

Pyroptosis in gastric mucosal injury-related diseases (Review)

BEI JI¹, ZHIYUAN MA¹, SHUHUI LIU¹, SHUN YAO¹, KENICHI MIZUNO²,
SHUJI TERA², BIGUANG TUO¹, TAOLANG LI^{3,4*} and XUEMEI LIU^{1*}

¹Department of Gastroenterology, Digestive Disease Hospital, Affiliated Hospital of Zunyi Medical University, Zunyi, Guizhou 563003, P.R. China; ²Division of Gastroenterology and Hepatology, Graduate School of Medical and Dental Sciences, Niigata University, Niigata 9502181, Japan; ³Department of General Surgery, Affiliated Hospital of Zunyi Medical University, Zunyi, Guizhou 563003, P.R. China; ⁴Department of Thyroid and Breast Surgery, Affiliated Hospital of Zunyi Medical University, Zunyi, Guizhou 563003, P.R. China

Received April 17, 2025; Accepted July 23, 2025

DOI: 10.3892/ijmm.2025.5606

Abstract. Gastric mucosal epithelial cells, immune cells and signaling molecules constitute the innate and adaptive immune systems of the gastric mucosa, working together to maintain its integrity. Once the balance is disrupted, gastric mucosal diseases may occur. Pyroptosis, as a unique inflammatory programmed cell death mechanism, participates in the dynamic balance between innate and adaptive immunity by identifying and responding to damage factors, and participating in the maturation and release process of inflammatory factors. Pyroptosis is involved in the association of gastric mucosal resistance with microbial invasion and endogenous damage.

By releasing inflammatory factors, the immune environment of the gastric mucosa is reshaped, thereby affecting repair mechanisms and the specific direction of cell differentiation. The present review summarizes the important role of pyroptosis in focal and diffuse gastric mucosal injury. The review aims to provide a novel theoretical basis for the optimization of prevention strategies and treatment plans for current gastric mucosal diseases, and proposes a new option for the scientific management of these diseases.

Contents

1. Introduction
2. Functional role of pyroptosis
3. Pyroptosis in gastric mucosal diseases
4. Conclusion

1. Introduction

Under physiological conditions, the immune system of the gastric mucosa interacts with gastric epithelial cells, immune cells and signaling molecules to form a protective barrier (1). Innate and adaptive immunity maintain the homeostasis of the gastric mucosal immune microenvironment (2-8), whereas a disruption of the balance of the immune microenvironment results in gastric mucosal diseases, such as autoimmune gastritis and gastric neoplasia (5,8,9). Chronic and persistent inflammatory microenvironment stimulation can lead to cellular differentiation disorders and tumor-related lesions; for example, the occurrence and progression of spasmolytic polypeptide-expressing metaplasia (SPEM) (9-11).

Pyroptosis is a type of inflammatory programmed cell death (12,13), which can regulate the balance between innate and adaptive immunity by identifying injury factors, and participating in the maturation and release of inflammatory factors (12,14-16). As an important target of immune regulation, pyroptosis is involved in almost all processes related to the resistance of the gastric mucosa to microbial infections and endogenous damage. In addition, pyroptosis manipulates immune remodeling in the gastric mucosa by releasing

Correspondence to: Professor Xuemei Liu, Department of Gastroenterology, Digestive Disease Hospital, Affiliated Hospital of Zunyi Medical University, 149 Dalian Road, Zunyi, Guizhou 563003, P.R. China

E-mail: onlyoneliuxuemei@163.com

Professor Taolang Li, Department of Thyroid and Breast Surgery, Affiliated Hospital of Zunyi Medical University, 149 Dalian Road, Zunyi, Guizhou 563003, P.R. China

E-mail: 0078029@sina.com

*Contributed equally

Abbreviations: PRRs, pattern recognition receptors; ASC, apoptosis associated speck-like protein containing a CARD; PAMP, pathogen-associated molecular pattern; GSDM, gasdermin; HMGB1, high mobility group protein B1; DCs, dendritic cells; WIRS, water immersion restraint stress; ROS, reactive oxygen species; NLRP3, nucleotide-binding domain and leucine-rich repeat protein 3; PGE2, prostaglandin E2; AIG, autoimmune gastritis; IFN- γ , interferon- γ ; NLRC, nucleotide-binding domain and leucine-rich repeat containing family CARD domain-containing protein 4; SPEM, spasmolytic polypeptide-expressing metaplasia; GC, gastric cancer; MALT lymphoma, mucosa-associated lymphoid tissue lymphoma

Key words: pyroptosis, gastric mucosal diseases, focal gastric mucosal injury, diffuse gastric mucosal injury

inflammatory factors, further affecting the repair process and cell differentiation direction (17-21). The present review summarizes the role of pyroptosis in gastric mucosal diseases, including focal and diffuse gastric mucosal injury. The aim of the current review is to provide a novel theoretical basis for the optimization of prevention strategies and treatment plans for current gastric mucosal diseases, proposing a new perspective for disease management (Fig. 1).

2. Functional role of pyroptosis

Pyroptosis is an inflammatory form of programmed cell death characterized by plasma membrane pore formation and the release of inflammatory contents (12,22-24).

Triggering of pyroptosis. Inflammasomes, which include pattern recognition receptors (PRRs), apoptosis-associated speck-like protein containing a CARD (ASC) proteins and caspase-1, recognize damage signals such as damage-associated molecular patterns or pathogen-associated molecular patterns (PAMPs) (16,25,26). PRRs are representative of immune receptors involved in innate immunity, and the mutual recognition and interaction between PRRs and PAMPs are key to initiating innate immune responses (27). In cases of microbial infection or tissue damage, PRRs rapidly activate innate immunity and inflammasomes, promote pyroptosis and recruit inflammatory cells to guide the initiation of adaptive immune responses (28).

Activation of pyroptosis. Classical caspase-1-dependent activation occurs as follows: PRR signals activate caspase-1 via ASC, and activated caspase-1 cleaves gasdermin (GSDM) D causing membrane rupture and activation of IL-1 β /IL-18, thus amplifying inflammation (29). Non-classical activation occurs as follows: Human caspase-4/5 or murine caspase-11 directly recognize cytosolic lipopolysaccharide, cleave GSDMD and may indirectly activate caspase-1, exacerbating inflammation (30).

Effector phase of pyroptosis. Cell rupture releases inflammatory mediators [such as IL-1 β , IL-18, IL-33 and high mobility group protein B1 (HMGB1)], which recruit and activate immune cells [such as dendritic cells (DCs) and macrophages] to promote antigen presentation and initiate adaptive immunity (16,24,21-33).

Therefore, pyroptosis acts as a bridge between innate and adaptive immunity, clearing infected/damaged cells and remodeling the immune microenvironment for antimicrobial defense and tissue repair (34,35). However, excessive inflammation exacerbates damage, remodels the microenvironment, and can promote autoimmune diseases or tumorigenesis (6,9,12,14). Research regarding pyroptosis-mediated microenvironment remodeling is crucial for understanding disease mechanisms and developing therapeutic strategies (34,36-38).

3. Pyroptosis in gastric mucosal diseases

Gastric mucosal diseases can be divided into focal mucosal injury and diffuse mucosal injury (2,39). Focal mucosal injury is a repairable injury that does not alter cell differentiation

patterns (4,40). When injury and chronic inflammation persist, cells undergo changes in differentiation patterns and develop diffuse mucosal injury (4,41). Notably, damage to the gastric mucosa (via factors such as stress, *Helicobacter pylori* infection and alcohol) is recognized by inflammasomes, and pyroptosis activates the rapid response of the innate immune response, initiates adaptive immunity, reshapes the immune microenvironment, affects cell differentiation, and participates in the occurrence and development of various gastric mucosal diseases.

Role of pyroptosis in focal mucosal injury diseases

Pyroptosis may serve a bidirectional regulatory role in stress-induced gastric mucosal injury. Stress-induced gastric mucosal injury refers to ulcers or erosions that occur due to strong and persistent stress stimuli, such as trauma, shock, burns or surgery, causing an imbalance between the protective and injury mechanisms of the gastric mucosa (42,43). Stress-induced gastric mucosal injury is a serious complication of physical and mental stress caused by factors such as neuroendocrine imbalance (44), disruption of the gastric mucosal protective barrier (45) and enhancement of gastric mucosal injury factors (46).

Stress activates pro-IL-18 in the adrenal cortex via the adrenocorticotrophic hormone/superoxide-mediated caspase-1 activation pathway, converting it into mature IL-18 for release into the bloodstream (17). IL-18 has been reported to mediate water immersion restraint stress (WIRS)-induced gastric injury in an animal model by increasing gastric histidine decarboxylase activity and histamine production, and synergizes with sympathetic overexcitation to exacerbate gastric hemorrhage following WIRS (47).

Local reactive oxygen species (ROS) serve as initiating factors in stress-induced gastric mucosal injury (48). ROS promote gastrophilic 2 expression, activate NF- κ B, increase nucleotide-binding domain and leucine-rich repeat protein 3 (NLRP3) activation and ultimately exacerbate WIRS-induced inflammation (49). This process triggers neutrophil-dominated inflammation, in which elevated NLRP3/IL-1 β levels are positively associated with neutrophil infiltration and ulcer severity (49). Zhang *et al* (50) demonstrated that cold-induced stress increases IL-1 β /IL-18 expression, whereas the caspase-1 inhibitor AC-YVAD-CMK protects the gastric mucosa by suppressing the NLRP3 inflammasome, thereby mitigating inflammation and pyroptosis. However, Higashimori *et al* (51) reported opposing conclusions. NLRP3/IL-1 β levels in the gastric mucosa were revealed to be transiently increased at 0.5 h post-stress (returning to baseline by 3 h) without a concurrent elevation in IL-18. The NLRP3 inflammasome-derived IL-1 β exerted gastric protective effects by activating NF- κ B, inducing the cyclooxygenase-2/prostaglandin E2 (PGE2) axis, and upregulating PGE2 production. The notable discrepancy with the observations of Zhang *et al* (50) of elevated IL-1 β /IL-18 at 8 h post-stress may stem from distinct observational timepoints (0.5-3 h vs. 8 h). Therefore, a phase-dependent bidirectional regulatory role for the NLRP3 inflammasome may be hypothesized in stress-induced gastric injury: In the early phase ($\leq$ 3 h), IL-1 β secretion may mediate mucosal protection, whereas in the late phase ($\geq$ 8 h), IL-18 release could

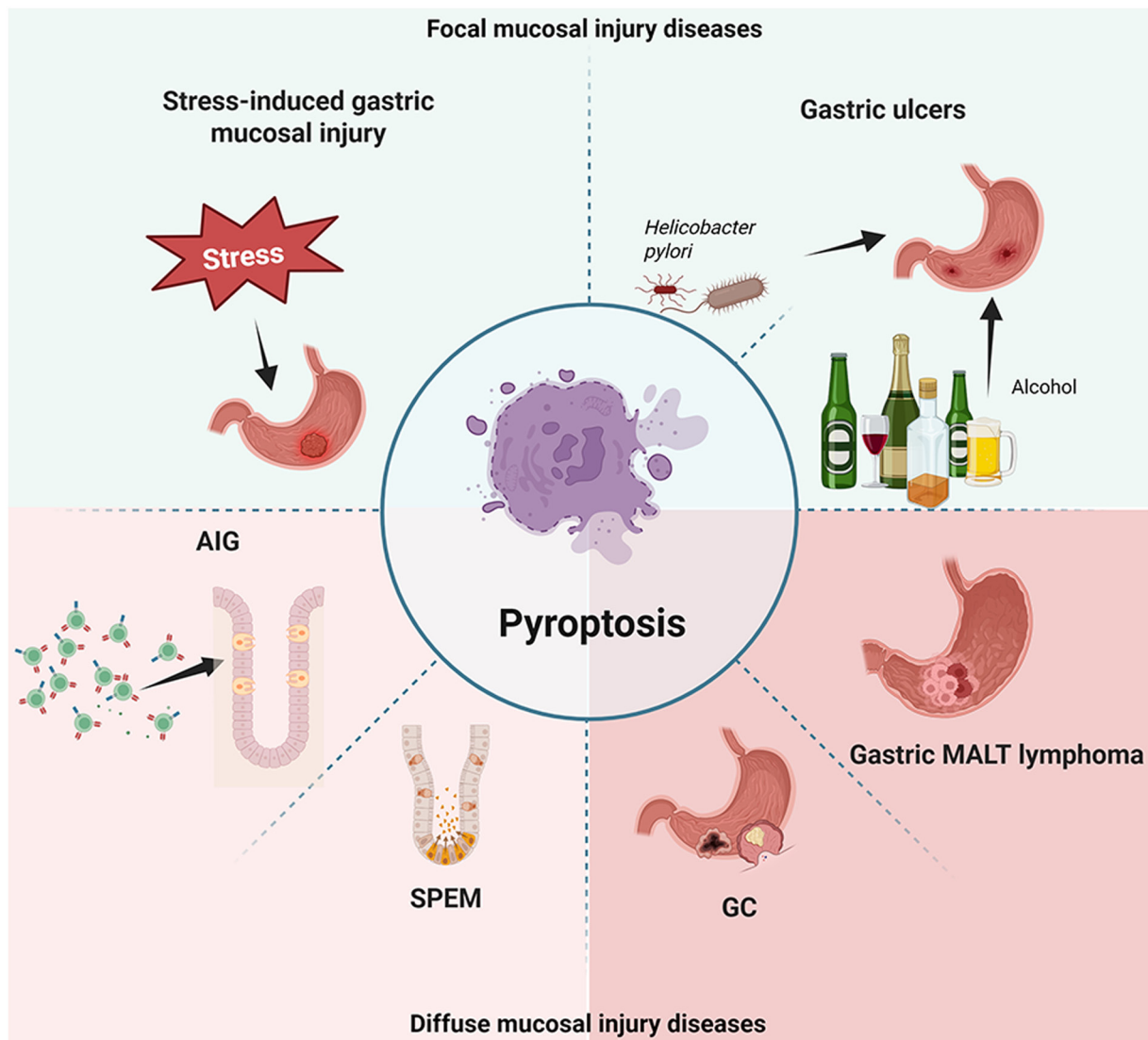


Figure 1. Role of pyroptosis in gastric mucosal injury-related diseases, including both focal injuries (such as stress-induced gastric mucosal injury and gastric ulcers) and diffuse injuries, which can be initiated by AIG, and include SPEM, GC and gastric MALT lymphoma. AIG, autoimmune gastritis; SPEM, spasmolytic polypeptide-expressing metaplasia; GC, gastric cancer; MALT lymphoma, mucosa-associated lymphoid tissue lymphoma.

contribute to mucosal damage. The dynamic equilibrium between IL-1 β and IL-18 dictates pathological progression.

Collectively, pyroptosis-associated mediators serve key regulatory roles, although their precise mechanisms require further elucidation to establish novel therapeutic targets.

Role of pyroptosis in gastric ulcers. The occurrence of gastric ulcers is the comprehensive result of one or more invasive and damaging factors. When the action of mucosal injury factors exceeds that of mucosal protective factors, causing an imbalance between resistance to injury and self-repair ability, the injury can penetrate the muscle layer of the mucosa, leading to the occurrence of gastric ulcers (52). The present review discusses the role of pyroptosis in gastric ulcers from two perspectives: Mucosal injury and mucosal protection.

Pyroptosis serves an important proinflammatory role in the formation of gastric ulcers. In gastric ulcers caused by *Helicobacter pylori* infection, macrophages simultaneously activate the classical caspase-1-dependent pyroptosis pathway and the non-classical pyroptosis pathway mediated by caspase-11 (a direct murine homolog of human caspase-4),

activating the NLRP3 inflammasome, triggering pyroptosis, and promoting the maturation and secretion of IL-1 β (18,53,54). IL-1 β can inhibit gastric acid secretion and contraction of the stomach muscles, and further drive the expression of adhesion molecules on immune cells; regulate neutrophil recruitment, macrophage activation, circulating monocyte infiltration and T-cell expansion; amplify inflammatory responses; and reshape the microenvironment of gastric mucosal tissue (55).

In ethanol-induced gastric mucosal injury, the expression of NLRP3 and GSDMD has been shown to be increased in gastric tissue. Further research revealed that ethanol can directly induce pyroptosis in GES-1 cells, leading to the activation of caspase-1, and the release of IL-1 β and IL-18, causing tissue inflammatory damage (19). Moreover, ethanol can activate NF- κ B p65 and the NLRP3 inflammasome, leading to an increase in HMGB1 expression in the gastric mucosa (56). HMGB1 can stimulate cytokine production through receptor for advanced glycation end products or Toll-like receptor 4, trigger inflammatory responses, attract immune cells to the site of injury and further shape the immune microenvironment (57-60). The

increased expression of HMGB1 in gastric ulcers can accelerate and maintain inflammatory damage, delay tissue healing and increase the risk of tumor formation (60). The inhibition of the HMGB1/NLRP3/NF- κ B pathway results in notable anti-inflammatory and anti-ulcer effects in ethanol-induced gastric ulcers (55). In addition, the caspase-1 inhibitor AC-YVAD-CMK can protect mice from ethanol-induced acute gastric injury by reducing pyroptosis and the inflammatory response, further confirming the important proinflammatory role of pyroptosis in ethanol-induced acute gastric ulcers (50).

Furthermore, research regarding treatment strategies for gastric ulcers has shown that various drugs, such as rabeprazole (61), fucoidan (62), ALDH2 (63), saxagliptin (64), C-phycocyanin (56) and irbesartan (65), inhibit the activation of NLRP3 and pyroptosis, reduce IL-1 β release, notably alleviate inflammation and promote ulcer healing. Therefore, in the complex pathological process of gastric ulcers, pyroptosis has been identified as a key proinflammatory factor, and exploring pyroptosis as a potential therapeutic target may provide new effective avenues for the treatment of gastric ulcers.

Pyroptosis may lead to an increase in the release of the gastric mucosal protective factor PGE2, which is beneficial for promoting wound repair. PGE2 is an important mucosal protective factor for gastric ulcers (66). PGE2 can inhibit caspase-11-driven pyroptosis in macrophages, limiting the activation of typical and atypical inflammasomes, and effectively blocking the inflammatory cascade (54). Notably, a recent study (67) confirmed the protective role of pyroptosis in epithelial injury repair from a new perspective. This previous study used a system (denoted Pyro-1) that was shown to induce macrophage pyroptosis without the release of IL-1 β or IL-1 α , and reported that Pyro-1 supernatant can promote the migration of primary fibroblasts and macrophages, facilitate faster wound closure *in vitro* and improve tissue repair *in vivo*. The presence of oxidized lipids and metabolites in the supernatant of Pyro-1 was identified through lipidomics and metabolomics. The mechanism of action of Pyro-1 was shown to involve the synthesis of PGE2 during the late stage of pyroptosis and PGE2 release through pores opened by GSDMD during pyroptosis to promote tissue regeneration. These findings suggest that the occurrence of pyroptosis may balance tissue damage and regeneration, and that pyroptotic secretion may promote wound repair. Although it is unknown whether pyroptosis also participates in tissue repair through the same mechanism in gastric ulcer injury repair, these results highlight the ‘double-edged sword’ of pyroptosis in immune microenvironment regulation. Therefore, extensive research is needed to further clarify whether pyroptosis serves a dual role in promoting inflammation and repair in gastric mucosal injury and repair.

Overall, pyroptosis has an important regulatory role in damage to and repair of the gastric mucosa in gastric ulcers by reshaping the gastric mucosal tissue microenvironment. Elucidating the specific related mechanisms of pyroptosis may enrich the understanding of gastric mucosal injury and repair, and provide new targets for the treatment of gastric ulcers.

Functional role of pyroptosis in diffuse mucosal injury diseases. Diffuse gastric mucosal injury alters cell differentiation patterns, and is typically associated with gastric tumors

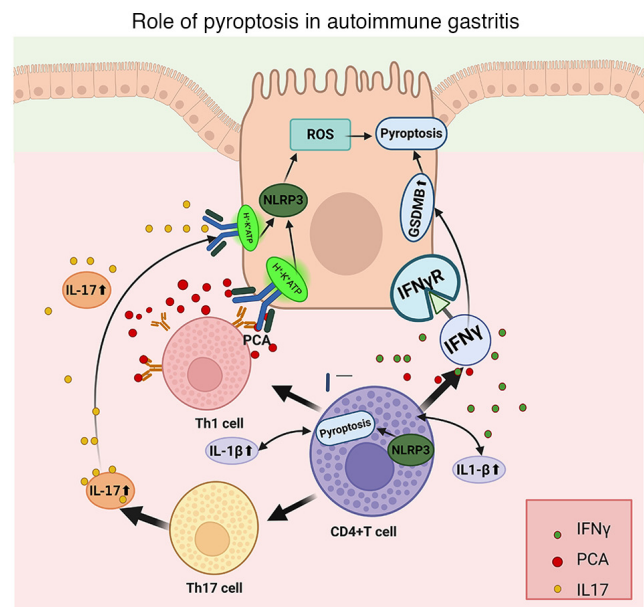


Figure 2. Pyroptosis participates in the regulation of the immune micro-environment of autoimmune gastritis by affecting CD4⁺ T cells. GSDMB, gasdermin B; IFN γ , interferon γ ; IFN γ , IFN γ receptor; NLRP3, nucleotide-binding domain and leucine-rich repeat protein 3; ROS, reactive oxygen species; Th, T helper; PCA, parietal cell antibody.

and precancerous lesions (4,40,41). Pyroptosis affects immune remodeling of the gastric mucosa by releasing inflammatory factors, further affecting cell differentiation, determining cell fate and causing diffuse damage to the gastric mucosa, leading to disease.

Role of pyroptosis in autoimmune gastritis (AIG) (Fig. 2). AIG is type of chronic progressive inflammation mediated by organ-specific immunity, which characterized by anti-parietal cell antibodies that target the H⁺/K⁺ ATPases of parietal cells, leading to CD4⁺ T cell-mediated parietal cell death and progressive atrophy of the secretory gland (68). AIG can lead to hypergastrinemia, resulting in enhanced lymphocyte proliferation and an increased risk of type 1 gastric neuroendocrine tumor development (69). In addition, immune cell-cytokine interactions further disrupt chief/mucous neck cell differentiation, triggering cellular phenotype transformation, SPEN, intestinal metaplasia and intestinal-type gastric carcinogenesis (70). Therefore, AIG is considered the basis for the occurrence of diffuse damage to the gastric mucosa.

The type 1 immune response, which is characterized by T helper (Th)1 CD4⁺ cells and the appearance of interferon- γ (IFN- γ), is a key driving factor in the pathology of AIG (71,72). This pathological cascade is initiated when CD4⁺ T cells specifically recognize H⁺/K⁺ ATPase (73,74), activating the NLRP3 inflammasome/ROS pathway (75) to induce pyroptosis and exacerbate gastric inflammation (76,77). Pyroptosis further fuels disease progression by regulating CD4⁺ T-cell differentiation. Complement-driven assembly of the NLRP3 inflammasome in CD4⁺ T cells triggers pyroptosis-dependent IL-1 β secretion, which promotes Th1 differentiation and IFN- γ production via autocrine signaling (78). Upon binding with IFN- γ receptor on gastric epithelial cells, IFN- γ not only directly induces epithelial death but also upregulates GSDMB

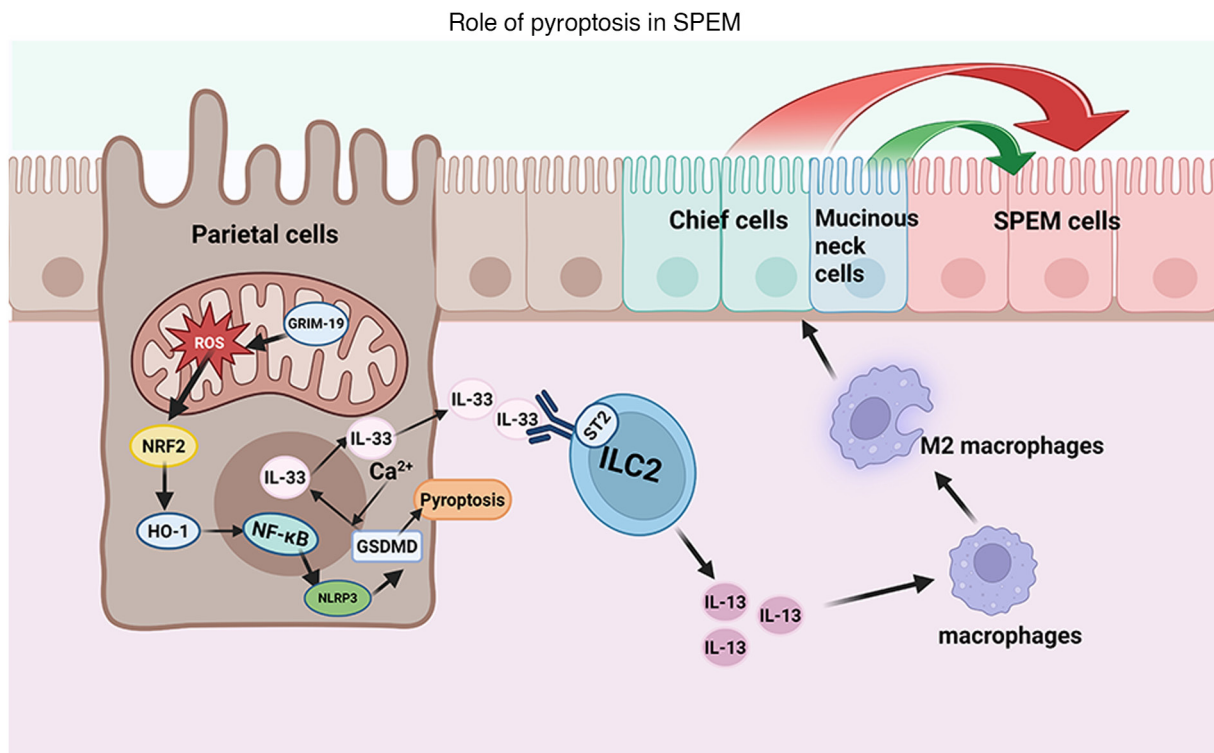


Figure 3. Parietal cells are regulated by mitochondrial GRIM-19 and activate the NLRP3 inflammasome through the ROS/NRF2/HO-1/NF-κB axis, initiating the classical pyroptosis pathway. GRIM-19, gene associated with retinoid-interferon-induced mortality 19; GSDMD, gasdermin D; HO-1, heme oxygenase-1; NLRP3, nucleotide-binding domain and leucine-rich repeat protein 3; NRF2, nuclear factor (erythroid-derived 2)-like 2; ROS, reactive oxygen species; SPEM, spasmolytic polypeptide-expressing metaplasia.

expression to accelerate pyroptotic cell death (79), collectively reshaping the gastric mucosal immune microenvironment.

Additionally, CD4⁺ T cells differentiate into Th17 cells (79) that secrete IL-17 to recognize H⁺/K⁺-ATPase and activate the NLRP3 inflammasome/ROS pathway, driving parietal cell death and AIG pathogenesis (80-82). Notably the Th17 immune response is regulated by the nucleotide-binding domain and leucine-rich repeat containing family CARD domain-containing protein (NLRC)4 inflammasome (83,84). Several studies (84-88) have confirmed that mutations in NLRC4 and NLR family apoptosis inhibitory proteins are involved in the occurrence of various autoinflammatory diseases in humans by affecting pyroptosis and inflammatory responses. Therefore, it may be hypothesized that NLRC4-mediated pyroptosis further regulates the immune microenvironment of the gastric mucosa by modulating the Th17 immune response, and may thus be a novel target for the treatment of AIG.

In summary, pyroptosis critically regulates CD4⁺ T cells in the pathogenesis of AIG, although its precise mechanisms require further validation. Elucidating pyroptosis-mediated remodeling of the gastric mucosal immune microenvironment is essential for discovering novel therapeutic targets.

Pyroptosis is involved in regulating SPEM (Fig. 3). SPEM cells express mucin 6 and trefoil factor 2, and have a morphology similar to that of deep pyloric gland cells or duodenal Brunner gland cells. SPEM cells can be seen as a repair lineage, and under continuous stimulation by chronic inflammation, SPEM can develop into intestinal metaplasia, which is an important precancerous lesion in gastric cancer (GC) (40,41,89).

Recent research has suggested that the absence of parietal cells is the initiating factor for the occurrence of SPEM (90). Parietal cells are regulated by gene associated with retinoid-IFN-induced mortality 19, which activates the NLRP3 inflammasome through the ROS/nuclear factor (erythroid-derived 2)-like 2/heme oxygenase-1/NF-κB axis, initiating the classical pyroptosis pathway (20). After pyroptosis in parietal cells, intracellular activated GSDMD mediates the transport of the inflammatory factor IL-33 from the nucleus to the cytoplasm under the synergistic effect of Ca²⁺ (91). The cell membrane of parietal cells ruptures, and IL-33 in the cytoplasm is passively released into the extracellular space (92,93). The release of IL-33 promotes the secretion of Th2 cytokines (mainly IL-13) and the polarization of M2 macrophages through the IL-33/ST2 signaling pathway, reshapes the immune microenvironment of the gastric mucosal region, initiates epithelial cell reprogramming and promotes the occurrence of SPEM (94,95).

In the absence of parietal cells, the immune microenvironment is reshaped, and epithelial cells are reprogrammed, leading to the transdifferentiation of mature host cells, mucinous neck cells or isthmus stem cells into SPEM cells. SRY-box transcription factor 9 (Sox9) is the main regulatory factor for the differentiation of mucinous neck cells during gastric development (89) and is also an essential mediator of chief cell recruitment to promote SPEM after acute gastric injury. Under inflammatory conditions, macrophage Sox9 directly targets the transcription of S100A9 in the nucleus. Macrophage S100A9 is involved in regulating the inflammatory response and pyroptosis driven by macrophage NIMA-related

kinase 7/NLRP3 (96). However, the role of pyroptosis in the process of gastric mucosal epithelial cell differentiation remains unclear, and its specific regulatory role requires extensive research. In summary, exploring the mechanisms by which pyroptosis reshapes the immune microenvironment and initiates epithelial cell reprogramming can help identify therapeutic targets for SPEM, and prevent the development of more severe phenotypes of gastric mucosal damage.

Role of pyroptosis in the development of gastric neoplasia

Accurately locating and identifying the cell types that undergo pyroptosis will help achieve precise treatment of GC. GC is a common malignant tumor of the digestive system. A number of reviews have summarized pyroptosis as an inflammatory cell death mechanism that reshapes the tumor microenvironment, and affects the occurrence and development of GC. However, due to the high heterogeneity of GC, the role of pyroptosis among different cells in tumor tissue is not consistent, and pyroptosis also dynamically changes as a tumor progresses, making targeted interventions for GC more challenging (97-100).

As an example, the pyroptosis inflammasome NLRP3 serves a dual role in the pathological and physiological processes of GC. First, *H. pylori* infection and its virulence factor CagA promote the upregulation of the NLRP3 inflammasome in GC by enhancing the microRNA (miR)-1290/NKD1/NLRP3 axis (21). NLRP3 upregulation not only drives cancer cell pyroptosis, invasion, migration (via inflammasome activation) and malignant progression, but also induces M2 macrophage polarization through the IL-6/IL-10/JAK2/STAT3 signaling pathway, and modulates the infiltration of CD4⁺ T cells and M2 macrophages within the tumor microenvironment (21). NLRP3 upregulation ultimately accelerates GC progression and is a predictor of poor prognosis (21). In addition, miR-22 has been confirmed to directly target and suppress NLRP3 expression, inhibiting its pro-tumorigenic effects. *H. pylori* infection suppresses miR-22, leading to NLRP3 upregulation, disruption of gastric mucosal homeostasis and initiation of carcinogenesis (38). By inhibiting NLRP3 activity, the carcinogenic potential of NLRP3 has been shown to be effectively suppressed in *in vitro* experiments and animal models, further confirming the core role of NLRP3 in the progression of GC (101).

However, the functional complexity of NLRP3 is not limited to its carcinogenic potential. The occurrence of pyroptosis may increase the sensitivity of GC to chemotherapy. Specifically, activation strategies targeting lensin (a crystalline lens protein highly expressed in cancer stem cells that is associated with malignant progression in patients with GC) can induce pyroptosis in GC stem cells, thereby restoring the responsiveness of GC to chemotherapy drugs (102). In addition, low-dose diosbulbin-B activates the endogenous programmed death ligand 1/NLRP3 signaling pathway in tumors, triggering pyroptosis and notably increasing the sensitivity of GC cells to cisplatin chemotherapy (103). Furthermore, West *et al* (104) suggested that NLRP3 has no notable prognostic value in predicting patient survival outcomes and that it does not serve a dominant role in the inflammatory environment-driven development of gastric tumors. These findings challenge the traditional understanding of the comprehensive role of

NLRP3 in promoting cancer, emphasizing the diversity and complexity of pyroptosis functions under specific pathological conditions. Therefore, only by mechanistically elucidating the bidirectional regulation of pyroptosis and its critical molecular switches can human trials of pyroptosis inhibitors be rationally guided, ultimately achieving the precise therapeutic goal of selectively inducing pyroptosis in target cells, enhancing treatment sensitivity while circumventing tumor-promoting microenvironments.

However, a relative lack of precise identification and related evidence for the phenomenon of pyroptosis in specific single-cell populations in GC tissues remains. How different cell subpopulations in the GC microenvironment trigger complex interactions between cells through pyroptotic mechanisms and further reshape the specific mechanisms of the tumor microenvironment remains unclear; this directly leads to notable differences in the conclusions of the aforementioned studies. Therefore, the scientific validity and effectiveness of solely adopting strategies to inhibit or promote pyroptosis as a cancer treatment method are questionable. Furthermore, considering that the role of pyroptosis is regulated by complex factors, such as the tumor microenvironment and cell type, its biological effects exhibit marked bidirectionality and can affect the development trajectory and treatment response of tumors through diverse mechanisms. This complexity requires the use of a more comprehensive and detailed strategy when designing experiments. In summary, future research regarding pyroptosis in GC should focus on specific analyses of cell types and occurrence periods, in order to achieve a comprehensive evaluation and precise regulation of the effects of pyroptosis. The findings of these studies may provide a solid theoretical basis for optimizing treatment strategies for patients with cancer, and novel ideas for improving patient prognosis and survival status.

Pyroptosis serves a role in the immune regulation of gastric mucosa-associated lymphoid tissue lymphoma (MALT lymphoma). Gastric MALT lymphoma is one of the most common types of non-Hodgkin's lymphoma (105). The proliferation and differentiation of gastric mucosa-associated lymphoma cells are regulated by antigen-specific intratumoral T cells (via CD40-mediated signaling, Th2-type cytokines, chemokines, costimulatory molecules and FOXP3⁺ regulatory T cells) and their communication with B cells (106).

There is a strong causal relationship between MALT lymphoma and chronic *H. pylori*-associated gastritis (107,108). NLRC5 expression is upregulated in the macrophages and gastric tissues of mice and humans after *H. pylori* infection (109). Mice with bone marrow-specific deletion of NLRC5 develop precursor B-cell lesions of MALT lymphoma 3 months after *H. pylori* infection (109). The absence of NLRC5 inhibits GSDMD cleavage and the activation of IL-1 β and caspase-3, leading to the upregulation of IFN γ expression and the activation of lipopolysaccharide-induced proinflammatory responses in macrophages (110), as well as increased IL-1 β and CD40 (111). Anti-CD40L antibodies can prevent gastric B-cell damage in NLRC5-deficient mice, reduce the number of DCs, and CD8⁺ and FOXP3⁺ T cells, and decrease B-cell lymphoma gene expression in the stomach (109,111). Therefore, the involvement of NLRC5 in pyroptosis affects antigen-specific T cells and their communication with

B cells in tumors, and further regulates the occurrence of MALT lymphoma. However, further research and exploration regarding the specific intercellular dialog and mechanisms involved are needed.

4. Conclusion

As scientific research progresses, the understanding of the mechanisms by which pyroptosis contributes to gastric mucosal injury and repair has become increasingly refined. However, key questions remain unanswered. In stress-induced injury, elucidating the phase transition mechanism whereby the NLRP3 inflammasome shifts from early protection to late damage requires the definition of precise neural signaling controls. Furthermore, gastric ulcer healing hinges on cellular sources of pyroptosis, inflammatory mediator (such as IL-1 β and IL-18) and microenvironmental integration, particularly regarding how PGE2 spatiotemporally coordinates anti-inflammatory and pro-repair functions. For SPEM, the molecular mechanisms underlying GSDMD-mediated IL-33 release (especially Ca²⁺-dependent regulation) and whether additional factors from pyroptotic parietal cells directly drive mucous neck/stem cell reprogramming must be resolved. Furthermore, it remains unknown as to whether pyroptosis or its effectors directly modulate key transcription factors to initiate SPEM, or whether targeting pyroptosis can halt/reverse SPEM progression. In heterogeneous GC microenvironments, identifying which cellular subpopulations undergo pyroptosis at specific stages (with cell type-dependent triggers) and defining their stage-dependent roles (early tumor suppression vs. late metastasis) are essential for developing strategies for selectively inducing cancer cell pyroptosis to enhance chemosensitization while avoiding tumor-promoting microenvironments. These focused efforts will provide more precise targets for elucidating disease pathogenesis, and hold promise for facilitating innovative and highly effective interventions for gastric mucosal disorders.

Acknowledgements

The authors are grateful to Ms. Guorong Wen, Professor Hai Jin and Professor Jiaying An (Department of Gastroenterology, Digestive Disease Hospital, Affiliated Hospital of Zunyi Medical University, Zunyi, China), who provided suggestions for the article.

Funding

The present review was funded by the National Natural Science Foundation of China (National Science Foundation of China) (grant nos. 82070536, 82073087, 82470540, 32460215 and 82160505), the Guizhou Province International Science and Technology Cooperation (Gastroenterology) Base [grant no. Qian Ke He Platform Talents-HZJD (2021) 001], the Major Project of Guizhou Province Basic Research Program [grant no. Qian Ke He basic research-ZK (2023) major project 059], the Guizhou Province Science Plan Program [grant no. Qian Ke He Foundation-ZK (2021) General 461], the Guizhou Province High-level Innovative Talent Selection and Training Plan (100 level) [grant no. Qian Ke He Platform Talents-GCC

(2023) 043] and the Guizhou Innovative Talent Team on Ion Channels and Malignant Tumors of Epithelial Origin [grant no. Qian Ke He Platform Talents-CXTD (2023) 001].

Availability of data and materials

Not applicable.

Authors' contributions

XL and TL conceived and designed the paper. BJ drafted the manuscript. ZM and BT edited and revised the manuscript. SL, SY, KM and ST participated in the literature search and analysis of the data to be included in the review. Data authentication is not applicable. All authors read and approved the final version of the 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.

References

1. Liu S, Deng Z, Zhu J, Ma Z, Tuo B, Li T and Liu X: Gastric immune homeostasis imbalance: An important factor in the development of gastric mucosal diseases. *Biomed Pharmacother* 161: 114338, 2023.
2. Mills JC and Shivdasani RA: Gastric epithelial stem cells. *Gastroenterology* 140: 412-424, 2011.
3. Goldenring JR and Nam KT: Oxyntic atrophy, metaplasia, and gastric cancer. *Prog Mol Biol Transl Sci* 96: 117-131, 2010.
4. Goldenring JR and Mills JC: Cellular plasticity, reprogramming, and regeneration: metaplasia in the stomach and beyond. *Gastroenterology* 162: 415-430, 2022.
5. Zhou CB and Fang JY: The role of pyroptosis in gastrointestinal cancer and immune responses to intestinal microbial infection. *Biochim Biophys Acta Rev Cancer* 1872: 1-10, 2019.
6. Yang W, Niu L, Zhao X, Duan L, Wang X, Li Y, Chen J, Zhou W, Zhang Y, Fan D and Hong L: Pyroptosis impacts the prognosis and treatment response in gastric cancer via immune system modulation. *Am J Cancer Res* 12: 1511-1534, 2022.
7. Villarroel-Espindola F, Ejsmentewicz T, Gonzalez-Stegmaier R, Jorquera RA and Salinas E: Intersections between innate immune response and gastric cancer development. *World J Gastroenterol* 29: 2222-2240, 2023.
8. Gobert AP and Wilson KT: Induction and regulation of the innate immune response in *Helicobacter pylori* infection. *Cell Mol Gastroenterol Hepatol* 13: 1347-1363, 2022.
9. Jiao Y, Yan Z and Yang A: The roles of innate lymphoid cells in the gastric mucosal immunology and oncogenesis of gastric cancer. *Int J Mol Sci* 24: 6652, 2023.
10. Ianiro G, Molina-Infante J and Gasbarrini A: Gastric microbiota. *Helicobacter* 20 (Suppl 1): S68-S71, 2015.
11. Goldenring JR: Pyloric metaplasia, pseudopyloric metaplasia, ulcer-associated cell lineage and spasmolytic polypeptide-expressing metaplasia: Reparative lineages in the gastrointestinal mucosa. *J Pathol* 245: 132-137, 2018.
12. Barnett KC, Li S, Liang K and Ting JPY: A 360° view of the inflammasome: Mechanisms of activation, cell death, and diseases. *Cell* 186: 2288-2312, 2023.
13. Li Z, Guo J and Bi L: Role of the NLRP3 inflammasome in autoimmune diseases. *Biomed Pharmacother* 130: 110542, 2020.

14. Mridha AR, Wree A, Robertson AAB, Yeh MM, Johnson CD, Van Rooyen DM, Haczeiny F, Teoh NC, Savard C, Ioannou GN, et al: NLRP3 inflammasome blockade reduces liver inflammation and fibrosis in experimental NASH in mice. *J Hepatol* 66: 1037-1046, 2017.
15. Kayagaki N, Kornfeld OS, Lee BL, Stowe IB, O'Rourke K, Li Q, Sandoval W, Yan D, Kang J, Xu M, et al: NINJ1 mediates plasma membrane rupture during lytic cell death. *Nature* 591: 131-136, 2021.
16. Fu J and Wu H: Structural mechanisms of NLRP3 inflammasome assembly and activation. *Annu Rev Immunol* 41: 301-316, 2023.
17. Sekiyama A, Ueda H, Kashiwamura SI, Sekiyama R, Takeda M, Rokutan K and Okamura H: A stress-induced, superoxide-mediated caspase-1 activation pathway causes plasma IL-18 upregulation. *Immunity* 22: 669-677, 2005.
18. Tran LS, Ying L, D'Costa K, Wray-McCann G, Kerr G, Le L, Allison CC, Ferrand J, Chaudhry H, Emery J, et al: NOD1 mediates interleukin-18 processing in epithelial cells responding to *Helicobacter pylori* infection in mice. *Nat Commun* 14: 3804, 2023.
19. Li G, Zhu L, Cao Z, Wang J, Zhou F, Wang X, Li X and Nie G: A new participant in the pathogenesis of alcoholic gastritis: Pyroptosis. *Cell Physiol Biochem* 49: 406-418, 2018.
20. Zeng X, Yang M, Ye T, Feng J, Xu X, Yang H, Wang X, Bao L, Li R, Xue B, et al: Mitochondrial GRIM-19 loss in parietal cells promotes spasmolytic polypeptide-expressing metaplasia through NLR family pyrin domain-containing 3 (NLRP3)-mediated IL-33 activation via a reactive oxygen species (ROS)-NRF2-Heme oxygenase-1(HO-1)-NF- κ B axis. *Free Radic Biol Med* 202: 46-61, 2023.
21. Wan C, Wang P, Xu Y, Zhu Y, Chen H, Cao X and Gu Y: Mechanism and role of *H. pylori* CagA-induced NLRP3 inflammasome in gastric cancer immune cell infiltration. *Sci Rep* 15: 14335, 2025.
22. Cookson BT and Brennan MA: Pro-inflammatory programmed cell death. *Trends Microbiol* 9: 113-114, 2001.
23. Ketelut-Carneiro N and Fitzgerald KA: Apoptosis, pyroptosis, and necroptosis-Oh My! The many ways a cell can die. *J Mol Biol* 434: 167378, 2022.
24. Shi J, Zhao Y, Wang K, Shi X, Wang Y, Huang H, Zhuang Y, Cai T, Wang F and Shao F: Cleavage of GSDMD by inflammatory caspases determines pyroptotic cell death. *Nature* 526: 660-665, 2015.
25. Van Opdenbosch N, Gurung P, Vande Walle L, Fossoul A, Kanneganti TD and Lamkanfi M: Activation of the NLRP1b inflammasome independently of ASC-mediated caspase-1 autoproteolysis and speck formation. *Nat Commun* 5: 3209, 2014.
26. Man SM, Hopkins LJ, Nugent E, Cox S, Glück IM, Tourlomousis P, Wright JA, Cicuta P, Monie TP and Bryant CE: Inflammasome activation causes dual recruitment of NLRC4 and NLRP3 to the same macromolecular complex. *Proc Natl Acad Sci USA* 111: 7403-7408, 2014.
27. Berry R and Call ME: Modular activating receptors in innate and adaptive immunity. *Biochemistry* 56: 1383-1402, 2017.
28. Que X, Zheng S, Song Q, Pei H and Zhang P: Fantastic voyage: The journey of NLRP3 inflammasome activation. *Genes Dis* 11: 819-829, 2023.
29. Rathinam VAK and Fitzgerald KA: Inflammasome complexes: Emerging mechanisms and effector functions. *Cell* 165: 792-800, 2016.
30. Viganò E and Mortellaro A: Caspase-11: The driving factor for noncanonical inflammasomes. *Eur J Immunol* 43: 2240-2245, 2013.
31. Pérez-Figueroa E, Torres J, Sánchez-Zaucó N, Contreras-Ramos A, Alvarez-Arellano L and Maldonado-Bernal C: Activation of NLRP3 inflammasome in human neutrophils by *Helicobacter pylori* infection. *Innate Immun* 22: 103-112, 2016.
32. Kumar S and Dhiman M: Inflammasome activation and regulation during *Helicobacter pylori* pathogenesis. *Microb Pathog* 125: 468-474, 2018.
33. Yang J, Liu Z, Wang C, Yang R, Rathkey JK, Pinkard OW, Shi W, Chen Y, Dubyak GR, Abbott DW and Xiao TS: Mechanism of gasdermin D recognition by inflammatory caspases and their inhibition by a gasdermin D-derived peptide inhibitor. *Proc Natl Acad Sci USA* 115: 6792-6797, 2018.
34. Fink SL and Cookson BT: Pyroptosis and host cell death responses during *Salmonella* infection. *Cell Microbiol* 9: 2562-2570, 2007.
35. Man SM: Inflammasomes in the gastrointestinal tract: Infection, cancer and gut microbiota homeostasis. *Nat Rev Gastroenterol Hepatol* 15: 721-737, 2018.
36. Toldo S, Mezzaroma E, Buckley LF, Potere N, Di Nisio M, Biondi-Zoccai G, Van Tassell BW and Abbate A: Targeting the NLRP3 inflammasome in cardiovascular diseases. *Pharmacol Ther* 236: 108053, 2022.
37. Wen J, Xuan B, Liu Y, Wang L, He L, Meng X, Zhou T and Wang Y: NLRP3 inflammasome-induced pyroptosis in digestive system tumors. *Front Immunol* 14: 1074606, 2023.
38. Li S, Liang X, Ma L, Shen L, Li T, Zheng L, Sun A, Shang W, Chen C, Zhao W and Jia J: MiR-22 sustains NLRP3 expression and attenuates *H. pylori*-induced gastric carcinogenesis. *Oncogene* 37: 884-896, 2018.
39. Zhao Y, Deng Z, Ma Z, Zhang M, Wang H, Tuo B, Li T and Liu X: Expression alteration and dysfunction of ion channels/transporters in the parietal cells induces gastric diffused mucosal injury. *Biomed Pharmacother* 148: 112660, 2022.
40. Liu X, Ma Z, Deng Z, Yi Z, Tuo B, Li T and Liu X: Role of spasmolytic polypeptide-expressing metaplasia in gastric mucosal diseases. *Am J Cancer Res* 13: 1667-1681, 2023.
41. Meyer AR and Goldenring JR: Injury, repair, inflammation and metaplasia in the stomach. *J Physiol* 596: 3861-3867, 2018.
42. Brzozowski T, Zwirska-Korczala K, Konturek PC, Konturek SJ, Sliwowski Z, Pawlik M, Kwiecien S, Drodzowicz D, Mazurkiewicz-Janik M, Bielanski W and Pawlik WW: Role of circadian rhythm and endogenous melatonin in pathogenesis of acute gastric bleeding erosions induced by stress. *J Physiol Pharmacol* 58 (Suppl 6): S53-S64, 2007.
43. Nithiwathanapong C, Reungrongrat S and Ukarapol N: Prevalence and risk factors of stress-induced gastrointestinal bleeding in critically ill children. *World J Gastroenterol* 11: 6839-6842, 2005.
44. Kromin AA and Zenina OI: Hypothalamic control of the myoelectric activity of the gastric antrum in rabbits during acute emotional stress. *Eksp Klin Gastroenterol*: 71-76, 165, 2007 (In Russian).
45. Bregonzio C, Armando I, Ando H, Jezova M, Baiardi G and Saavedra JM: Anti-inflammatory effects of angiotensin II AT1 receptor antagonism prevent stress-induced gastric injury. *Am J Physiol Gastrointest Liver Physiol* 285: G414-G423, 2003.
46. Olaleye SB, Adaramoye OA, Erigbali PP and Adeniyi OS: Lead exposure increases oxidative stress in the gastric mucosa of HCl/ethanol-exposed rats. *World J Gastroenterol* 13: 5121-5126, 2007.
47. Seino H, Ueda H, Kokai M, Tsuji NM, Kashiwamura S, Morita Y and Okamura H: IL-18 mediates the formation of stress-induced, histamine-dependent gastric lesions. *Am J Physiol Gastrointest Liver Physiol* 292: G262-G267, 2007.
48. Das D, Bandyopadhyay D, Bhattacharjee M and Banerjee RK: Hydroxyl radical is the major causative factor in stress-induced gastric ulceration. *Free Radic Biol Med* 23: 8-18, 1997.
49. Zhang Z, Xue H, Dong Y, Hu J, Jiang T, Shi L and Du J: Inhibition of GKN2 attenuates acute gastric lesions through the NLRP3 inflammasome. *Adv Wound Care (New Rochelle)* 9: 219-232, 2020.
50. Zhang F, Wang L, Wang JJ, Luo PF, Wang XT and Xia ZF: The caspase-1 inhibitor AC-YVAD-CMK attenuates acute gastric injury in mice: Involvement of silencing NLRP3 inflammasome activities. *Sci Rep* 6: 24166, 2016.
51. Higashimori A, Watanabe T, Nadatani Y, Nakata A, Otani K, Hosomi S, Tanaka F, Kamata N, Taira K, Nagami Y, et al: Role of nucleotide binding oligomerization domain-like receptor protein 3 inflammasome in stress-induced gastric injury. *J Gastroenterol Hepatol* 36: 740-750, 2021.
52. Bojanowicz K, Zubowski A, Durasiewicz Z and Szeszenia N: Gastric or duodenal ulcer location and the more important internal and environmental factors. *Przegl Lek* 28: 457-460, 1971 (In Polish).
53. Yu Q, Shi H, Ding Z, Wang Z, Yao H and Lin R: The E3 ubiquitin ligase TRIM31 attenuates NLRP3 inflammasome activation in *Helicobacter pylori*-associated gastritis by regulating ROS and autophagy. *Cell Commun Signal* 21: 1, 2023.
54. Zaslon Z, Flis E, Nulty C, Kearney J, Fitzgerald R, Douglas AR, McNamara D, Smith S, O'Neill LAJ and Creagh EM: Caspase-4: A therapeutic target for peptic ulcer disease. *Immunohorizons* 4: 627-633, 2020.
55. Yuan XY, Zhang Y, Zhao X, Chen A and Liu P: IL-1 β , an important cytokine affecting *Helicobacter pylori*-mediated gastric carcinogenesis. *Microb Pathog* 174: 105933, 2023.
56. Alzokaky AA, Abdelkader EM, El-Dessouki AM, Khaleel SA and Raslan NA: C-phycocyanin protects against ethanol-induced gastric ulcers in rats: Role of HMGB1/NLRP3/NF- κ B pathway. *Basic Clin Pharmacol Toxicol* 127: 265-277, 2020.

57. Sims GP, Rowe DC, Rietdijk ST, Herbst R and Coyle AJ: HMGB1 and RAGE in inflammation and cancer. *Annu Rev Immunol* 28: 367-388, 2010.
58. Yang H, Wang H and Andersson U: Targeting inflammation Driven by HMGB1. *Front Immunol* 11: 484, 2020.
59. El-Gendy ZA, Taher RF, Elgamal AM, Serag A, Hassan A, Jaleel GAA, Farag MA and Elshamy AI: Metabolites profiling and bioassays reveal *bassia indica* ethanol extract protective effect against stomach ulcers development via HMGB1/TLR-4/NF- κ B pathway. *Antioxidants (Basel)* 12: 1263, 2023.
60. Elbaz EM, Abdel Rahman AAS, El-Gazar AA and Ali BM: Protective effect of dimethyl fumarate against ethanol-provoked gastric ulcers in rats via regulation of HMGB1/TLR4/NF- κ B, and PPAR γ /SIRT1/Nrf2 pathways: Involvement of miR-34a-5p. *Arch Biochem Biophys* 759: 110103, 2024.
61. Xie J, Fan L, Xiong L, Chen P, Wang H, Chen H, Zhao J, Xu Z, Geng L, Xu W and Gong S: Rabepazole inhibits inflammatory reaction by inhibition of cell pyroptosis in gastric epithelial cells. *BMC Pharmacol Toxicol* 22: 44, 2021.
62. Selim HM, Negm WA, Hawwal MF, Hussein IA, Elekhawey E, Ulber R and Zayed A: Fucoidan mitigates gastric ulcer injury through managing inflammation, oxidative stress, and NLRP3-mediated pyroptosis. *Int Immunopharmacol* 120: 110335, 2023.
63. Zhang Y, Yuan Z, Chai J, Zhu D, Miao X, Zhou J and Gu X: ALDH2 ameliorates ethanol-induced gastric ulcer through suppressing NLRP3 inflammasome activation and ferroptosis. *Arch Biochem Biophys* 743: 109621, 2023.
64. Arab HH, Ashour AM, Gad AM, Mahmoud AM and Kabel AM: Activation of AMPK/mTOR-driven autophagy and inhibition of NLRP3 inflammasome by saxagliptin ameliorate ethanol-induced gastric mucosal damage. *Life Sci* 280: 119743, 2021.
65. Arab HH, Eid AH, El-Sheikh AAK, Arafa EA and Ashour AM: Irbesartan reprofiling for the amelioration of ethanol-induced gastric mucosal injury in rats: Role of inflammation, apoptosis, and autophagy. *Life Sci* 308: 120939, 2022.
66. Suleyman H, Albayrak A, Bilici M, Cadirci E and Halici Z: Different mechanisms in formation and prevention of indomethacin-induced gastric ulcers. *Inflammation* 33: 224-234, 2010.
67. Mehrotra P, Maschalidi S, Boeckaerts L, Maueröder C, Tixeira R, Pinney J, Burgoa Cardás J, Sukhov V, Incik Y, Anderson CJ, *et al*: Oxylipins and metabolites from pyroptotic cells act as promoters of tissue repair. *Nature* 631: 207-215, 2024.
68. Soykan İ, Er RE, Baykara Y and Kalkan C: Unraveling the mysteries of autoimmune gastritis. *Turk J Gastroenterol* 36: 135-144, 2024.
69. Jove A, Lin C, Hwang JH, Balasubramanian V, Fernandez-Becker NQ and Huang RJ: Serum gastrin levels are associated with prevalent neuroendocrine tumors in autoimmune metaplastic atrophic gastritis. *Am J Gastroenterol* 120: 1140-1143, 2025.
70. Huang J, Fang M, Wu C and Qiao Z: Autoimmune atrophic gastritis complicated with oxyntic gland adenoma and low-grade intraepithelial neoplasia. *Asian J Surg*: Sep 12, 2024 (Epub ahead of print).
71. Park JY, Lam-Himlin D and Vemulapalli R: Review of autoimmune metaplastic atrophic gastritis. *Gastrointest Endosc* 77: 284-292, 2013.
72. Neumann WL, Coss E, Rugge M and Genta RM: Autoimmune atrophic gastritis-pathogenesis, pathology and management. *Nat Rev Gastroenterol Hepatol* 10: 529-541, 2013.
73. D'Elios MM, Bergman MP, Azzurri A, Amedei A, Benagiano M, De Pont JJ, Cianchi F, Vandenbroucke-Grauls CM, Romagnani S, Appelmek BJ and Del Prete G: H(+),K(+)-atpase (proton pump) is the target autoantigen of Th1-type cytotoxic T cells in autoimmune gastritis. *Gastroenterology* 120: 377-386, 2001.
74. Toh BH, SENTRY JW and Alderuccio F: The causative H+/K+ ATPase antigen in the pathogenesis of autoimmune gastritis. *Immunol Today* 21: 348-354, 2000.
75. Hu Z and Chai J: Structural mechanisms in NLR inflammasome assembly and signaling. *Curr Top Microbiol Immunol* 397: 23-42, 2016.
76. van Driel IR, Baxter AG, Laurie KL, Zwar TD, La Gruta NL, Judd LM, Scarff KL, Silveira PA and Gleeson PA: Immunopathogenesis, loss of T cell tolerance and genetics of autoimmune gastritis. *Autoimmun Rev* 1: 290-297, 2002.
77. Benítez J, Marra R, Reyes J and Calvete O: A genetic origin for acid-base imbalance triggers the mitochondrial damage that explains the autoimmune response and drives to gastric neuroendocrine tumours. *Gastric Cancer* 23: 52-63, 2020.
78. Arbore G, West EE, Spolski R, Robertson AAB, Klos A, Rheinheimer C, Dutow P, Woodruff TM, Yu ZX, O'Neill LA, *et al*: T helper 1 immunity requires complement-driven NLRP3 inflammasome activity in CD4⁺ T cells. *Science* 352: aad1210, 2016.
79. Lee GR: The balance of Th17 versus Treg cells in autoimmunity. *Int J Mol Sci* 19: 730, 2018.
80. Lei L, Sun J, Han J, Jiang X, Wang Z and Chen L: Interleukin-17 induces pyroptosis in osteoblasts through the NLRP3 inflammasome pathway in vitro. *Int Immunopharmacol* 96: 107781, 2021.
81. Stummvoll GH, DiPaolo RJ, Huter EN, Davidson TS, Glass D, Ward JM and Shevach EM: Th1, Th2, and Th17 effector T cell-induced autoimmune gastritis differs in pathological pattern and in susceptibility to suppression by regulatory T cells. *J Immunol* 181: 1908-1916, 2008.
82. Feng WQ, Zhang YC, Xu ZQ, Yu SY, Huo JT, Tuersun A, Zheng MH, Zhao JK, Zong YP and Lu AG: IL-17A-mediated mitochondrial dysfunction induces pyroptosis in colorectal cancer cells and promotes CD8⁺ T-cell tumour infiltration. *J Transl Med* 21: 335, 2023.
83. Faure E, Mear JB, Faure K, Normand S, Couturier-Maillard A, Grandjean T, Balloy V, Ryffel B, Dessein R, Chignard M, *et al*: *Pseudomonas aeruginosa* type-3 secretion system dampens host defense by exploiting the NLR4-coupled inflammasome. *Am J Respir Crit Care Med* 189: 799-811, 2014.
84. Kitamura A, Sasaki Y, Abe T, Kano H and Yasutomo K: An inherited mutation in NLRC4 causes autoinflammation in human and mice. *J Exp Med* 211: 2385-2396, 2014.
85. Kay C, Wang R, Kirkby M and Man SM: Molecular mechanisms activating the NAIP-NLRC4 inflammasome: Implications in infectious disease, autoinflammation, and cancer. *Immunol Rev* 297: 67-82, 2020.
86. Triantafilou K, Ward CJK, Czubala M, Ferris RG, Koppe E, Haffner C, Piguat V, Patel VK, Amrine-Madsen H, Modis LK, *et al*: Differential recognition of HIV-stimulated IL-1 β and IL-18 secretion through NLR and NAIP signalling in monocyte-derived macrophages. *PLoS Pathog* 17: e1009417, 2021.
87. Zhao Y and Shao F: The NAIP-NLRC4 inflammasome in innate immune detection of bacterial flagellin and type III secretion apparatus. *Immunol Rev* 265: 85-102, 2015.
88. Romberg N, Al Moussawi K, Nelson-Williams C, Stiegler AL, Loring E, Choi M, Overton J, Meffre E, Khokha MK, Huttner AJ, *et al*: Mutation of NLRC4 causes a syndrome of enterocolitis and autoinflammation. *Nat Genet* 46: 1135-1139, 2014.
89. Willet SG, Thanintorn N, McNeill H, Huh SH, Ornitz DM, Huh WJ, Hoft SG, DiPaolo RJ and Mills JC: SOX9 governs gastric mucosal neck cell identity and is required for injury-induced metaplasia. *Cell Mol Gastroenterol Hepatol* 16: 325-339, 2023.
90. Petersen CP, Weis VG, Nam KT, Sousa JF, Fingleton B and Goldenring JR: Macrophages promote progression of spasmolytic polypeptide-expressing metaplasia after acute loss of parietal cells. *Gastroenterology* 146: 1727-1738.e8, 2014.
91. Chen W, Chen S, Yan C, Zhang Y, Zhang R, Chen M, Zhong S, Fan W, Zhu S, Zhang D, *et al*: Allergen protease-activated stress granule assembly and gasdermin D fragmentation control interleukin-33 secretion. *Nat Immunol* 23: 1021-1030, 2022.
92. Kita H: Gasdermin D pores for IL-33 release. *Nat Immunol* 23: 989-991, 2022.
93. Chauvin C, Retnakumar SV and Bayry J: Gasdermin D as a cellular switch to orientate immune responses via IL-33 or IL-1 β . *Cell Mol Immunol* 20: 8-10, 2023.
94. Bernink JH, Germar K and Spits H: The role of ILC2 in pathology of type 2 inflammatory diseases. *Curr Opin Immunol* 31: 115-120, 2014.
95. Meyer AR, Engevik AC, Madorsky T, Belmont E, Stier MT, Norlander AE, Pilkinton MA, McDonnell WJ, Weis JA, Jang B, *et al*: Group 2 innate lymphoid cells coordinate damage response in the stomach. *Gastroenterology* 159: 2077-2091.e8, 2020.
96. Sheng M, Weng Y, Cao Y, Zhang C, Lin Y and Yu W: Caspase 6/NR4A1/SOX9 signaling axis regulates hepatic inflammation and pyroptosis in ischemia-stressed fatty liver. *Cell Death Discov* 9: 106, 2023.
97. Qiang R, Li Y, Dai X and Lv W: NLRP3 inflammasome in digestive diseases: From mechanism to therapy. *Front Immunol* 13: 978190, 2022.
98. Shadab A, Mahjoor M, Abbasi-Kolli M, Afkhami H, Moeinian P and Safdarian AR: Divergent functions of NLRP3 inflammasomes in cancer: A review. *Cell Commun Signal* 21: 232, 2023.

99. Si Y, Liu L and Fan Z: Mechanisms and effects of NLRP3 in digestive cancers. *Cell Death Discov* 10: 10, 2024.
100. Liu W, Peng J, Xiao M, Cai Y, Peng B, Zhang W, Li J, Kang F, Hong Q, Liang Q, et al: The implication of pyroptosis in cancer immunology: Current advances and prospects. *Genes Dis* 10: 2339-2350, 2023.
101. Zhang X, Li C, Chen D, He X, Zhao Y, Bao L, Wang Q, Zhou J and Xie Y: *H. pylori* CagA activates the NLRP3 inflammasome to promote gastric cancer cell migration and invasion. *Inflamm Res* 71: 141-155, 2022.
102. Li YT, Tan XY, Ma LX, Li HH, Zhang SH, Zeng CM, Huang LN, Xiong JX and Fu L: Targeting LGSN restores sensitivity to chemotherapy in gastric cancer stem cells by triggering pyroptosis. *Cell Death Dis* 14: 545, 2023.
103. Li C, Qiu J and Xue Y: Low-dose Diosbulbin-B (DB) activates tumor-intrinsic PD-L1/NLRP3 signaling pathway mediated pyroptotic cell death to increase cisplatin-sensitivity in gastric cancer (GC). *Cell Biosci* 11: 38, 2021.
104. West AJ, Deswaerte V, West AC, Gearing LJ, Tan P and Jenkins BJ: Inflammasome-associated gastric tumorigenesis is independent of the NLRP3 pattern recognition receptor. *Front Oncol* 12: 830350, 2022.
105. Raderer M, Kiesewetter B and Ferreri AJ: Clinicopathologic characteristics and treatment of marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma). *CA Cancer J Clin* 66: 153-171, 2016.
106. Kuo SH, Wu MS, Yeh KH, Lin CW, Hsu PN, Chen LT and Cheng AL: Novel insights of lymphomagenesis of *Helicobacter pylori*-dependent gastric mucosa-associated lymphoid tissue lymphoma. *Cancers (Basel)* 11: 547, 2019.
107. Kiesewetter B and Raderer M: Immunomodulatory treatment for mucosa-associated lymphoid tissue lymphoma (MALT lymphoma). *Hematol Oncol* 38: 417-424, 2020.
108. Della Bella C, Soluri MF, Puccio S, Benagiano M, Grassi A, Bitetti J, Cianchi F, Sblattero D, Peano C and D'Elia MM: The *Helicobacter pylori* CagY protein drives gastric Th1 and Th17 inflammation and B cell proliferation in gastric MALT lymphoma. *Int J Mol Sci* 22: 9459, 2021.
109. Chonwerawong M, Ferrand J, Chaudhry HM, Higgins C, Tran LS, Lim SS, Walker MM, Bhathal PS, Dev A, Moore GT, et al: Innate immune molecule NLRC5 protects mice from helicobacter-induced formation of gastric lymphoid tissue. *Gastroenterology* 159: 169-182.e8, 2020.
110. Deng Y, Fu Y, Sheng L, Hu Y, Su L, Luo J, Yan C and Chi W: The regulatory NOD-like receptor NLRC5 promotes ganglion cell death in ischemic retinopathy by inducing microglial pyroptosis. *Front Cell Dev Biol* 9: 669696, 2021.
111. Ying L, Liu P, Ding Z, Wray-McCann G, Emery J, Colon N, Le LH, Tran LS, Xu P, Yu L, et al: Anti-CD40L therapy prevents the formation of precursor lesions to gastric B-cell MALT lymphoma in a mouse model. *J Pathol* 259: 402-414, 2023.



Copyright © 2025 Ji et al. This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) License.