Role of PANoptosis in the development of gastric immunity and related gastric mucosal disease (Review)

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Abstract. PANoptosis is a novel and unique form of programmed cell death associated with innate immune responses, which is primarily regulated by the aggregation and activation of the PANoptosome, and exhibits characteristics of apoptosis, pyroptosis and necroptosis. Therefore, the PANoptosome complex has become a key target for preventing this type of cell death. PANoptosis is considered to have a role in infectious diseases and cancer; however, to the best of our knowledge, its role in gastric mucosal diseases has not been comprehensively explored. With the advancement of research on the mechanisms underlying gastric mucosal diseases, a shared regulation and crosstalk among pyroptosis, apoptosis and necroptosis has been suggested to exist during the development and progression of these diseases. The present review briefly introduces the relevant mechanisms and features of PANoptosis, with a focus on its role in gastric mucosal diseases (such as acute gastric mucosal injury, infectious gastritis, autoimmune gastritis, spasmolytic polypeptide-expressing metaplasia, gastric cancer and gastric-associated lymphomas), with the aim of providing additional targets for the treatment of gastric mucosal diseases.

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Abbreviations: AIM2, absence in melanoma 2; Akt, protein kinase B; ADAR1, adenosine deaminase 1; CASP, caspase; DAMP, damage-associated molecular pattern; dsDNA, double-stranded DNA; GSDM, gasdermin; cGAS, cyclic GMP-AMP synthase; HSV-1, herpes simplex virus type 1; HO-1, heme oxygenase-1; HMGB1, high mobility group box 1; IRF1, IFN regulatory factor 1; IAV, influenza A virus; iNOS, inducible NO synthase; mROS, mitochondrial reactive oxygen species; mtDNA, mitochondrial DNA; MALT, mucosa-associated lymphoid tissue; NLRP, NLR family pyrin domain containing; NLRC4, NLR family CARD domain containing 4; NRF2, nuclear factor erythroid 2-related factor 2; NO, nitric oxide; PCD, programmed cell death; PAMP, pathogen-associated molecular pattern; PRR, pattern recognition receptor; PANoDEG, PANoptosis-related gene; RIPK, receptor-interacting protein kinase; RHIM, receptor-interacting protein kinase homotypic interaction motif; SPEM, spasmolytic polypeptide expressing metaplasia; STING, stimulator of IFN genes; TLR, Toll-like receptor; TAK1, TGF-β activating kinase 1; TBK1, TANK-binding kinase 1; ZBP1, Z-DNA-binding protein 1; FADD, Fas-associated death domain protein; ASC, apoptosis-associated Speck-like protein containing a CARD

Key words: PANoptosis, gastric mucosal diseases, pyroptosis, apoptosis

Contents

1. Introduction

PANoptosis is a distinct pathway of programmed cell death (PCD), which was initially proposed in 2019 by Kanneganti (1). PANoptosis is initiated by specific triggers, such as cellular stress or pathogenic infections, which activate designated sensors, including Z-DNA-binding protein 1 (ZBP1), absence in melanoma 2 (AIM2), receptor-interacting protein kinase (RIPK)1 and NLR family pyrin domain containing (NLRP)12, to initiate the assembly of the PANoptosome complex, which subsequently mediates the simultaneous occurrence of apoptosis, pyroptosis and necroptosis. The core mechanism of PANoptosis lies in crosstalk among the pathways involved in

these three types of PCD, which exerts regulatory effects on cell death and inflammatory signaling (2). With developing exploration and improved understanding, PANoptosis has been validated in multiple organs; however, direct experimental evidence in gastric tissues and gastric disease models remains limited. Most current mechanisms are extrapolated from other systemic diseases, including acute lung injury (3), cardiovascular disease (4), neurological disorders (5), fungal keratitis (6), metabolic diseases (7), immune disorders (8) and tumors [e.g. esophageal cancer (9), colorectal adenocarcinoma (10), gastric cancer (11), glioma (12) and lung cancer (13)]. In addition, the emergence of PANoptosis has been suggested to aid the host in eliminating infected cells and overcoming pathogen immune evasion (14). As a pivotal component of the PANoptosis immune response, the PANoptosome has emerged as a novel therapeutic target for disease prevention and treatment (Table I) (15-29). Relevant references are listed in the table.

The gastrointestinal mucosa serves as a defensive barrier against numerous pathogens and immunogens, maintaining local immune homeostasis through dynamic regulation by the mucosal barrier and immune system (30). Imbalances in gastric mucosal immunity trigger various mucosal disorders, including focal mucosal lesions (such as gastritis and gastric ulcers) and diffuse mucosal damage [including spasmolytic polypeptide-expressing metaplasia (SPEM) and gastric carcinoma] (30,31). PCD is a key pathological factor mediating gastric mucosal disorders (32); however, interventions targeting only pyroptosis, apoptosis or necroptosis have demonstrated limited efficacy in ameliorating gastric mucosal diseases (30). Consequently, investigating the role of PANoptosis in gastric mucosal disorders may yield more effective therapeutic targets.

Notably, previous studies (29,33-35) have revealed that key sensors of PANoptosis, including ZBP1, AIM2, NLRP12 and RIPK1, are activated during the development of gastric mucosal diseases. The crosstalk between distinct cellular PCD pathways resembling PANoptosis may represent a potential therapeutic target for gastric mucosal disorders, potentially aiding in the prevention and suppression of disease progression. The present review briefly outlines the characteristics and regulatory mechanisms of PANoptosis; summarizes its role in acute gastric mucosal injury, infectious gastritis, autoimmune gastritis, SPEM, gastric cancer and gastric-associated lymphoma; and explores its potential as a therapeutic target. The current study aims to provide novel research perspectives for understanding the pathogenesis and treatment of gastric mucosal diseases.

2. PANoptosis

PANoptosis is initiated by innate immune sensors, and constitutes an inflammatory, lytic cell death pathway driven by caspases (CASPs) and RIPKs (36). Its fundamental mechanism involves the assembly and regulation of the PANoptosome complex, and it exhibits characteristics of apoptosis, pyroptosis and necroptosis without being reducible to any single pathway. While it serves an important role in cancer and infectious diseases, its function in gastric mucosal disorders remains to be elucidated. Therefore, investigating PANoptosome assembly, and the crosstalk between pyroptosis, apoptosis and necroptotic cell death signals, may facilitate the identification of regulatory targets for PANoptosis in gastric diseases.

PANoptosome and its assembly. The PANoptosome constitutes a regulatory platform formed by inflammasomes associated with apoptosis, pyroptosis and necroptotic cell death (37), simultaneously mediating the occurrence of PANoptosis. The activation and assembly of the PANoptosome are crucial for PANoptosis. Its assembly domain comprises three components: i) Recognition of pathogen-associated molecular patterns (PAMPs), damage-associated molecular patterns (DAMPs) and sensors (for example, ZBP1, AIM2, NLRP3 and NLRP12); ii) sensor-adapter complex formation [e.g., apoptosis-associated Speck-like protein containing a CARD (ASC) and Fas-associated death domain protein (FADD)]; and iii) recruitment of catalytic effectors (such as RIPK3, RIPK1, CASP-1, CASP-8 and NLRP3) (14). Variations in specific sensors activate distinct PANoptosome assemblies. There are currently four known primary types of PANoptosomes: ZBP1, AIM2, RIPK1 and NLRP12 PANoptosomes (38). Furthermore, studies have indicated that activation of the gastric epithelial cell pattern recognition receptor (PRR) NLR family CARD domain containing 4 (NLRC4) promotes the activation of factors including ASC, NLRP3, CASP-8, RIPK1, RIPK3 and ZBP1, Caspase-1 and FADD (39), thereby inducing inflammasome assembly.

The PANoptosome, which functions as a molecular scaffold, is driven primarily by CASPs and RIPKs, subsequently promoting the activation of downstream executioner molecules. It triggers pyroptosis via the NLRP3-ASC-CASP-1-gasdermin (GSDM)D pathway (40,41), whereas CASP-8 activates the effector CASPs CASP-3/6/7 to cleave BID and induce its mitochondrial translocation, inducing cytochrome *c* release (42,43), and concurrently activating RIPK1 and RIPK3 to induce mixed lineage kinase domain-like protein (MLKL) phosphorylation, thereby mediating necroptosis (44). Given the close association of PANoptosis with inflammatory diseases and tumorigenesis, the PANoptosome and its assembly may serve pivotal roles in these processes. Consequently, the PANoptosome is a key therapeutic target.

Signal crosstalk among pyroptosis, apoptosis and necroptosis. Apoptosis is a noninflammatory form of cell death characterized by intact cell membranes, whereas necroptosis and pyroptosis represent soluble and inflammatory forms of cell death (2), respectively. Complex signal crosstalk occurs among these three pathways and serves a notable role in disease progression (45,46). CASP-8 serves as a pivotal factor in signal crosstalk between apoptosis, pyroptosis and necroptosis, and can inhibit RIPK3- and MLKL-mediated necroptosis (47). However, CASP-8 has distinct functions in different states. In its activated form, CASP-8 mediates pyroptosis by cleaving GSDMD and GSDME via CASP-1 and CASP-3, respectively. Inactivated CASP-8 promotes ASC (inflammasome component) and CASP-1 activation (48), facilitating pyroptosis and the secretion of proinflammatory cytokines (such as IL-1β and IL-18). CASP-1, in turn, induces apoptosis via the BID-CASP-9-CASP-3 axis (BID being a BCL-2 family member) or by directly activating CASP-6 and CASP-3 (41,49,50). However, in the presence

Table I. Diseases associated with PANoptosis.

Disease/disease category	Main PANoptosome complex/ key member	Regulatory mechanisms	(Refs.)
Viral infection (e.g., IAV, COVID-19)	ZBP1-PANoptosome	IRF1 upregulates ZBP1, ZBP1 detects viral RNA, resulting in the recruitment of RIPK3 and CASP-8, and promoted PANoptosome formation	(15,16)
Bacterial infection (for example, *Yersinia*)	RIPK1-PANoptosome	TAK1 mediates PANoptosis	(17)
Tumors (such as breast cancer, thyroid cancer and hepatocellular carcinoma)	Various regulatory factors, including ZBP1-RIPK3-CASP-6, ADAR1 and TAK1	Composition of the PANoptosome varies among different types of cancer, involving ZBP1, AIM2, RIPK1 and NLRP12	(15,18)
Neurodegenerative diseases (Alzheimer's disease, Parkinson's disease, stroke and glioma)	ZBP1, AIM2, RIPK1, NLRP12 and NINJ1 are representative related factors	PANoptosome-mediated cell death can exacerbate neuroinflammation	(12,19,21)
Autoimmune diseases (such as systemic lupus erythematosus and rheumatoid arthritis)	AIM2-ASC-CASP-1, IRF1-ZBP1, TAK1-RIPK1, are representative related factors	PANoptosome cross-regulates through inflammasomes and death complexes	(22,23)
Inflammatory diseases (inflammatory bowel disease, vasculitis and diabetic retinopathy)	NLRP12-PANoptosome	PANoptosis can be regulated by adjusting adaptors or inhibitors	(24-26)
Metabolic diseases (obesity and metabolic syndrome)	IRF1-ZBP1 and JAK/STAT-IRF1	Inflammatory signals drive PANoptosome formation	(26,27)
Other infections (fungal and parasitic)	Multiple sensors (ZBP1, AIM2, NLRP12) combine to form a specific PANoptosome	Type of pathogen determines differences in the composition of the PANoptosome	(28,29)

ADAR1, adenosine deaminase 1; AIM2, absence in melanoma 2; CASP, caspase; COVID-19, coronavirus disease 2019; IAV, influenza A virus; IRF1, IFN regulatory factor 1; NINJ1, NINJURIN 1; NLRP12, NLR family pyrin domain containing 12; RIPK, receptor-interacting protein kinase; TAK1, TGF-β activating kinase 1; ZBP1, Z-DNA-binding protein 1.

of inactivated CASP-8, TNF-α activates RIPK1 to bind to CASP-8, shifting the apoptotic pathway toward necroptosis via the RIPK1-RIPK3-MLKL axis (51,52). Stimulation of Fas, TNF-related apoptosis-inducing ligand receptor, Toll-like receptor (TLR)3 and TLR4 also induces necroptosis (53). The concept of PANoptosis was initially proposed to offer mutually alternative and complementary pathways for PCD, thus expanding the understanding of cell death and the pathogenesis of inflammatory diseases, potentially aiding disease diagnosis, treatment and prevention.

Experimental criteria for identifying PANoptosis and distinguishing it from parallel cell death activation. A major challenge in PANoptosis research is to distinguish PANoptosome-dependent integrated PANoptosis from the parallel, independent activation of apoptosis, pyroptosis and necroptosis. To ensure conceptual rigor and avoid overinterpretation in gastric mucosal studies, the following clear and practical experimental criteria are proposed:

i) Molecular criterion: Direct demonstration of PANoptosome assembly. The gold standard for PANoptosis is the formation of a physical PANoptosome complex. This requires evidence such as co-immunoprecipitation, proximity ligation assay (54) or immunofluorescence colocalization (55) confirming the interaction of core sensors (ZBP1/AIM2/RIPK1/NLRP12) (56), adaptors (ASC/FADD) and effectors (RIPK3, CASP-1, CASP-8) in gastric cells or tissues (37).

ii) Functional criterion: Simultaneous blockade of all three death pathways. Inhibition or knockout of a core PANoptosome component [e.g., ZBP1, AIM2 or IFN regulatory factor 1 (IRF1)] (29,57) must simultaneously suppress apoptosis, pyroptosis and necroptosis. By contrast, inhibition of a single pathway (such as CASP-3, GSDMD or MLKL) should only partially reduce cell death, indicating PANoptosis rather than parallel activation.

iii) Phenotypic criterion: Concurrent biochemical and morphological features. PANoptotic cells simultaneously display (54): Apoptotic markers, cleaved CASP-3/7 and PARP; pyroptotic markers, cleaved GSDMD/GSDME; and necroptotic markers: Phosphorylated (p)-RIPK3 and p-MLKL. They should also exhibit a combined morphology: Cell shrinkage, nuclear fragmentation, membrane swelling and rupture (58).

Notably, the mere coexistence of apoptotic, pyroptotic and necroptotic markers does not confirm PANoptosis. Only when cell death is driven by a unified PANoptosome complex can

Table II. Evidence of PANoptosis in gastric mucosal diseases.

Disease	Direct gastric evidence	Indirect/extrapolated evidence	Unproven hypothesis	(Refs.)
Acute gastric mucosal injury	Confirmed (cells and mice)	None	None	(38,65)
Helicobacter pylori-induced gastritis	Confirmed (humans and mice)	Other bacterial infections	None	(32,69)
Viral gastritis	HSV-1	Other viral systems	EBV-PANoptosis	(67,68)
Autoimmune gastritis	Partial	Systemic autoimmunity	Full mechanism	(77,78)
SPEM	Indirect	Macrophage studies	Direct PANoptosome (directly initiated and assembled PANoptosome)	(83,84)
Gastric cancer	Cell lines	Tumor immunology	*In vivo* models	(11,100)
MALT lymphoma	Partial	Lymphoma studies	Clinical validation	(107,108)

This table categorizes the level of evidence supporting PANoptosis involvement in each gastric mucosal disease, distinguishing between direct gastric evidence (validated in gastric epithelial cells, mouse models or human gastric tissues), indirect/extrapolated evidence (inferred from non-gastric systems or other disease contexts), and unproven hypotheses (mechanisms proposed based on structural or pathway homology but not yet verified in gastric-specific models). EBV, Epstein-Barr virus; HSV-1, herpes simplex virus type 1; MALT, mucosa-associated lymphoid tissue; SPEM, spasmolytic polypeptide-expressing metaplasia.

it be defined as PANoptosis. This distinction is critical for mechanistic studies in gastric mucosal diseases.

3. Role of PANoptosis in gastric mucosal immune homeostasis

Under normal physiological conditions, the maintenance of gastric mucosal cell homeostasis relies upon a dynamic equilibrium between cell proliferation and cell death. PANoptosis, a novel form of PCD, serves a crucial regulatory role in gastric mucosal homeostasis through the integration of the core molecular mechanisms of apoptosis, pyroptosis and necroptosis. By eliminating damaged or dysfunctional gastric epithelial cells, PANoptosis prevents their accumulation and subsequent tissue damage, thereby preserving the integrity of the gastric mucosal barrier. For example, upon minor injury or infection of gastric epithelial cells, PANoptosis activates sensors such as ZBP1 or AIM2 (16), promoting PANoptosome assembly and the rapid initiation of PANoptosis. This process restricts intracellular pathogen replication, stimulates immune responses and the release of multiple cytokines (for example, IL-1β, IL-18, IL-6, TNF-α and TGF-β) to induce clearance of damaged cells and pathogens. This prevents excessive inflammatory activation from damaging the gastric mucosa while accelerating tissue repair. In healthy gastric mucosa, senescent or functionally deteriorated cells are promptly eliminated via PANoptosis (59), making space for new cells and thus maintaining dynamic equilibrium. In summary, PANoptosis is indispensable in maintaining gastric mucosal homeostasis, barrier function and immune equilibrium through the precise regulation of the cell death process.

4. Role of PANoptosis in gastric mucosal diseases

The discovery of PANoptosis offers a novel perspective on the mechanisms of PCD, providing new therapeutic targets for disease pathogenesis and immunotherapy. As a distinct form of inflammatory cell death (38), PANoptosis has a dual role in mucosal injury disorders: It regulates damage to and repair of the mucosal barrier, while also regulating the activation of multiple inflammasomes and cellular death pathways. This multidimensional involvement renders it a crucial entry point for investigating the pathological mechanisms of gastric mucosal injury. Consequently, examining the role of PANoptosis in both focal and diffuse gastric mucosal damage may provide a theoretical foundation for exploring novel, effective therapeutic strategies for gastric mucosal diseases (Table II).

Role of PANoptosis in acute gastric mucosal injury. Common diseases causing acute gastric mucosal injury include acute gastritis and gastric ulceration. Previous studies have revealed that their pathogenesis is associated with PANoptosis (Fig. 1) (60,61). Previous studies have indicated that the gastric mucosa, under various stimuli, such as heavy alcohol consumption, nonsteroidal anti-inflammatory drug use and *Helicobacter pylori* (HP) infection, exhibits mitochondrial damage and dysfunction. This leads to increased release of DAMPs, including mitochondrial reactive oxygen species (mROS) and mitochondrial DNA (mtDNA). Upon recognition by TLRs in gastric epithelial cells, mtDNA binds to ZBP1 and AIM2, regulating inflammation via the TANK-binding kinase 1 (TBK1)/IRF pathway (38,62,63). This process stimulates the activation of multiple inflammasomes, including NLRP3, NLRP12 and NLRC4 (60,64), which are key regulatory factors in PANoptosis in gastric epithelial cells. For example, ethanol activates the NLRP3 inflammasome via the nuclear factor erythroid 2-related factor 2 (NRF2)-heme oxygenase-1 (HO-1)-NF-κB signaling pathway (65), which combines with calcium ion channel proteins to promote the release of mtDNA and mROS. The release of mtDNA and mROS activates the cyclic GMP-AMP synthase (cGAS)-stimulator of IFN genes (STING) pathway, upregulating the expression of ZBP1 and

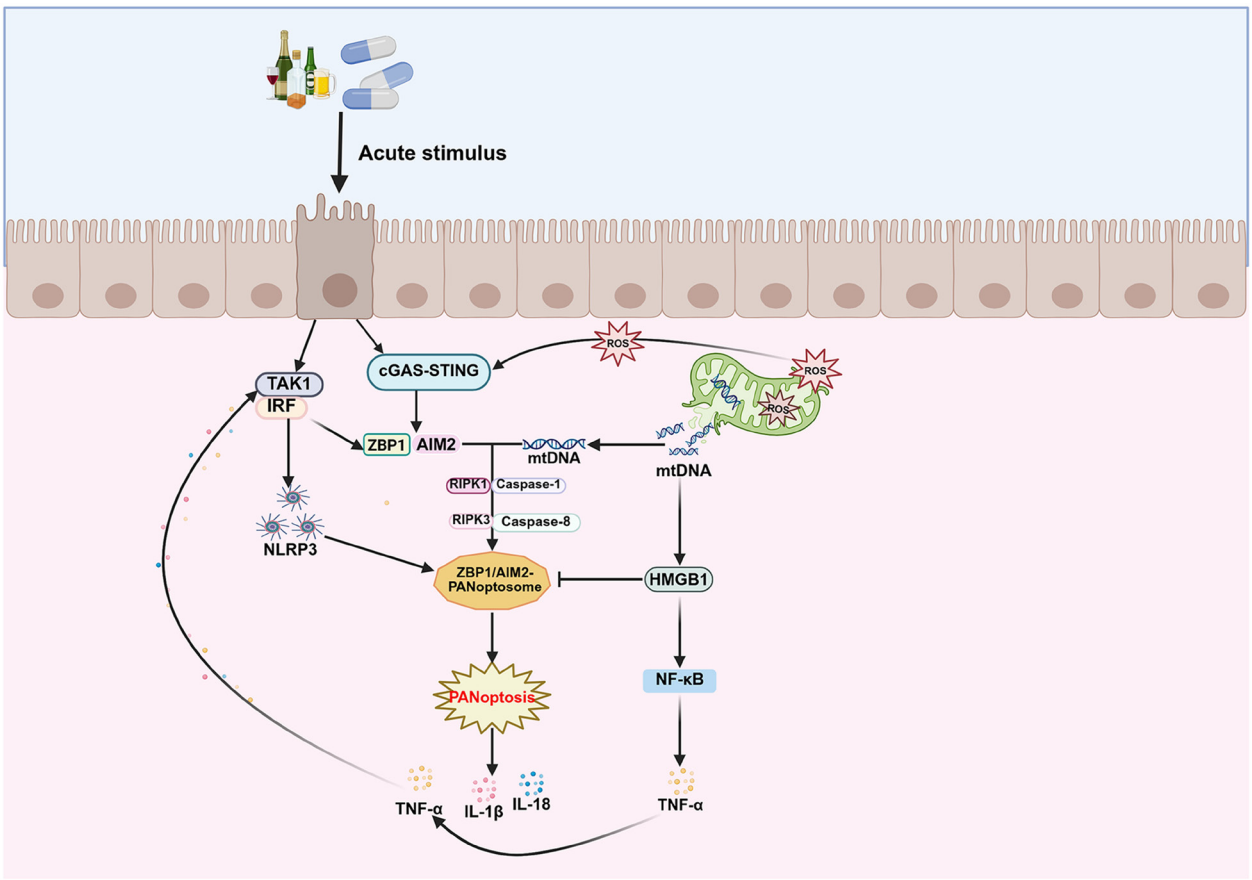

Figure 1. Regulation of PANoptosis in acute gastric mucosal diseases. Created with BioRender.com. AIM2, absence in melanoma 2; cGAS, cyclic GMP-AMP synthase; HMGB1, high mobility group box 1; IRF, IFN regulatory factor; mtDNA, mitochondrial DNA; NLRP3, NLR family pyrin domain containing 3; RIPK, receptor-interacting protein kinase; ROS, reactive oxygen species; STING, stimulator of IFN genes; TAK1, TGF-β activating kinase 1; ZBP1, Z-DNA-binding protein 1.

AIM2 and facilitating their binding (62,66). Concurrently, it recruits RIPK1, RIPK3, CASP-1 and CASP-8 in gastric glandular parietal cells (33,64). These proteins participate in the assembly of the AIM2-ZBP1-PANoptosome complex, thereby inducing PANoptosis. Activation of PANoptosis leads to the excessive release of proinflammatory cytokines, including IL-1β, IL-18 and TNF-α, amplifying the immune response, and exacerbating the onset and progression of acute gastric mucosal injury.

Notably, substantial amounts of high mobility group box 1 (HMGB1) released during gastric mucosal injury can bind to mtDNA (66), thereby limiting excessive AIM2 activation and competitively inhibiting PANoptosis. However, as a DAMP, HMGB1 binds to TLR4 and receptor for advanced glycation end products (61), activating the NF-κB pathway to increase TNF-α production. This subsequently induces PANoptosis in gastric mucosal cells, thereby contributing to the development and progression of gastric ulcers. Thus, in acute gastric mucosal injury, the complex regulation of local gastric immunity leads to excessive activation of PANoptosis during the mucosal immune response, promoting the progression of mucosal damage. Moderate activation of generalized apoptosis may be a therapeutic target for gastric mucosal injury diseases.

Role of PANoptosis in infectious diseases of the gastric mucosa. Infectious diseases of gastric epithelial cells include viral gastritis, bacterial gastritis and fungal gastritis, among others. Numerous studies have indicated that during the initial phase of infection by various pathogens, including viruses, bacteria and fungi, PAMPs can limit intracellular pathogen replication by initiating PANoptosis (38,67,68), a form of PCD, thereby facilitating host recovery. However, persistent infection leads to excessive activation of PANoptosis, resulting in the massive release of inflammatory cytokines; this triggers an inflammatory storm, exacerbating damage to gastric mucosal tissue (Fig. 2).

Viral gastritis. PANoptosis was initially identified and proposed in the context of influenza A virus infection (38). In addition, gastric herpes simplex virus type 1 (HSV-1) infection is regulated by PANoptosis. HSV-1 is a double-stranded DNA (dsDNA) virus (67), and when it invades the gastric mucosal epithelium, it promotes the activation of AIM2, pyrin, ZBP1, ASC, RIPK3, RIPK1, FADD, CASP-1 and CASP-8 to assemble AIM2-PANoptosomes and ZBP1-PANoptosomes (16), thereby mediating PANoptosis to inhibit viral replication. However, when viral infection stimulates excessive activation of immune cells and massive cytokine release, the release of TNF-α and IFN-γ jointly enhances PANoptosome assembly, driving PANoptosis to exacerbate damage to the gastric mucosal epithelium (38). Similarly, although no studies have yet demonstrated that the ability of the dsDNA virus

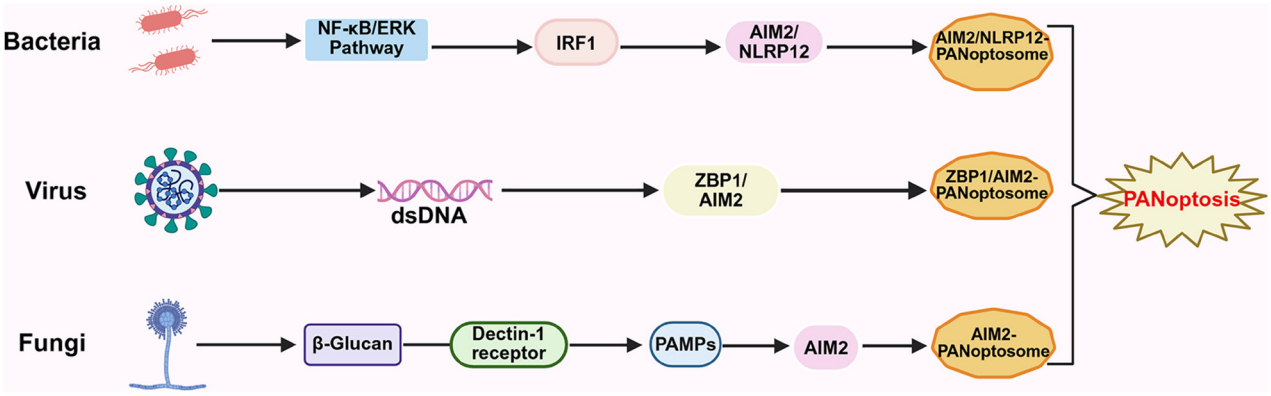

Figure 2. Regulation of PANoptosis in infectious gastric mucosal diseases. Created with BioRender.com. AIM2, absence in melanoma 2; dsDNA, double-stranded DNA; IRF1, IFN regulatory factor 1; NLRP12, NLR family pyrin domain containing 12; PAMPs, pathogen-associated molecular patterns; ZBP1, Z-DNA-binding protein 1.

Epstein-Barr virus (EBV) (68) to infect gastric epithelial cells is linked to PANoptosis, its viral structural properties suggest that this may be possible; however, direct evidence in gastric epithelial cells is lacking. EBV may potentially activate ZBP1/AIM2, but this remains to be verified in gastric models. The mechanisms underlying viral gastric mucosal infection remain incompletely understood; however, PANoptosis in early infection confers protection to a certain degree, offering novel therapeutic perspectives for viral gastritis.

Bacterial gastritis. HP, *Francisella* and *Yersinia* species are common pathogens involved in gastric mucosal cell bacterial infections. As PAMPs, they activate TLRs, which are primary PRRs in the gastrointestinal tract that respond to pathogenic infection. PAMPs (e.g., β-glucan, chitin, mannans and fungal nucleic acids) bind to hemoglobin, stimulating specific TLRs (TLR2 and TLR4) on the gastric mucosa to activate the NF-κB and ERK pathways (61,69). This increases the expression of IRF1, leading to the upregulation of AIM2 and NLRP12 expression (34,70). This in turn induces the assembly of AIM2-PANoptosomes and NLRP12-PANoptosomes, mediating widespread PANoptosis in immune cells and promoting inflammatory damage to the gastric mucosa. By contrast, *Yersinia*-induced gastritis occurs via the *Yersinia* outer protein J, which inhibits TGF-β activating kinase 1 (17), thereby promoting RIPK1-mediated assembly of the RIPK1-ASC-CASP-1-FADD complex, CASP-8 and FADD, leading to the formation of the RIPK1-PANoptosome and thereby inducing PANoptosis to promote the onset and progression of gastritis.

For common HP infectious gastritis, mitochondrial damage is induced through the virulence factors CagA and VacA, promoting the accumulation and release of large amounts of mtDNA and ROS, which induces PANoptosis in gastric epithelial cells, driving cell death and inflammatory responses (32). Traditional anti-HP treatments primarily focus on eradicating the pathogen and alleviating mucosal inflammation, but they cannot reverse already formed mucosal damage, chronic inflammation or infection-induced cascades of cell death (71). By contrast, inhibiting PANoptosis can directly block the vicious cycle of inflammation and cell death, more effectively alleviating mucosal damage by reducing the excessive release of IL-1β, IL-18 and TNF-α (32,72); when combined with HP eradication therapy, it may help accelerate mucosal repair and reduce the risk of inflammation-related precancerous lesions. These findings demonstrate that PANoptosis serves a role in the development of bacterial gastritis and may represent a novel therapeutic target.

Fungal gastritis. Fungal infections commonly occur in immunocompromised individuals, with *Candida albicans* and *Aspergillus* species being the most prevalent causative agents of gastric mucosal fungal infections (16,28). Research has indicated that ZBP1 serves as an apical sensor for fungal infection (28). Upon infection by *C. albicans* or *Aspergillus fumigatus*, substantial amounts of PAMPs (e.g., fungal cell wall components, nucleic acids and glycans) are secreted, activating ZBP1 to promote ZBP1-PANoptosome assembly. Furthermore, another study has revealed that during *Aspergillus* invasion (6,73), the fungus is recognized by host cells via TLRs, specifically TLR2, TLR4, TLR9 and dectin-1. Dectin-1 specifically recognizes β-glucans in fungal cell walls (74), triggering the release of substantial PAMPs that activate the cytoplasmic sensor AIM2. This activity mediates AIM2-PANoptosome assembly, inducing PANoptosis. This pathway may underlie the pathogenesis of fungal gastritis.

In the early stages of infection by pathogens such as viruses, bacteria and fungi in the gastric mucosal epithelium, the activation of PANoptosis aids in preventing pathogen replication and invasion. However, excessive and sustained activation of PANoptosis may promote the progression of inflammation and exacerbate damage to gastric mucosal epithelial tissue. Therefore, achieving a balanced activation of PANoptosis is crucial for the early prevention of infectious diseases of the gastric mucosa. For pathogenic infection-mediated chronic mucosal inflammation and epithelial cell damage, compared with traditional anti-infective treatments, targeted inhibition of PANoptosis may block the vicious cycle of inflammation and cell death, and promote repair of the mucosal barrier.

Role of PANoptosis in autoimmune gastritis. Autoimmune gastritis occurs when the autoantigen H^+-K^+ adenosine triphosphatase on parietal cells is recognized by autoreactive $CD4^+$ T cells (75), leading to spontaneous inflammatory infiltration and atrophy of the gastric mucosa. This suggested mechanism has been extrapolated from

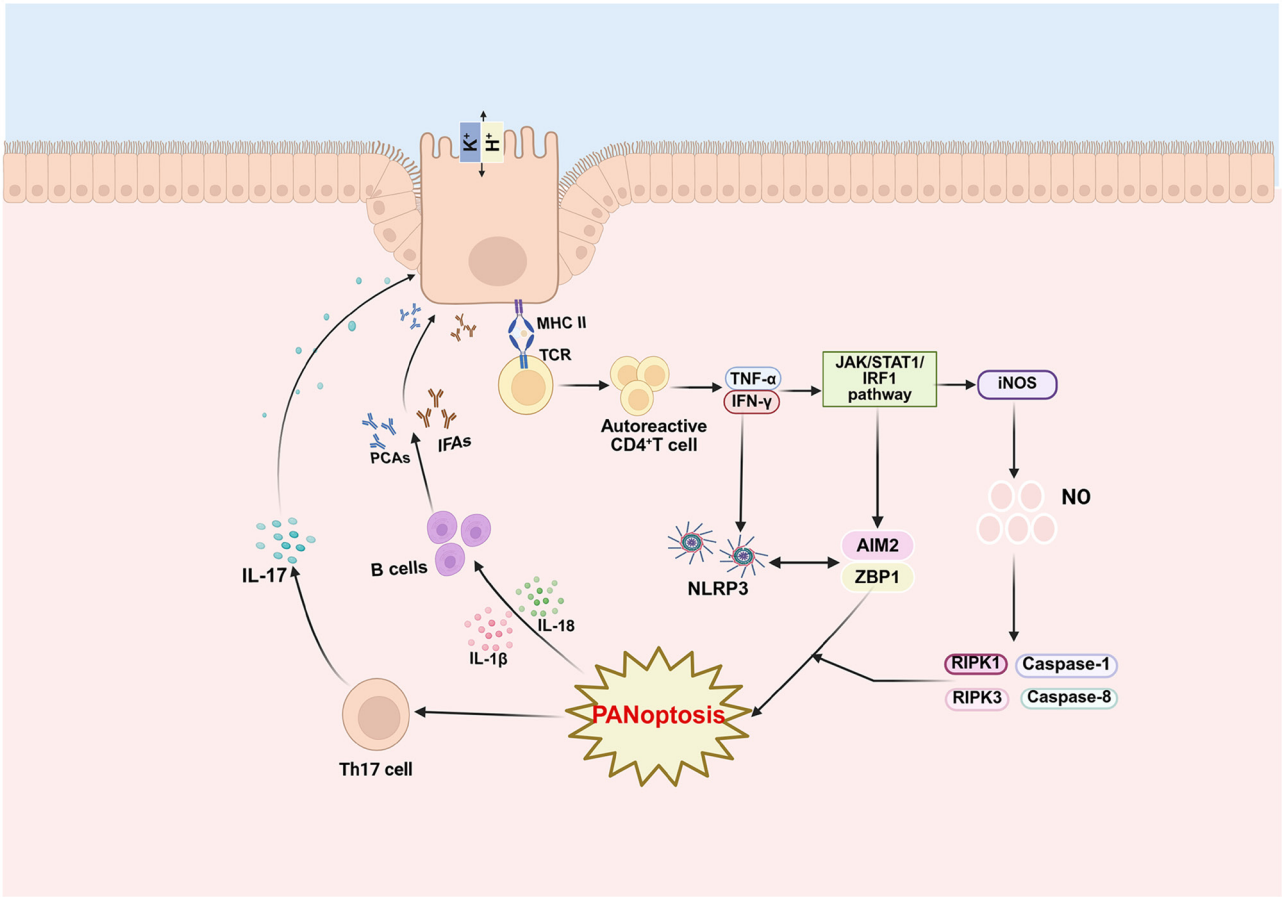

Figure 3. Regulation of PANoptosis in autoimmune gastritis. Created with BioRender.com. AIM2, absence in melanoma 2; IFAs, intrinsic factor antibodies; iNOS, inducible NO synthase; MHC II, major histocompatibility complex class II; NLRP3, NLR family pyrin domain containing 3; NO, nitric oxide; PCAs, parietal cell antibodies; RIPK, receptor-interacting protein kinase; TCR, T-cell receptor; Th17, T helper 17; ZBP1, Z-DNA-binding protein 1.

autoimmune disease models; direct *in vivo* evidence in gastric tissues is still insufficient. TNF-α and IFN-γ may act via JAK/STAT1/IRF1 (36) to drive inducible nitric oxide (NO) synthase to produce NO. This activates FADD/RIPK1/RIPK3-mediated CASP-8/Fas-associated protein ZBP1 and AIM2-PANoptosome assembly, inducing gastric epithelial cell PANoptosis to promote autoimmune gastritis. Moreover, TNF-α binds to the TNF receptor, stimulating RIPK1 to interact on CASP-8 via FADD and induce apoptosis (76). Simultaneously, RIPK1 binds to RIPK3 through the RIPK homotypic interaction motif (RHIM) domain, inducing necroptosis (77). Furthermore, activated ZBP1 promotes IL-17 secretion by $CD4^+$ T helper 17 cells, which directly act on gastric parietal cells. This activates CASP-3-mediated apoptosis via the p53 and PI3K/Akt signaling pathways (78) or drives pyroptosis, thereby advancing autoimmune gastritis progression (Fig. 3).

In summary, PANoptosis may be an important regulatory factor exacerbating the progression of autoimmune gastritis, and appropriately blocking its activation represents an effective therapeutic strategy for this condition. Previous studies have confirmed that IRF1 is a key upstream regulator of PANoptosis mediated by factors including ZBP1, AIM2 and NLRP12 (70,79), and IRF1 deficiency reduces the activation of PANoptotic molecules. Conversely, mutations or loss of function in adenosine deaminase 1 generates endogenous Z-RNA, activating ZBP1-mediated PANoptosis (36). This mechanism presents a potential therapeutic target for autoimmune gastritis.

Role of PANoptosis in SPEM. SPEM constitutes an important mucosal repair lineage capable of progressing to intestinal metaplasia, thereby promoting gastric carcinogenesis. Evidence has clearly indicated that IL-13 acts as an initiating factor in SPEM development (80), whereas IL-33 acts as an upregulating factor (81), inducing SPEM through stimulating M2 macrophage activation. Notably, SPEM development is closely associated with PANoptosis. Gastric AIM2 is produced primarily by gastric $B220^+$ IgM^+ immune cells (82). During gastric mucosal injury, elevated AIM2 expression activates ZBP1 through the sensing of endogenous dsDNA or mtDNA (83), which participate in AIM2-PANoptosome assembly to mediate gastric mucosal cell PANoptosis. Subsequently, CASP-6 is activated as a downstream component and interacts with IL-4 to promote macrophage activation via nonapoptotic pathways (84). Concurrently, IL-10 secretion inhibits M1 macrophage activation (85) while enhancing M2 macrophage activation and expression, thereby promoting the development of SPEM in the gastric mucosa (Fig. 4). However, most evidence comes from gastric injury models; direct evidence of PANoptosome assembly in SPEM-specific lineages is lacking.

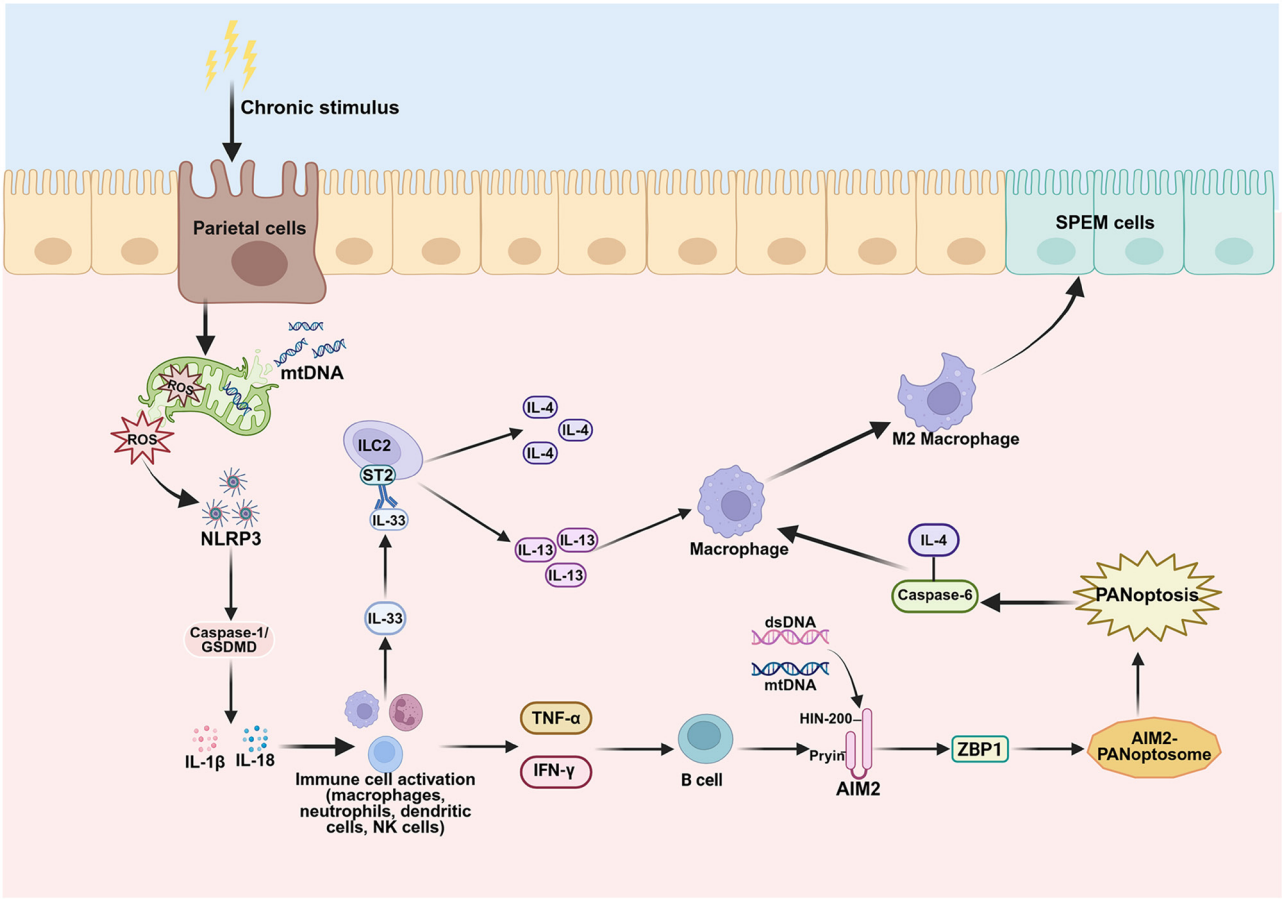

Figure 4. Regulation of PANoptosis in SPEM. Long-term chronic stimulation participates in the immune microenvironment regulation of gastric mucosal SPEM through PANoptosis. Created with BioRender.com. AIM2, absence in melanoma 2; dsDNA, double-stranded DNA; GSDMD, gasdermin D; ILC2, type II innate lymphoid cells; mtDNA, mitochondrial DNA; NK, natural killer; NLRP3, NLR family pyrin domain containing 3; ROS, reactive oxygen species; SPEM, spasmolytic polypeptide-expressing metaplasia; ZBP1, Z-DNA-binding protein 1.

Furthermore, M2 macrophage activation induces CASP-6 upregulation, the release of N-terminal GSDME, the phosphorylation of MLKL (86), and the binding of RIPK3 to the RHIM domain of ZBP1 to stimulate ZBP1-PANoptosome assembly (87), thereby increasing PANoptotic activity. However, the noninflammasome AIM2 can inhibit the progression of SPEM by restricting $CD8^+$ T-lymphocyte accumulation in chronic gastritis through the suppression of CXCL16 (produced by gastric B cells) (82).

Research has revealed that the absence of GRIM-19 in parietal cell mitochondria can promote NLRP3/IL-33 activation via the ROS-NRF2-HO-1-NF-κB pathway, thereby mediating the development of SPEM (88). Following gastric mucosal injury, NLRP3 upregulation is induced, promoting M2 macrophage activation and $CD8^+$ T-cell recruitment. This contributes to gastric SPEM development by increasing IFN-γ production (89). The mechanism by which NLRP3 induces M2 macrophage activation remains unclear. On the basis of these findings, it may be hypothesized that gastric mucosal injury increases NLRP3 expression, which, via the CASP-1 pathway, triggers the massive release and secretion of inflammatory cytokines. This enhances the activity of dendritic cells, neutrophils, gastric B cells and natural killer cells (90); promotes the upregulation of TNF-α and IRF1; and induces activation of the AIM2 inflammasome through guanine nucleotide-binding protein (66). Stimulation of AIM2-PANoptosome assembly mediates SPEM development. Transcriptomic analysis has further revealed that these immune cells express PANoptosis-related genes (PANoDEGs), such as IL1B, IL18, TNF, CASP1 and MLKL, indicating that the aforementioned immune cells are involved in the pathogenesis of SPEM (66). This stimulates AIM2-PANoptosome assembly, mediating SPEM via PANoptosis. Transcriptomic analysis has revealed strong associations between these immune cells and PANoDEGs (91). Furthermore, heightened inflammatory cell activity increases the secretion of the gastric mucosal injury alarmins IL-33 and HMGB1 (92). These DAMPs may activate inflammasomes such as ZBP1 and AIM2, mediating the recruitment of NLRP3, RIPK3, RIPK1 and CASP-8 to assemble PANoptosomes. This PANoptosis pathway thereby promotes SPEM progression. Current direct evidence of PANoptosome assembly in SPEM-specific epithelial cells is still lacking; therefore, PANoptosis is a potential regulatory factor in SPEM, and its core role requires further verification.

Role of PANoptosis in gastric cancer. The incidence and mortality rates of malignant gastric cancer remain high, ranking fifth in cancer incidence and fourth in cancer-related mortality globally (93,94). The emergence of PANoptosis,

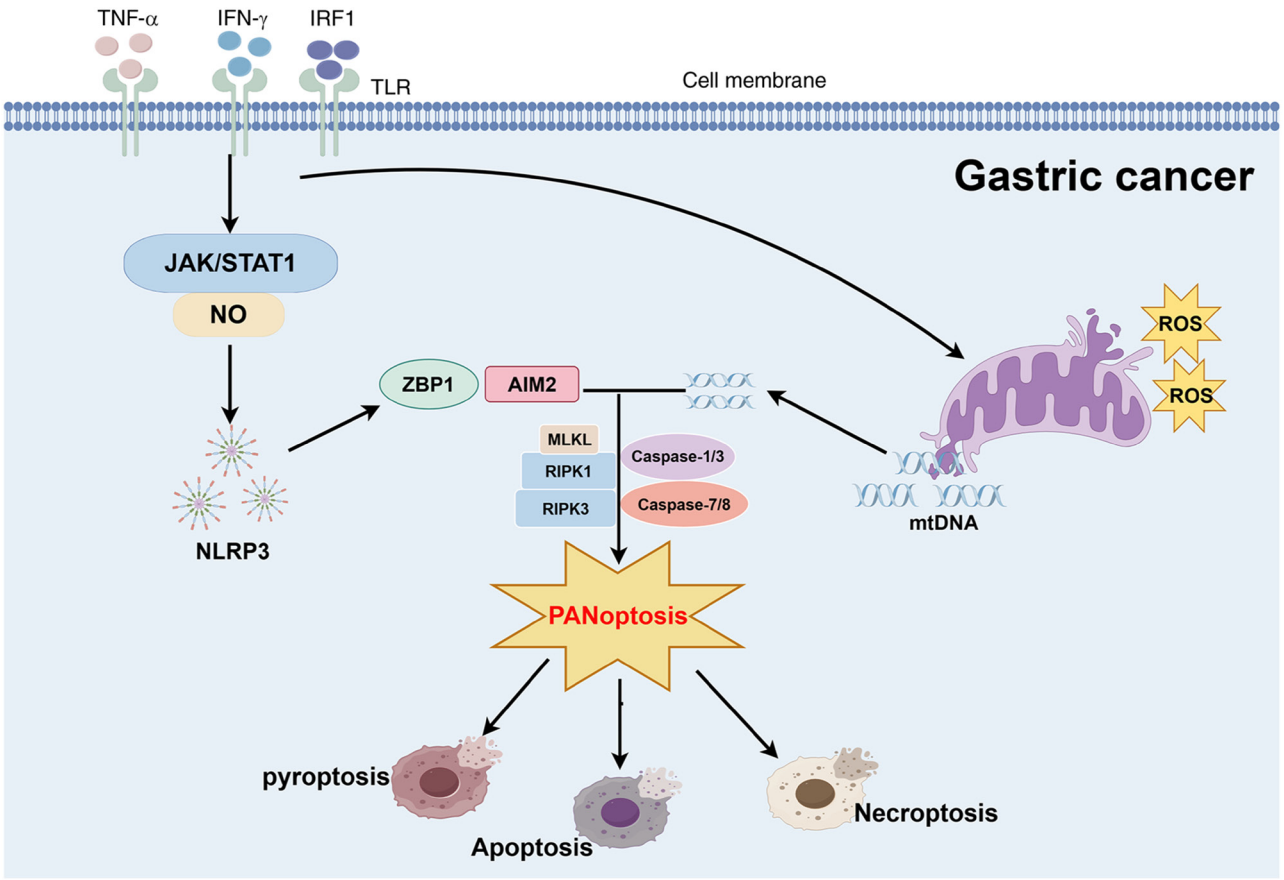

Figure 5. Regulation of PANoptosis in gastric cancer. IRF1, TNF-α and IFN-γ induce PANoptosis in gastric cancer cells, thereby inhibiting tumor growth. Created with Figdraw (https://www.figdraw.com). AIM2, absence in melanoma 2; IRF1, IFN regulatory factor 1; mtDNA, mitochondrial DNA; NLRP3, NLR family pyrin domain containing 3; NO, nitric oxide; RIPK, receptor-interacting protein kinase; ZBP1, Z-DNA-binding protein 1.

a novel form of cell death, offers fresh therapeutic options for tumor management. In gastric cancer, AIM2 upregulation is induced (35), thereby initiating the assembly of AIM2-PANoptosomes within tumor cells. IRF1, TNF-α and IFN-γ have been demonstrated to induce PANoptosis to prevent tumorigenesis (29,95,96). As an upstream regulator of PANoptosis, IRF1 produces NO to modulate TNF-α and IFN-γ expression via the JAK/STAT1 signaling pathway (90,97). The interaction of TNF-α and IFN-γ activates GSDME, CASP-8/3/7 and MLKL phosphorylation, thereby inducing PANoptosome assembly. Furthermore, the combination of IFN with a nuclear export inhibitor (98) enhances ZBP1-PANoptosome assembly, inducing robust PANoptosis in tumor cells and inhibiting their proliferation (Fig. 5).

The therapeutic effect of cisplatin on gastric cancer cell is mediated by the activation of CASP-8/9 and downstream CASP-3/7 to induce apoptosis (99). This occurs because CASP-1 stimulates increased CASP-3 expression, lysing GSDMD/E to mediate pyroptosis (100) and activating RIPK3 to induce MLKL phosphorylation and necroptosis (101). It has been hypothesized that cisplatin treatment in gastric cancer may increase chemotherapeutic sensitivity and inhibit tumor growth by inducing PANoptosis in cancer cells. However, this requires *in vivo* validation in clinical samples. Furthermore, another study indicated that the use of a PANoptosis score may aid in predicting gastric cancer prognosis and survival rates, as well as immunotherapy outcomes (11). PANoptosis may inhibit tumor growth and progression by stimulating inflammatory factor activity within tumor cells, thereby exacerbating PCD and inhibiting tumor cell immune evasion.

Role of PANoptosis in mucosa-associated lymphoid tissue (MALT) lymphoma. MALT lymphoma is a rare gastric tumor that originates as an indolent B-cell non-Hodgkin lymphoma within the marginal zone of the gastric lymphoid tissue (102). MALT is frequently induced by HP infection and chronic stimulation by autoantigens, and is primarily manifested as abnormal proliferation of small B lymphocytes within the gastric mucosa (103). NF-κB serves as a crucial mediator of immune responses and was first described in B lymphocytes. Activation of NF-κB stimulates unlimited B-cell proliferation and the transcription of antiapoptotic genes, ultimately contributing to lymphoma development (104). During chronic HP-induced inflammatory infection, released bacterial dsDNA is recognized by the cytoplasmic DNA sensor cGAS (3), triggering a DNA damage response that activates the STING-TBK1-IRF3 signaling pathway (105), consequently promoting formation of the ZBP1/CASP-8/RIPK3/ASC multiprotein complex. This further induces MLKL phosphorylation, CASP-3 cleavage and GSDME cleavage (106), thereby promoting gastric lymphoma cell death and inhibiting tumor cell proliferation. These findings demonstrate that STING suppresses MALT tumor formation by mediating

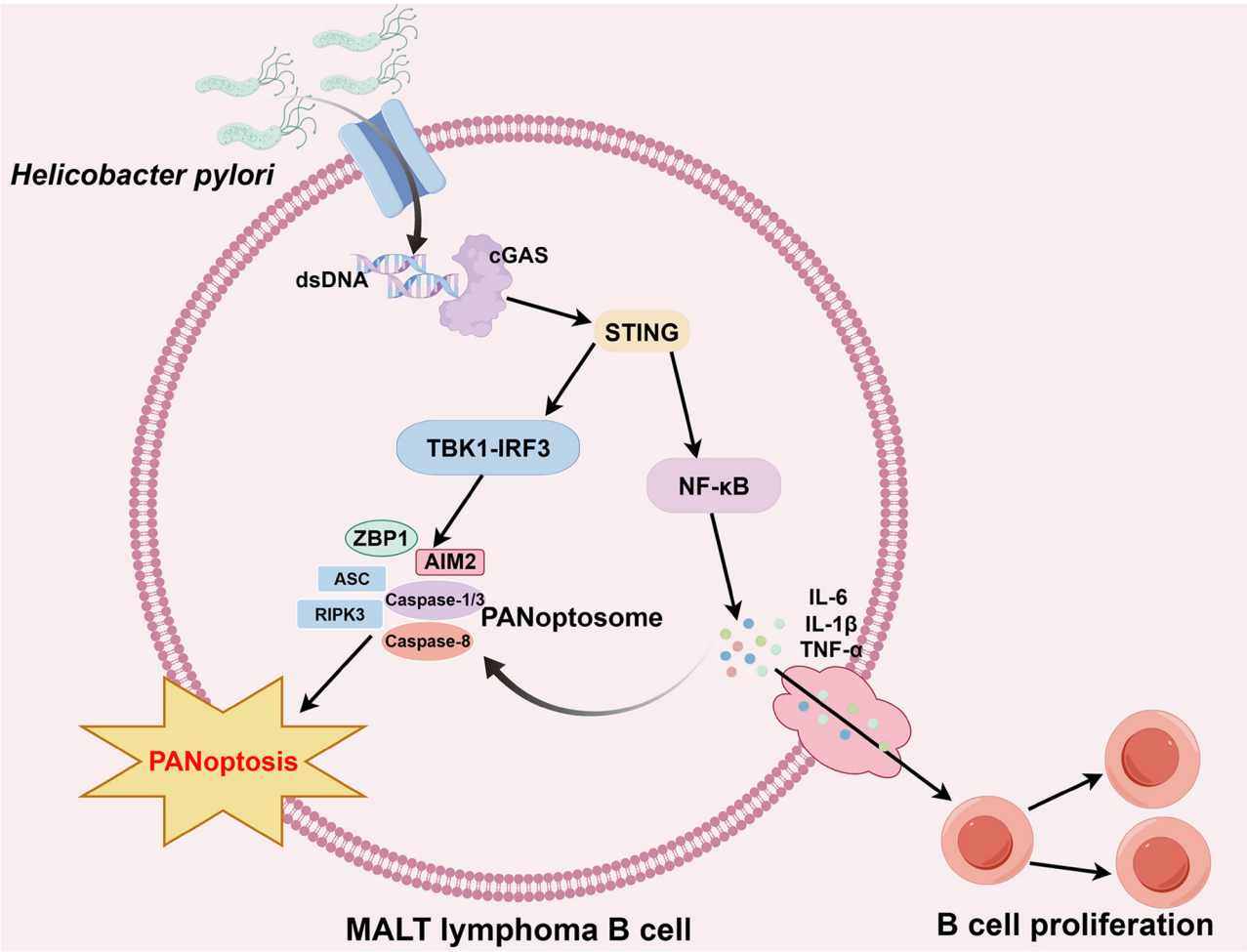

Figure 6. Regulation of PANoptosis in MALT lymphoma. Regulation of PANoptosis in gastric lymphoma cells mediated by *Helicobacter pylori* infection. Created with Figdraw (https://www.figdraw.com). AIM2, absence in melanoma 2; cGAS, cyclic GMP-AMP synthase; dsDNA, double-stranded DNA; IRF3, IFN regulatory factor 3; RIPK3, receptor-interacting protein kinase 3; STING, stimulator of IFN genes; TBK1, TANK-binding kinase 1; ZBP1, Z-DNA-binding protein 1.

PANoptosis. However, STING activation may simultaneously promote NF-κB activation and production of the proinflammatory cytokines TNF-α and IL-6 (84). On the one hand, this induces B-cell proliferation (Fig. 6), potentially driving MALT progression; however, it may also amplify the effects of PANoptosis within MALT, enhancing antitumor immune responses. Traditional anti-HP targeted therapy has a notable effect on early HP-infection type MALT lymphoma (107), but its efficacy is poor for advanced non-HP-infection type MALT lymphoma (108). However, PANoptosis-targeted therapy can induce lymphoma cell-specific death while modulating the immunosuppressive state of the tumor microenvironment. When combined with HP eradication therapy, it may improve the cure rate of early lesions and reduce the risk of recurrence. Consequently, understanding the activation of PANoptosis and investigating its balanced targets may hold key therapeutic potential for MALT.

5. Conclusion

Through investigations into the interconnections and crosstalk between multiple cell death pathways, PANoptosis has emerged as a novel form of cell death that has garnered attention. In gastric epithelial cells during early injury or infection, PANoptosis has a protective effect; in immune cells or epithelial cells during chronic or excessive activation, it has a pathological effect; and in tumor cells, it exerts an antitumor effect through activation. Currently, PANoptosis research is particularly advanced in infectious and neoplastic diseases, offering novel perspectives for advancing human disease prevention and treatment. However, global inhibition of PANoptosis may weaken host defense, impair mucosal repair and increase infection risk; and non-specific activation may damage normal gastric epithelial cells and exacerbate inflammation. Therefore, achieving a balanced activation of PANoptosis is crucial for the early prevention of infectious diseases of the gastric mucosa.

Currently, research on PANoptosis has a number of unavoidable limitations, such as the lack of stomach-specific *in vivo* models that can directly demonstrate the assembly and activation of the PANoptosome in gastric mucosal injury (20). Most of the current evidence comes from *in vitro* cell systems or models derived from other organs (109), which cannot adequately reflect the unique microenvironment, intercellular interactions and regulatory characteristics of the stomach. Moreover, accurately

distinguishing the concurrent activation of PANoptosis from apoptosis, pyroptosis and necroptosis in the gastric mucosal microenvironment poses notable technical challenges (110). Existing detection methods lack specificity, making it difficult to avoid misjudgments caused by signal overlap. In addition, multiple inflammatory signaling pathways (including NF-κB, TLR4 and JAK/STAT) converge on the same key molecular targets of PANoptosis (110), which may result in potential confounding effects in mechanistic interpretations.

Although there are numerous unknowns regarding the 'sensors' that trigger PANoptosis, and the regulatory mechanisms in gastric mucosal diseases lack relevant experimental validation, the involvement of PANoptosis in the regulation of gastric mucosal diseases may become a potential clinical intervention target. Research addressing these limitations is essential. In the future, focusing on establishing gastric-specific PANoptosis research models, developing specific detection and intervention tools, and elucidating precise regulatory mechanisms will provide new theoretical bases and potential therapeutic targets for the prevention and treatment of gastric mucosal diseases.

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Availability of data and materials

Not applicable.

Authors' contributions

LW, ZM BT, TL and XL conceived the study and were involved in its conception and design. LW drafted the manuscript. SL and ST were also involved in the design and conception of the study. BJ performed systematic literature retrieval, screened all relevant studies on PANoptosis and gastric mucosal diseases, and completed collation and comparative analysis of the data included in this review. ZM assisted in the preparation of the figures. ST reviewed the mechanistic framework and revised the manuscript for intellectual content. BT, TL and XL edited and revised the manuscript. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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