activates caspase-1, which cleaves GSDMD to trigger cell death and releases IL-1β and IL-18. In the non-traditional pathway, caspase-4, -5, or -11 binds to LPS, which activates and cleaves GSDMD to form cell membrane pores. Abbreviations FADD, Fas-associating protein with a novel death domain; MOMP, mitochondrial outer membrane permeabilization; TNF, tumor necrosis factor; TNFR, tumor necrosis factor receptor; TLRs, Toll-like receptors; RIPK1/3, receptor-interacting protein kinase 1/3; MLKL, mixed lineage kinase domain-like protein; PAMPs, Pathogen-associated molecular patterns; DAMPs, damage associated molecular patterns; GSDMD, Gasdermin-D. Figure created by figdraw

[13]. Apoptosis can be triggered via three distinct pathways: the intrinsic (mitochondrial) pathway, the extrinsic (death receptor) pathway, and the endoplasmic reticulum (ER) stress pathway. The intrinsic pathway is typically initiated by intracellular disturbances in homeostasis, often due to cytotoxic chemicals or DNA damage, leading to the upregulation of BH3-only proteins. These proteins bind tightly to BCL-2, releasing BAX and BAK to form oligomeric structures that cause mitochondrial outer membrane permeabilization (MOMP). This event releases cytochrome c from the mitochondria, which then forms apoptosomes in conjunction with apoptotic protease-activating factor-1 (APAF-1). The apoptosome activates the initiator caspase-9, which in turn activates caspases-3 and −7, ultimately executing apoptosis [11, 13, 14]. The extrinsic pathway is initiated by the activation of cell surface death receptors in response to external signals. Upon activation, these receptors—including Fas, TNFR1, DR3, DR4, DR5, and DR6—oligomerize and recruit adaptor proteins with death domains, such as FADD and TRADD. This recruitment activates the initiator caspase-8, leading to the activation of caspases-3 and caspase-7, which execute apoptosis [11, 13, 15]. The ER stress

pathway is activated by stressors such as misfolded proteins within the ER. Activation of ER stress-inducing molecules, including IRE1, PERK, and ATF6, elevates the expression of CHOP (C/EBP homologous protein) and alters other apoptosis-related markers, ultimately activating caspases and initiating cell death [16–18].

Pyroptosis, an inflammatory form of PCD associated with innate immunity, can be divided into two categories: the canonical and non-canonical signaling pathways. The canonical pathway operates through caspase-1, while the non-canonical pathway functions through caspases-4, -5, and −11 [19]. In the canonical pathway, apoptosis-associated speck-like protein containing a CARD (ASC) is recruited by inflammasome sensors such as NLRP3, NLRC4, AIM2, and Pyrin in response to specific stimuli, forming a platform for caspase-1 activation [20]. Activated caspase-1 cleaves Gasdermin D (GSDMD), leading to cell membrane disruption and cell death. To amplify the inflammatory response, caspase-1 also converts pro-IL-1β and pro-IL-18 into their active forms, releasing them into the extracellular matrix [20]. In contrast, in the non-canonical pathway, pyroptosis is triggered when caspases-4, -5, or -11 directly bind to lipopolysaccharide (LPS), leading to their oligomerization, activation, and subsequent cleavage of GSDMD, which creates pores in the cell membrane [21].

Necroptosis, a lytic form of PCD, is induced by certain death receptors, including TNFR and Fas, as well as TLR3 and TLR4, particularly when caspase activation is inhibited [22]. The initiation and regulation of necroptosis primarily involve tumor necrosis factor-α (TNF-α), caspase-8, receptor-interacting protein kinases 1 and 3 (RIPK1 and RIPK3), and the mixed lineage kinase domain-like protein (MLKL) [23]. Upon TNFR1 activation, RIPK1 interacts with RIPK3 to form necrosomes through the RIP homotypic interaction motif (RHIM). This interaction leads to the autophosphorylation of RIPK3, which subsequently activates MLKL. The activation of MLKL induces structural changes that enable it to translocate to the cell membrane, where it triggers membrane permeabilization and ultimately necroptosis [24]. Additionally, TLR3 and TLR4 can directly initiate necroptosis through the interaction of TRIF with RIPK via the RHIM [25].

Extensive research has explored the molecular mechanisms of apoptosis, pyroptosis, and necroptosis. Recent findings indicate that these pathways exhibit a degree of crosstalk, suggesting they are not entirely independent [13]. In 2019, the term "PANoptosis," representing pyroptosis, apoptosis, and necroptosis, was introduced [26]. PANoptosis is an inflammatory form of cell death regulated by the PANoptosome and is characterized by the simultaneous activation of these three pathways. It is not possible to ascribe this phenomenon to any single mechanism [27]. PANoptosis has been shown to play a significant role in tumorigenesis, pathogenic microbial infections, autoimmune disorders, neurodegenerative diseases, and other conditions.

To date, no comprehensive review has systematically addressed the role of PANoptosis in oral diseases. This paper aims to examine the molecular basis of PANoptosis and explore its manifestation in various oral conditions.

PANoptosome

The PANoptosome, a complex of proteins involved in apoptosis, pyroptosis, and necroptosis, mediates PANoptosis, which is often triggered by specific stimuli. Different triggers activate distinct sensors and regulators within PANoptosomes. Several types of PANoptosomes have been identified, each characterized by a unique composition of proteins. As a result, the cellular events leading to cell death may differ depending on the protein composition of these complexes. (Fig. 2)

Composition

The structure of the PANoptosome, similar to the inflammasome, typically consists of three components: (1) PAMP and DAMP sensors, such as NLRP3, NLRC4, ZBP1, AIM2, and Pyrin; (2) adaptors, including ASC and FADD; and (3) catalytic effectors, such as caspase-8, -1, -3, -6, RHIM domain-containing proteins like RIPK1 and RIPK3, pore-forming proteins GSDMD and GSDME, and mixed lineage kinase domain-like protein (MLKL) [27–29]. The PANoptosis signaling cascade usually begins when sensor proteins detect endogenous or exogenous danger signals. Adaptor proteins then transmit these signals to effector proteins, thereby initiating PANoptosis [30]. The proteins that constitute the PANoptosome have been extensively studied.

Z-DNA binding protein 1 (ZBP1)

ZBP1 is a protein that binds to both Z-DNA and Z-RNA. It possesses two N-terminal Z nucleic acid structural domains (Zα1 and Zα2) and two RIP homotypic interaction motifs (RHIM1 and RHIM2) [31]. Initially identified as an innate immune sensor, ZBP1 activates NF-κB signaling and IFN-I responses to combat pathogen infections [32, 33]. Recent studies have shown that ZBP1 plays a crucial role in regulating PANoptosis and acts as a key regulator in the assembly of the PANoptosome [26], which detects influenza A virus (IAV) infection and subsequently promotes the activation of RIPK3 and caspase-8 [34].

The Zα2 structural domain of ZBP1 is responsible for specifically recognizing and binding to activating ligands,

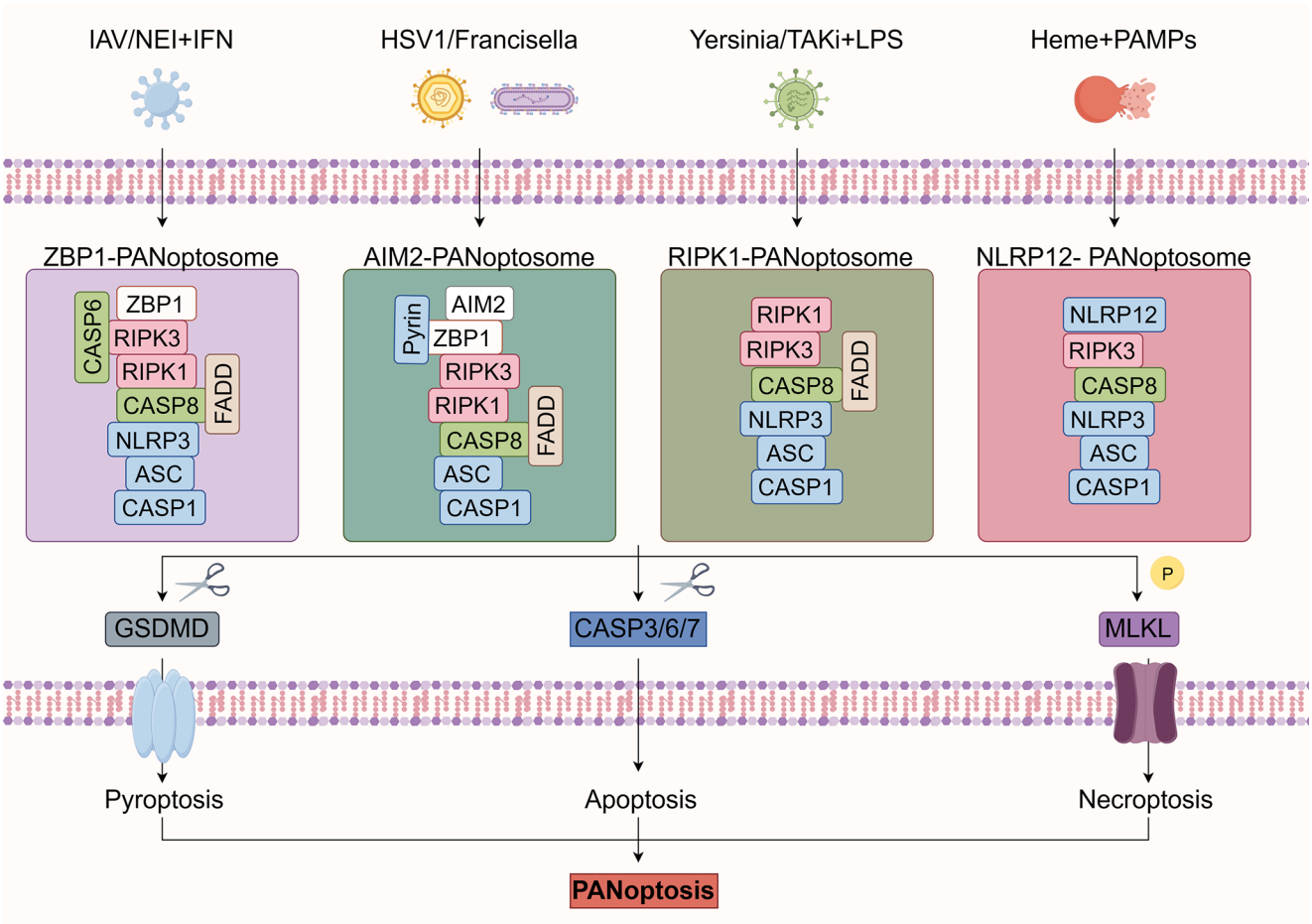

Fig. 2 PANoptosome. Different triggers can activate different PANoptosomes. Upon IAV infection or NEI + IFN stimulation, ZBP1 functions as an upstream sensor, causing ZBP1, RIPK1/3, NLRP3, ASC, caspases-1/-6/-8, and FADD to assemble to form the ZBP1-PANoptosome. similarly, upon HSV1 or F. novicida infection, the AIM2 sensor recognises the pathogen, causing AIM2, ZBP1, pyrin, ASC, caspase-1/-8, FADD, and RIPK1/3 to assemble to form the AIM2-PANoptosome. In addition, *Yersinia* infection or TAK1i combined with LPS sensitisation resulted in the assembly of the RIPK1-PANoptosome (consisting of RIPK1/3, NLRP3, ASC, caspase-1/-8, and FADD). Further, NLRP12 - PANoptosome assembly (consisting of NLRP12/3, ASC, caspase-1/-8, RIPK3) was stimulated by Heme + PAMPs. The assembly of these PANoptosomes activates downstream proteins involved in apoptosis, pyroptosis and necroptosis, which ultimately result in PANoptosis. Abbreviations IAV, Influenza A virus; NEI, nuclear export inhibitors; IFN, interferon; HSV1, herpes simplex virus-1; TAK1i, TAK1 inhibition; LPS, lipopolysaccharide; PAMPs, Pathogen-associated molecular patterns; ZBP1, Z-DNA Binding Protein 1; CASP, caspase; RIPK1/3, receptor-interacting protein kinase 1/3; FADD, Fas-associating protein with a novel death domain; NLRP3/12, NOD-like receptor family pyrin domain containing 3/12; ASC, apoptosis-associated speck-like protein containing CARD; AIM2, absent in melanoma 2; GSDMD, Gasdermin-D; MLKL, mixed lineage kinase domain-like pseudokinase. Figure created by figdraw

including viruses and endogenous Z-RNAs. This interaction enables binding with the RHIM structural domains of RIPK3 and RIPK1, which together form the core framework of the PANoptosome. Within this framework, RIPK3 is crucial for promoting MLKL phosphorylation and its transmembrane translocation, processes that lead to necrosome formation and subsequent necroptosis. Meanwhile, RIPK1 triggers apoptosis by activating caspase-8 and caspase-3/-7 through its interaction with FADD. Additionally, the ZBP1-PANoptosome facilitates the assembly and activation of the NLRP3 inflammasome, leading to GSDMD cleavage, IL-1β and IL-18 maturation, and ultimately pyroptosis [35].

Transforming growth factor-β-activated kinase 1 (TAK1)

TAK1 is a serine/threonine kinase that belongs to the MAPK kinase kinase (MAPKKK) family. Initially identified as a crucial mediator in transforming growth factor β (TGF-β) and bone morphogenetic protein 4 (BMP-4) signaling, TAK1 has since been shown to be activated by various stimuli. This activation leads to the phosphorylation of multiple target proteins, thereby regulating signaling pathways and cellular responses under diverse stress conditions and in different cell types [36].

TAK1 functions as a master regulator of PANoptosis quiescence. It prevents the assembly of the

RIPK1-RIPK3-FADD-caspase-8 complex by inhibiting RIPK1 kinase activity, thereby avoiding PANoptosis. When TAK1 function is inhibited, this complex assembles, triggering a cascade of processes, including apoptosis, pyroptosis, and necroptosis. Impaired TAK1 function leads to excessive activation of PANoptosis, potentially contributing to the development of inflammatory diseases [26, 37].

Fas-associated death domain (FADD)

FADD functions as an adaptor protein activated through interactions with either TNFR1 or active RIPK1. This activation is essential for binding and activating caspase-8 [38, 39]. As a component of the PANoptosome, FADD plays a crucial role in apoptosis and necroptosis. In the apoptosis regulatory mechanism, the death domain (DD) of FADD interacts with the death effector domain (DED) of caspase-8 to assemble the death-inducing signaling complex (DISC). This complex promotes the oligomerization and autocatalytic activation of caspase-8, which then initiates a cascade of events leading to the cleavage of substrate proteins, such as PARP and caspase-3, and ultimately results in apoptosis [40]. FADD/caspase-8-mediated proteolytic cleavage of RIPK1 has been shown to inhibit necroptosis induced by TNFR1 ligation, as RIPK1 is necessary for RIPK3 activation in this context [41].

The activation of inflammasomes in macrophages has been shown to depend on FADD [42]. Additionally, ASC cannot oligomerize without FADD or caspase-8, demonstrating that both FADD and caspase-8 are essential for ASC oligomerization in macrophages [43]. These findings collectively highlight the significant role of FADD in cell death.

Caspase-6

Caspase-6 is a protease from the caspase family that plays a crucial role in mediating cell death. It is a key regulator in PANoptosis, a process involved in the cross-regulation of the three cell death pathways: pyroptosis, apoptosis, and necroptosis.

In pyroptosis, caspase-6 plays a crucial role in regulating NLRP3 inflammasome activation and GSDMD cleavage. In an influenza A virus (IAV) infection model, caspase-6 deletion resulted in decreased GSDMD and caspase-1 cleavage, leading to reduced IL-1β and IL-18 release and inhibition of pyroptosis [44]. During apoptosis, caspase-6 is activated and initiates the cleavage of various transcription factors, including nuclear factor (NF)-κB, adenine-thymine sequence-rich binding protein 1, and structural proteins, resulting in nuclear atrophy and chromosomal DNA fragmentation [44–46]. Additionally, caspase-6 cleaves both large and small subunits, forming active dimers that target apoptosis-related substrates such as poly(ADP-ribose) polymerase (PARP) and lamin A, thus inducing cell death [44]. Caspase-6 can also be activated by caspase-3/-7, leading to the cleavage of caspase-8, which in turn modulates caspase-3/-7 activation and promotes apoptosis [47, 48]. Regarding necroptosis, caspase-6 exhibits a dual role: it can inhibit necroptosis by cleaving RIPK1 and potentially facilitate necroptosis by promoting RIPK3 binding to ZBP1 [49, 50]. Thus, caspase-6 plays a multifaceted and critical role in regulating various cell death pathways.

Caspase-8

Caspase-8, a protease in the caspase family, plays a critical role in regulating PANoptosis. Its function is broad, involving multiple signaling pathways and protein interactions. In apoptosis, caspase-8 is crucial for both the extrinsic and intrinsic pathways. In the extrinsic pathway, caspase-8 forms a death-inducing signaling complex (DISC) with FADD and procaspase-8, which activates downstream effectors caspase-3 and caspase-7, leading to apoptosis [51]. In the intrinsic pathway, caspase-8 contributes to apoptosis by cleaving Bid proteins, thus activating the mitochondrial pathway [52, 53]. In pyroptosis, caspase-8 can induce this process by acting upstream of caspase-3 or by directly cleaving GSDMD or GSDME [54, 55]. Additionally, in the presence of caspase-1, caspase-8 synergizes with ASC proteins to assemble and activate the NLRP3 inflammasome, ultimately leading to pyroptosis [26, 56]. Caspase-8 also forms the Ripoptosome with RIPK1 and cFLIP, regulating RIPK3 activity and influencing necroptosis [51]. However, when the Ripoptosome recruits p90 ribosomal S6 kinase (RSK) and phosphorylates caspase-8, it can negate caspase-8's inhibitory effect on necroptosis, thereby facilitating necroptosis [57].

In summary, caspase-8 regulates cell death by modulating the activity and expression of key proteins through various signaling pathways, thereby influencing apoptosis, pyroptosis, and necroptosis.

ZBP1-PANoptosome

The Zα structural domain of ZBP1 functions as a key innate immune sensor for Z-RNA, which is produced by DNA and RNA viruses [58]. Further research on influenza A virus (IAV) infection and cellular death has underscored ZBP1's role as a critical upstream sensor in the defense against IAV-induced cell death [26]. The structural configuration of ZBP1 enables it to regulate PANoptosome assembly and initiate PANoptosis upon IAV infection. Studies have demonstrated that deletion of the Zα2 domain of ZBP1 impairs

PANoptosis and inflammation caused by IAV infections [59, 60]. Additionally, the presence of the RHIM domain allows ZBP1 to interact with other RHIM-containing proteins, including RIPK1 and RIPK3 [33].

Upon activation, ZBP1 forms a cell death signaling scaffold through protein-protein interactions and the recruitment of associated proteins, including RIPK1, RIPK3, MLKL, FADD, caspase-1, caspase-6, caspase-8, NLRP3, and ASC. This ZBP1-PANoptosome complex stimulates kinase and protein hydrolysis signaling pathways, leading to inflammation and the initiation of PANoptosis [28, 31, 61]. Necroptosis is initiated when RIPK3 recruits and phosphorylates MLKL to form necrosomes, a process dependent on kinase activity [34, 62]. Extrinsic apoptosis is triggered by RIPK1 binding to FADD via the death domain (DD), which then interacts with caspase-8 to activate and cleave the executioner caspases, -3 and − 7 [63, 64]. Additionally, GSDMD cleavage and the production of IL-1β and IL-18 are associated with the activation of the ZBP1-NLRP3 inflammasome, which induces pyroptosis [31, 65].

In conclusion, research has demonstrated that the ZBP1-PANoptosome orchestrates pyroptosis, apoptosis, and necroptosis. Deletion of individual cell death effector molecules does not significantly protect against IAV-induced cell death. However, knockdown of ZBP1 or simultaneous loss of key PANoptosome components, such as RIPK3 and caspase-8, can prevent the onset of PANoptosis [31].

AIM2-PANoptosome

AIM2 is a sensor for double-stranded DNA (dsDNA) that recognizes a variety of microbes. It plays a crucial role in the treatment of tumors, inflammatory diseases, and infections [66–68]. This study demonstrates that during infections with herpes simplex virus-1 (HSV-1) and *Francisella novicida*, AIM2 regulates Pyrin and ZBP1 to enhance inflammation and initiate PANoptosis in bone marrow-derived macrophages (BMDMs) [69].

Independently of NLRP3/NLRC4, infection with HSV-1 or *F. novicida* triggers AIM2-dependent caspase-1 cleavage, leading to the production of IL-1β and IL-18 and resulting in cell death through an inflammasome-related mechanism. In contrast, Mefv$^{-/-}$ and ZBP1$^{-/-}$ BMDMs exhibit reduced inflammasome activation and diminished cell death following infection. This suggests that Pyrin and ZBP1 are integral to the AIM2-mediated cell death pathway induced by HSV-1 and *F. novicida* infections. Additionally, studies have shown decreased activity of caspase-1, GSDMD, GSDME, caspase-8, caspase-3, caspase-7, RIPK3, and MLKL in Mefv$^{-/-}$ and ZBP1$^{-/-}$ BMDMs after infection, with activity being completely absent in AIM2$^{-/-}$ and Mefv$^{-/-}$ZBP1$^{-/-}$ BMDMs. These findings indicate that Pyrin and ZBP1 work together to facilitate AIM2-mediated PANoptosis in the context of HSV-1 and *F. novicida* infections [69].

In conclusion, infection with *F. novicida* or HSV-1 activates AIM2, leading to the assembly of PANoptosomes. These complexes, consisting of AIM2, Pyrin, ZBP1, and other components such as FADD, RIPK3, RIPK1, ASC, caspase-1, and caspase-8, trigger PANoptosis. This process provides a protective response for the host [69].

RIPK1-PANoptosome

An important regulator of the NLRP3 inflammasome is transforming growth factor-β-activated kinase 1 (TAK1). TAK1 deficiency causes spontaneous activation of the NLRP3 inflammasome independent of RIPK1, leading to PANoptosis, which includes pyroptosis, apoptosis, and necroptosis [37, 70]. The effector protein *Yop J*, produced by *Yersinia* infection, inhibits TAK1, disrupting cellular homeostasis and triggering programmed cell death pathways [71–73]. In *Yersinia*-infected BMDMs, multiple PCD pathways are activated, as evidenced by the activation of caspase-1, -3, -7, and − 8, GSDMD cleavage, and MLKL phosphorylation. Immunoprecipitation studies reveal the formation of a complex involving RIPK1, RIPK3, caspase-8, ASC, FADD, and NLRP3 during infection, termed the RIPK1-PANoptosome [71].

The absence of RIPK1 does not completely inhibit the initiation of cellular death pathways but rather diminishes cell death, underscoring its distinct role in regulating PANoptosis compared to ZBP1 and AIM2. Deletion of RIPK1 results in reduced pyroptosis and apoptosis while enhancing necroptosis [71]. This phenomenon may be attributed to the activation of different necroptotic pathways depending on the presence or absence of RIPK1. Previous studies indicate that necroptosis induced by RIPK1 deletion is dependent on ZBP1 [74, 75], whereas necroptosis induced by *Yersinia* in normal cells is independent of ZBP1 [71].

The findings indicate that RIPK1 is a critical component of *Yersinia*-induced PANoptosis, and TAK1 may serve as an upstream regulator in the assembly and activation of the RIPK1-PANoptosome.

NLRP12-PANoptosome

NLRP12 is a recently identified cytoplasmic innate immune sensor that recognizes heme and pathogen-associated molecular patterns (PAMPs). It activates inflammasomes, facilitates the assembly of PANoptosomes, and triggers inflammatory responses and cell death. Toll-like receptors TLR2 and TLR4 upregulate NLRP12 expression through the interferon regulatory factor 1 (IRF1)-mediated signaling pathway, leading to inflammasome production and the

subsequent release of IL-1β and IL-18. These inflammasomes, part of the NLRP12-PANoptosome complex, drive PANoptosis via caspase-8 and RIPK3 activation [76, 77].

PANoptosis in oral diseases

The study of programmed cell death (PCD) has become a significant focus in oral disease research, especially with the identification of PANoptosis, a newly recognized form of cell death. The role of PANoptosis in the pathogenesis of oral diseases has garnered increasing attention, with evidence suggesting its involvement in the development of various common oral conditions (Fig. 3)

Oropharyngeal candidiasis.

Candida albicans (C. albicans) typically colonizes the oral cavity asymptomatically, as well as the vaginal mucosa and gastrointestinal tract [78]. However, it can become pathogenic and induce illness when the host's immune system is compromised or the normal flora is disturbed. In the oral cavity, *C. albicans* infections commonly manifest as oropharyngeal candidiasis (OPC), which is particularly prevalent among newborns, young children, the elderly, individuals misusing antibiotics, and patients undergoing radiation therapy. Furthermore, *C. albicans* has been identified as a pathogenic microorganism in various oral Additionally, *C. albicans* has been implicated as a pathogen in various oral diseases affecting immunocompetent individuals, including denture stomatitis (DS), early childhood caries, periodontitis, and endodontic lesions [79]. Consequently, *C. albicans* plays a significant role in oral microecology.

Recent studies have demonstrated that *C. albicans* infection elicits inflammasome activation and PANoptosis. A dose-dependent elevation in the protein levels of apoptosis-associated factors (caspase-8, -3, -7), pyroptosis mediators (caspase-1, GSDMD), and necroptosis markers (pMLKL) suggests that PANoptosis is induced by *C. albicans* infection [59]. The underlying mechanisms of PANoptosis have garnered increasing research interest. ZBP1 is identified as one of the receptors that trigger PANoptosis [31]. The study

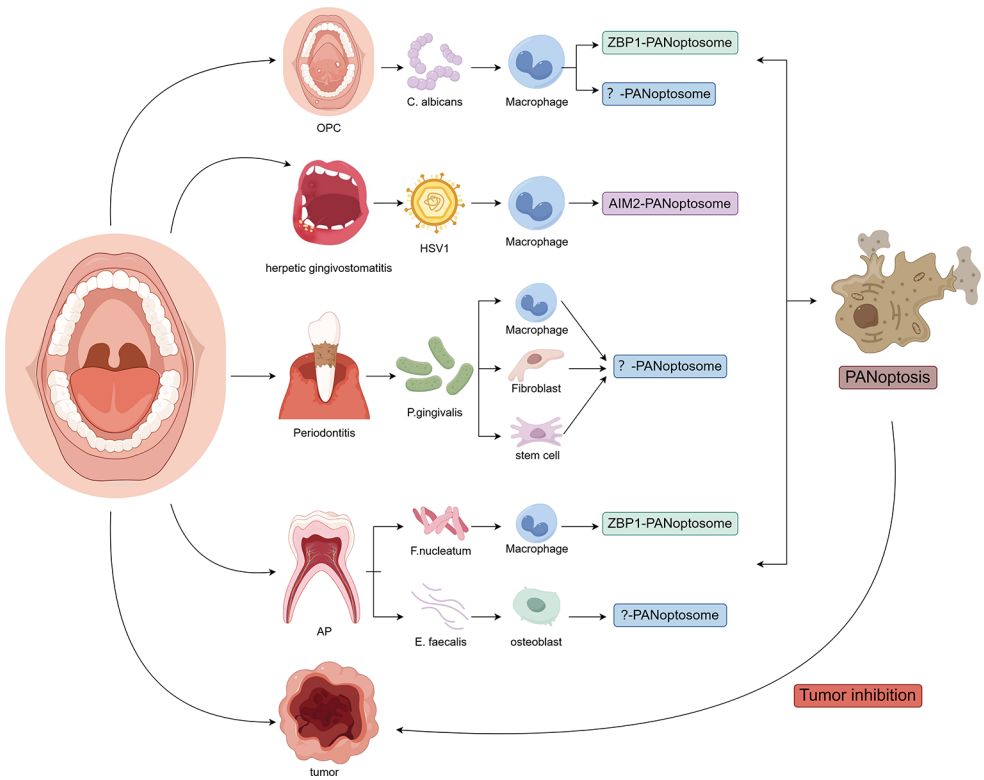

Fig. 3 PANoptosis in oral diseases. PANoptosis may be linked to many common oral diseases. oropharyngeal candidiasis (OPC) is often caused by infection with *C. albicans*, which infects macrophages and activates the ZBP1-PANoptosome or other PANoptosome to cause PANoptosis. Herpetic gingivostomatitis is frequently attributable to HSV1 infection, which infects macrophages and activates the AIM2-PANoptosome, thereby precipitating PANoptosis. In addition, *P. gingivalis*, the causative agent of periodontitis, induces apoptosis, pyroptosis, and necroptosis in fibroblasts, stem cells, and macrophages; however, the specific PANoptosome remains to be identified. The main causative organisms in AP, *F. nucleatum* and *E. faecalis*, can cause PANoptosis in Macrophages via the ZBP1-PANoptosome and in osteoblasts via an as yet unidentified PANoptosome, respectively. Furthermore, PANoptosis may have an inhibitory effect on tumour development. Abbreviations OPC, oropharyngeal candidiasis; AP, apical periodontitis; *C. albicans*, *Candida albicans;* HSV1, herpes simplex virus-1; *P. gingivalis*, *Porphyromonas gingivalis; F. nucleatum*, *Fusobacterium nucleatum; E. faecalis*, *Enterococcus faecalis*. Figure created by figdraw.

revealed that PANoptosis-related proteins were diminished n ZBP1$^{-/-}$ and ZBP1$^{\Delta Z\alpha 2/\Delta Z\alpha 2}$ BMDMs subsequent to *C. albicans* infection, as compared to wild-type (WT) BMDMs. This finding indicates that the Zα2 domain of ZBP1 is crucial for the detection of *C. albicans*, thereby initiating subsequent signaling cascades. Comparable outcomes were also noted in caspase-1/-11$^{-/-}$RIPK3$^{-/-}$caspase-8$^{-/-}$ BMDMs, emphasizing their significant role in *C. albicans*-induced PANoptosis [59].

The ablation of ZBP1, RIPK3, and caspase-8 in IAV-induced PANoptosis is significant, as it impedes both inflammasome activation and cell death. However, their deletion leads to a mere reduction in inflammasome activation and cell death following *C. albicans* invasion [59]. It is plausible that *C. albicans* infection engages alternative cell death pathways or additional PANoptosome components, necessitating further investigation to substantiate this hypothesis.

Herpetic gingivostomatitis

The herpes simplex virus (HSV) is a double-stranded DNA virus encompassing two serotypes: HSV-1 and HSV-2 [80]. HSV-1 is a widespread viral infection globally, mainly transmitted through direct contact with bodily fluids harboring the virus [81]. In addition to causing herpetic gingivostomatitis, HSV-1 infection can lead to recurrent herpetic stomatitis by establishing a latent infection within sensory neurons, persisting for the host's lifetime [82, 83].

Recent research indicates that AIM2 regulates the innate immune receptors Pyrin and ZBP1 to prevent HSV-1 infection by modulating the inflammatory signaling cascade and inducing inflammatory cell death, including PANoptosis. HSV-1 activates AIM2 by binding to the Zα2 domain of ZBP1 and inhibiting RhoA-GTP activity, which leads to the activation of Pyrin. Subsequently, Pyrin and ZBP1 work together to facilitate the assembly of the AIM2-PANoptosome, a molecular complex composed of AIM2, ASC, caspase-1, caspase-8, RIPK3, RIPK1, and FADD, which triggers PANoptosis [69].

The regulatory system elucidates how HSV-1 infection affects the host's innate immunity and coordinates the initiation of cell death signals. This process involves the formation of multiprotein complexes that lead to inflammatory cell death and cytokine release, thereby defining the molecular mechanisms underlying both host defense and the immune response.

Periodontitis

Periodontitis is a chronic inflammatory disorder arising from the interplay between microbial communities in dental biofilm and the host's immune response, which leads to the progressive degradation of periodontal support tissues. According to a 2021 guideline issued by the World Health Organization (WHO), severe periodontal disease has emerged as the primary cause of tooth loss [84]. Bacteria residing in the periodontal pocket can elicit an immune response, precipitating gingival inflammation, pocket formation, attachment loss, and alveolar bone resorption, ultimately resulting in oral dysfunction and tooth loss [85, 86]. Early studies have associated several bacterial species, including *Porphyromonas gingivalis (P. gingivalis)*, *Tannerella forsythia (T. forsythia)*, and *Treponema denticola (T. denticola)*, with periodontal disease. These bacteria, collectively known as the 'red complex', congregate at the site of infection and are strongly associated with periodontitis [87]. Furthermore, *P. gingivalis* is the predominant pathogen linked to chronic periodontitis and its detection is correlated with the recurrence and exacerbation of periodontitis following treatment [88].

During *P. gingivalis* infection, the bacterium initially invades gingival epithelial cells and compromises the epithelial barrier, triggering the recruitment of inflammatory cells that secrete inflammatory mediators, degrade extracellular matrix and tissue structures, and ultimately induce cell death. Concurrently, *P. gingivalis* can engage with the host's defenses and disrupt them, causing dysregulation of the host's innate immune system and exaggerated inflammatory responses. This enables the bacterium to evade immune detection and extend its survival within the host, thereby exerting its pathogenic influence [89]. Consequently, examining cell death in the context of periodontitis is vital for comprehending the disease's pathogenesis and developing effective treatments.

The progression of periodontitis is influenced by the roles of fibroblasts, stem cells, and macrophages. Macrophages play a pivotal role in the innate immune response to periodontal pathogens throughout the chronic evolution of periodontitis [90, 91]. Within the periodontal connective tissue, fibroblasts, including gingival fibroblasts (GFs) and periodontal fibroblasts (PDLFs), are the predominant cell type. Stem cells are crucial for tissue regeneration and repair, as they have the capacity to differentiate into a wide array of cell types. Numerous studies have shown that lipopolysaccharide (LPS) stimulation by *P. gingivalis* leads to significant upregulation of key proteins associated with apoptosis, pyroptosis, and necroptosis in macrophages, fibroblasts, and stem cells, including Bcl-2, Bax, caspase-1, caspase-3, caspase-7, caspase-8, GSDMD, NLRP3, ASC, MLKL, and the cytokines IL-1β and IL-18 [92–103], indicating that the development of periodontitis may involve PANoptosis. Furthermore, investigations into periodontal tissues and gingival crevicular fluid (GCF) from individuals with periodontitis have revealed that inflamed gingival tissues or

GCF exhibit heightened expressions of GSDMD, NLRP3, caspase-1, caspase-3, Bcl-2, Bax, MLKL, and IL-1β [4, 99, 100, 102, 104–107], which further corroborates the hypothesis. Moreover, components of the PANoptosome have been identified in the majority of these studies.

The experimental evidence collectively suggests a plausible link between PANoptosis and the initiation of periodontitis. Although there is a dearth of specific research on whether PANoptosome assembly occurs in periodontitis, the current data suggest that PANoptosome component proteins are overexpressed in the disease, which may serve as a molecular rationale for the occurrence of PANoptosis during periodontal injury. Further experiments are necessary to elucidate the molecular mechanisms that drive PANoptosis in periodontitis.

Caries

Dental caries is a multifactorial, chronic, and destructive disease prevalent in the human oral cavity. It is primarily caused by the consumption of carbohydrates, which are metabolized by oral microorganisms to produce acids, leading to the sustained demineralization of dental hard tissues. Currently, there is insufficient evidence to suggest that PANoptosis contributes to the caries process, and existing studies on this topic are inadequate. Therefore, further research is warranted.

Pulpitis and apical periodontitis

Pulpitis and apical periodontitis (AP) are prevalent inflammatory dental conditions resulting from microbial infections. The pulp and periapical tissues are typically sterile; however, dental injuries can permit microbial entry into the root canal through dentinal tubules or exposed pulp, leading to pulpitis. Subsequently, microbial migration through the apical foramen can result in apical periodontitis. Bacteria are the primary agents responsible for pulp and periapical diseases, with root canal bacteria predominantly comprising obligate anaerobic species organized into biofilms [108, 109]. Studies have identified *Prevotella*, *Porphyromonas*, *Fusobacterium*, *Parvimonas*, and *Streptococcus* as the most commonly detected bacteria within endodontic infections [110]. *Fusobacterium nucleatum (F. nucleatum)* is commonly found in infected root canals of teeth with AP due to its potent pro-inflammatory properties [111–113]. Moreover, *Enterococcus faecalis (E. faecalis)* is frequently present in infected root canals of teeth experiencing failed pulp therapy and refractory AP, highlighting its significance as a key microorganism in persistent and recurrent endodontic infections [114, 115].

F. Nucleatum-induced PANoptosis in macrophages

Researchers observed a substantial infiltration and accumulation of macrophages in the infected periapical tissues, accompanied by the presence of large clusters of *F. nucleatum*. With the progression of the infection, the death of macrophages increased steadily. This finding suggests that the antimicrobial response of macrophages following *F. nucleatum* infection is associated with the initiation of a complex inflammatory response, which ultimately leads to tissue damage. Moreover, the loss of these cells plays a pivotal role in the progression of the disease [116].

Experimental data indicate that macrophages infected with *F. nucleatum* exhibit an upregulation of ZBP1, N-GSDME, caspase-3, and pMLKL over time, with macrophage death being observed 24 h post-infection. Additionally, the expression of N-GSDME, caspase-3, and pMLKL was significantly reduced following ZBP1 knockdown after *F. nucleatum* infection. These observations suggest that *F. nucleatum* infection activates ZBP1, leading to the establishment of a hybrid cell death pathway known as PANoptosis [116].

To corroborate these findings, the researchers analyzed tissue samples from both apical periodontitis and healthy tissues independently. They observed markedly increased expression levels of N-GSDME, caspase-3, and pMLKL in the apical periodontitis samples, thereby confirming the presence of PANoptosis in this condition [116].

E. faecalis induces PANoptosis in osteoblasts

A defining feature of apical periodontitis is the progressive destruction of bone. Following root canal therapy, the healing of apical lesions is often associated with osteoblast-driven bone regeneration. Consequently, under normal physiological conditions, the activity and abundance of osteoblasts are pivotal for the restoration of periapical lesions.

Research indicates that *E. faecalis* induces both pyroptosis and apoptosis in human MG-63 osteoblastic cells. This effect was notably attenuated by NLRP3 knockdown using siRNA, suggesting that NLRP3 is a critical component involved in the regulation of apoptosis and pyroptosis in MG63 cells during *E. faecalis* infection [117]. Immunohistochemical analysis revealed that NLRP3, caspase-1, and IL-1β were significantly upregulated in periapical tissues compared to normal tissues [118], which further corroborates *E. faecalis*'s ability to induce osteoclast apoptosis and pyroptosis. Extensive recent research into programmed cell death (PCD) has led to the discovery that *E. faecalis* may also trigger necroptosis in MG63 cells through the RIPK3/MLKL signaling pathway [119].

The present findings imply that *E. faecalis* might induce osteoblasts to undergo PANoptosis. However, conclusive experiments demonstrating the occurrence of PANoptosis in osteoblasts induced by *E. faecalis* are currently unavailable. Further studies are required to delineate the downstream mechanisms of PANoptosome assembly and to identify the receptors involved in the response to *E. faecalis*.

Space infection with cranio-maxillofacial region

The oral and maxillofacial region is naturally inhabited by a multitude of microorganisms. Under conditions such as trauma, surgery, or reduced systemic immunity, this region is susceptible to infections, both endogenous and exogenous, which can disrupt the equilibrium of the normal microbial flora. The area's abundant vascular network and extensive network of interconnected fascial spaces facilitate the rapid dissemination of infections, potentially leading to life-threatening complications in severe cases. *Staphylococcus aureus (S. aureus)* is a clinically important pathogen known for causing a wide spectrum of human infections. It is a part of the normal skin microbiota in both animals and humans, with a prevalence ranging from 20 to 30% in healthy populations [120]. *S. aureus* is also among the most common bacteria associated with oral and maxillofacial infections. The most recent research suggests that *S. aureus* can induce host cell death during infection through the action of its virulence factors, which include apoptosis, pyroptosis, and necroptosis [121–123].

S. aureus triggers apoptosis in host cells during infection through a plethora of mechanisms that are integral to its pathogenic processes. The apoptosis of host immune cells may exacerbate the infection caused by *S. aureus*, while the apoptosis of tissue cells may impede the production of cytokines and the differentiation of T cells, thus diminishing the immune response [123]. *S. aureus* can induce apoptosis by activating FADD, RIPK3, and caspase-3/-8 through various cellular components or secreted virulence factors [123–125]. In the context of oral and maxillofacial infections, the role of *S. aureus*-derived staphylococcal protein A (SpA) in the pathogenesis of osteomyelitis has been noted, with apoptosis being a consequence [123, 126]. Furthermore, *S. aureus* has been shown to elicit pyroptosis in host cells through a variety of mechanisms, leading to cell death and the initiation of an inflammatory response. The bacterium can activate the NLRP3 inflammasome, triggering pyroptosis of macrophage-like cells (MAC-T cells) through the potassium efflux pathway [127, 128]. Evidence indicates that *S. aureus*-related PAMPs, including lipoteichoic acid (LTA), triacylated and diacylated lipoproteins, and peptidoglycan (PGN), along with toxins, enzymes, and effectors such as Panton-Valentine leukocidin (PVL), α-hemolysin (Hla), β-hemolysin (Hlb), and γ-hemolysin (Hlg), can induce pyroptosis [122, 123, 129–131]. Moreover, PVL, Hla, and phenol-soluble modulins (PSMs) have been observed to induce necroptosis in host cells following *S. aureus* infection [122, 123, 132]. Phagocytosis of *S. aureus* has been demonstrated to induce necroptosis in neutrophils. Conversely, when bacterial adhesion and entry into non-phagocytic cells are recognized by homologous host receptors, necroptosis can be triggered through the intrinsic pathway, leading to mitochondrial damage, or through the extrinsic pathway, involving cell surface receptors [122, 133–135].

Although *S. aureus* has been demonstrated to elicit apoptosis, pyroptosis, and necroptosis, its precise pathogenesis in oral and maxillofacial infections remains largely unexplored, and the question of whether it initiates PANoptosis remains uncertain. Therefore, there is an urgent need for further research to clarify the associated pathological mechanisms.

Tumors

Oral and maxillofacial neoplasms are significant diseases that can lead to severe health complications. Their development is a multifaceted, multistage biological process, and tumor cells are renowned for their resistance to cell death [136]. PANoptosis presents an alternative cell death mechanism that could circumvent this resistance, potentially offering novel strategies for cancer treatment. Although PANoptosis has been extensively investigated in vitro and in mouse models, its applicability to tumors is still a matter of debate. For example, in skin cutaneous melanoma (SKCM), high expression of PANoptosis-related proteins, such as ZBP1, NLRP1, caspase-8, and GSDMD, is associated with a favorable prognosis. Conversely, in low-grade glioma (LGG), high expression of ZBP1, ADAR, caspase-2, caspase-3, caspase-4, caspase-8, and GSDMD is associated with a poorer prognosis [137].

Nevertheless, the therapeutic potential of PANoptosis in inhibiting or combating tumor growth is gaining increasing recognition. Certain drug combinations, such as interferon (IFN) and nuclear export inhibitors (NEI) or tumor necrosis factor-alpha (TNF-α) and interferon-gamma (IFN-γ), have demonstrated anticancer effects [138, 139]. Elevated expression of ADAR1 inhibits the interaction between ZBP1 and RIPK3, thereby suppressing PANoptosis and fostering tumor progression. However, the combination of IFN and NEI has been found to alter the association between

ADAR1 and ZBP1. In a melanoma model, this drug cocktail notably diminished tumor size, indicating its promise as an anti-cancer approach [138]. Furthermore, TNF-α and IFN-γ have been demonstrated to collaborate in inducing PANoptosis, leading to cancer cell death and inhibiting tumor growth [139].

In conclusion, compounds that elicit PANoptosis show immense potential in cancer therapy. The function and therapeutic potential of PANoptosis in oral and maxillofacial cancers are still not fully understood, indicating the necessity for further research in this field.

Summary and perspectives

The innate immune system's capacity to orchestrate cell death is crucial for embryonic development, autoinflammatory disorders, host defense mechanisms, and maintaining organismal homeostasis. PANoptosis, recently recognized as a form of programmed cell death (PCD), is implicated in a spectrum of conditions and demonstrates a multifaceted regulatory network. It is thought to contribute to a range of viral and inflammatory diseases, as well as tumorigenesis, underscoring the significance of comprehending its role in disease pathogenesis for the development of effective management and treatment strategies. The PANoptosome, a pivotal mediator in the PANoptosis cascade, comprises molecules integral to other PCD pathways, such as inflammasomes, the death-inducing signaling complex (DISC), apoptosomes, and necrosomes. Its distinctive characteristics include the assembly and simultaneous activation of multiple signaling pathways associated with cell death. Therefore, a comprehensive understanding of PANoptosome assembly is instrumental in elucidating how they govern disease progression.

This paper systematically examines the concept and molecular processes of PANoptosis and summarizes its involvement in various oral diseases. It highlights PANoptosis' dual role in disease development: while it is crucial for combating microbial infections and maintaining immune homeostasis, it can also lead to excessive cytokine production, which may damage host tissues and trigger cytokine storms [140, 141] (Fig. 4) High cytokine levels are associated with multi-organ failure and lung damage [142–144]. Therefore, understanding the effects of PANoptosis on the host and various pathogens, and developing novel drugs that either enhance or inhibit PANoptosis, could be promising for disease treatment.

Overall, the significance of PANoptosis in various diseases, including oral diseases, has been well established, highlighting its potential for treating a broad range of conditions. However, several questions remain unanswered in PANoptosis research. For example, the precise mechanisms underlying PANoptosis are still unclear, and further research is needed to identify additional key factors within the PANoptosome. Moreover, the specific inducers and inhibitors of PANoptosis require investigation. Significant gaps also exist in understanding PANoptosis in the context of oral diseases, underscoring the need for more evidence to clarify its role in these conditions. Advancing novel molecular treatments for oral diseases necessitates a comprehensive understanding of the molecular mechanisms and regulation involved in PANoptosis.

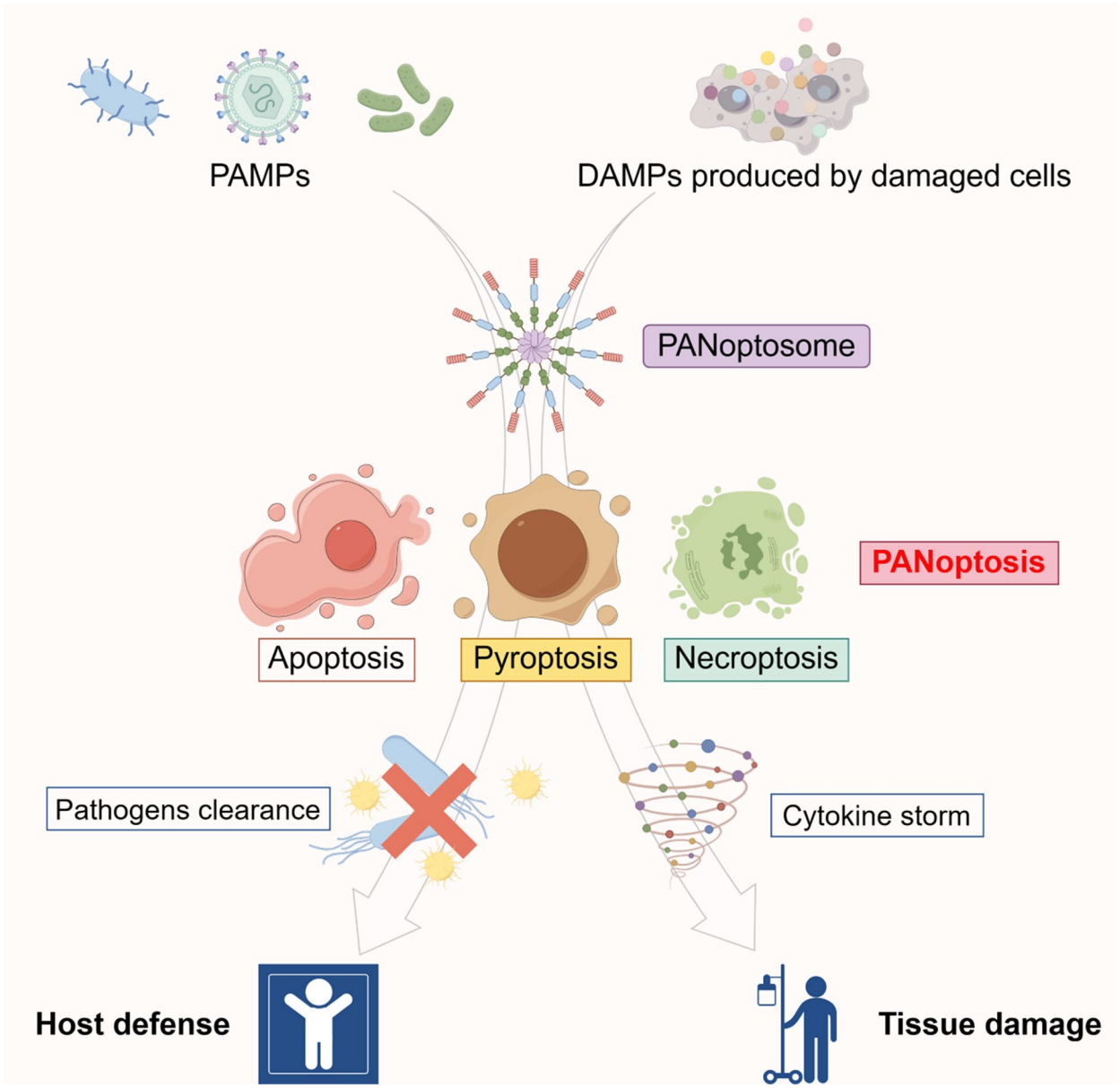

Fig. 4 PANoptosis' dual role in disease. PANoptosis has a dual role in disease development: on the one hand, PANoptosis is essential for fighting microbial infections and maintaining immune homeostasis; on the other hand, PANoptosis may lead to cytokine overproduction, which can injure host tissues and trigger a cytokine storm. Abbreviations PAMPs, Pathogen-associated molecular patterns; DAMPs, damage associated molecular patterns; Figure created by figdraw

Author contributions Jiang wrote the manuscript and designed the figures. Fu discussed the contents of the review. Huang conceived and revised the manuscript. All authors have read, contributed, and approved the submitted version of the article.

Funding This work was supported by the National Natural Science Foundation of China (82170989) and the Natural Science Foundation of Chongqing (CSTB2022NSCQ-MSX0794).

Data availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare no competing interests.

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