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Pyroptosis in Ulcerative Colitis: Recent Advances and Mechanistic Insights

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Abstract. Ulcerative colitis (UC) is an inflammatory disease involving the colonic mucosa, displaying chronic immune activation and tissue damage. It is initiated by multiple underlying factors such as genetic inheritance, environmental influence, gut dysbiosis and impaired integrity of the epithelial barrier. Pyroptosis is a new type of programmed cell death related to inflammation, and it is the major inflammatory type of programmed cell death associated with colonic pathology. Pyroptosis is related to intracellular contents leaking out of disrupted cell membrane and inflammatory signals activation. More and more evidence indicates that pyroptosis is closely related to the occurrence and progression of UC by amplifying inflammation and inducing damage of the intestinal wall. This paper reviews the current knowledge about pyroptosis-related mechanisms in UC and the possible role of pyroptosis as a therapeutic target.

Keywords: pyroptosis, inflammasome, ulcerative colitis, inflammatory bowel disease

1. Introduction

Ulcerative colitis (UC) is a chronic inflammatory disease mainly affecting the colonic epithelium and is usually characterized by relapsing injury of the colonic mucosa. Patients often present with symptoms such as dysentery and abdominal discomfort, and blood in the stool, which greatly interferes with daily life. The etiology of UC is generally perceived as a multifactorial process, with host susceptibility interacting with environmental factors. Alterations in the intestinal microflora, impairment of intestinal epithelial barrier function and immune abnormality are all main factors contributing to the pathogenesis of UC. A great deal of progress has been made in the past few years, but the precise molecular mechanism for the pathogenesis of UC initiation and progression is still yet to be clarified [1]. Although therapies such as biologics and small-molecule targeted agents have advanced dramatically in recent years, there are still challenges in patients with moderate-to-severe disease such as varied treatment response, high rate of relapse and poor response in a subgroup of patients. Thus, further insight into the mechanisms of disease and identification of new therapeutic targets are of great importance [2].

Pyroptosis is emerging as another type of programmed cell death involved in inflammatory activation. Unlike other types of cell death, pyroptosis is characterized by disruption of the cell membrane, cell swelling and eventual lysis, together with the release of intracellular content. It is initiated by intracellular signalling events that activate certain proteases, which then cleave the

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gasdermin family of proteins into their mature forms. The active fragments of these cleaved proteins incorporate into the membrane, inducing pore formation to disrupt cell homeostasis, resulting in cell death. In parallel, inflammatory cytokines, for instance interleukin-1β (IL-1β) and interleukin-18 (IL-18), are produced and released, facilitating local inflammation and immunity events further [3]. The effect of pyroptosis on inflammatory diseases is context dependent. On the one hand, it participates in antimicrobial defence by killing infected cells, whereas excessive or uncontrolled activation is harmful to mucosal barrier, disrupts immune homeostasis and worsens tissue damage under chronic disease conditions [4].

Pyroptosis is increasing gradually to be known as one of the processes underlying the pathogenesis of ulcerative colitis, inducing disease progression by coordinated effects on integrity of epithelium, inflammation, immune effects and making the pro-inflammatory microenvironment, enabling target key molecules and signals of pyroptosis to be promising therapeutic targets in experimental and preclinical studies [5]. Focusing on ulcerative colitis, this article considers the biological processes taking part in pyroptosis and correlated signals exerting regulation over pyroptosis in turn, integrates the latest progress; meanwhile, it also envisages the prospect for therapeutic targets to regulate pyroptosis, contributing to interpretation of disease mechanisms and a focus for clinical research prospects in the future.

2. Molecular mechanisms of pyroptosis

As a form of inflammatory cell death, pyroptosis plays an important role in the immune defence and is implicated in many inflammatory diseases. Pyroptosis execution relies on the Gasdermin proteins, whereas its initiation and progression are mediated via complex signalling networks.

2.1. Structure and function of the Gasdermin protein family

Pyroptosis is carried out mainly by proteins of the Gasdermin (GSDM) family, which include a number of family members. Although they have diverse functions, they share a common structure with distinct N-terminal and C-terminal domains, called GSDM-NT and GSDM-CT, respectively. Under resting conditions, the C-terminal domain inhibits the N-terminal domain in a self-inhibitory manner and the protein thus remains inactive [6].

In response to the inflammatory stimulus or pathogen signal, upstream inflammatory caspases become activated and cut GSDM proteins specifically to release the active N-terminal fragment. Of the GSDM proteins, GSDMD is considered to be a main bridging molecule between inflammation signals and membrane rupture. The active fragment of GSDMD N-terminal domain (GSDMD-NT) rapidly undergoes conformational changes to expose lipophilic regions. GSDMD-NT then oligomerizes in the cytosol, and preferentially associates with phospholipid-containing membranes, mainly with the cell membrane but also intracellular membranes such as mitochondrial membranes.

After associating with the cell membranes, the N terminus of GSDMD is able to incorporate into the lipid bilayer membrane and form transmembrane pores (~10–20 nm in diameter). Such pore formation causes membrane instability, disturbs the ionic homeostasis and causes an osmotic imbalance, which will eventually lead to the cell lysis and excretion of intracellular contents. Apart from triggering cell lysis, the pores of GSDMD also mediate the export of pro-inflammatory molecules, such as IL-1β and IL-18, further amplifying the local inflammatory response. An important feature of Gasdermin proteins is that they can be activated by different proteases under certain circumstances. For example, GSDME can be cleaved by caspase-3, allowing the conversion from apoptosis to pyroptosis under certain circumstances. Research works in current report indicate

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that the Gasdermin protein is crucial to coordinate the interaction and dynamic switch among different cell death pathways [7].

2.2. Canonical and non-canonical pyroptosis pathways

Pyroptosis can be generally divided into canonical and non-canonical pyroptotic pathways according to the different upstream activation signals. Meanwhile, the pathways are intimately linked to each other through many regulatory mechanisms, constituting an intricate signalling network.

2.2.1. Canonical pyroptosis pathway

Pyroptosis is initiated by inflammasome assembly. Once the intracellular PRR detects PAMPs or DAMPs, it becomes activated and aggregates. Activation of PRRs promotes subsequent activation of ASC and pro-caspase-1 recruitment, and ultimately a construction of the inflammasome complex occurs.

Assembly of the inflammasome leads to activation of caspase-1 via self-cleavage. Once activated, caspase-1 performs two functions. First, it cleaves GSDMD to release the N-terminal fragment, which mediates pore formation and pyroptotic cell death. Concurrently, caspase-1 processes the precursors of the inflammatory cytokines interleukin-1β (IL-1β) and interleukin-18 (IL-18) into their mature and functional forms. The IL-1β and IL-18 cytokines are consequently released by the pores mediated by GSDMD and participate in the start and amplification of the inflammatory reaction.

2.2.2. Non-canonical pyroptosis pathway

The non-canonical pyroptosis pathway is triggered by intracellular lipopolysaccharide (LPS) that directly activates inflammatory caspases. In human cells, it is caspase-4 and caspase-5, whereas in mice the homologue of these is caspase-11. This pathway is, unlike the canonical pathway, not dependent on a canonical assembly of inflammasomes. Once activated, caspase-4/5/11 cleaves GSDMD into a pore-forming N terminus and induces pyroptotic cell death. At the same time, this pathway also activates the Pannexin-1 channel, which promotes the release of ATP, which in turn activates the P2X7 receptor. This causes efflux of potassium (K+) that indirectly triggers activation of NLRP3 inflammasome. This results in a positive feedback loop that amplifies inflammatory signalling [8].

2.2.3. Additional regulatory pathways and crosstalk mechanisms

Nevertheless, emerging evidence has also revealed other caspases involved in pyroptosis besides the canonical and non-canonical pathways. For instance, caspase-3 can cleave GSDME in some circumstances to switch apoptosis to pyroptosis. Similarly, caspase-8 was found to mediate the regulation of inflammasome and to promote cell death induced by GSDMD in certain inflammation contexts [9]. Some other interaction mechanisms also occur among pyroptosis and other programmed cell death including apoptosis and necroptosis. This complicated hierarchy in cell death also serves a regulation of inflammation and tissue injury [10].

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3. Role of pyroptosis in intestinal barrier disruption in ulcerative colitis

The integrity of barrier maintains the intestinal homeostasis, which protects the invasion of pathogens into the intestinal tract. The disruption of the barrier results in pyroptosis and pyroptosis has been emerging as an essential factor for worsening UC. Especially, pyroptosis of intestinal epithelial cells and secretory cells markedly affects the mucosal defence function, which contributes to the survival and amplification of inflammation [5].

3.1. Pyroptosis of intestinal epithelial cells and physical barrier disruption

Intestinal barrier depends almost entirely on intestinal epithelial cells (IECs), the main structural basis of intestinal barrier, and disruption of IECs can directly decrease barrier stability. A growing body of evidence showed that enhanced cleavage of Gasdermin family proteins can be seen in colonic biopsy specimens from UC patients as well as in pre-established experimental models. More specifically, the active N-terminal fragments of GSDMD and GSDME (GSDMD-NT and GSDME-NT) were all increased, concomitantly with their typical characteristic pathology of pyroptotic cell death [11].

At the molecular level, pyroptosis in epithelial cells is triggered by activation of inflammasomes or by the noncanonical pathway of caspases. ZAKα has been reported to promote pyroptotic cell death in colonic epithelial cells through activation of the caspase-11/GSDMD pathway, which favours colonic inflammation and also aggravates mucosal damage. By contrast, inhibition of this pathway can relieve intestinal inflammation and repair the barrier function [12].

Pyroptotic death of intestinal epithelial cells (IECs) compromises the plasma membrane and eventually results in cell rupture, disrupting epithelial continuity and resulting in microscopic defects of the barrier. Microscopic barrier damage results in an augmented intestinal permeability, allowing luminal components (microorganisms, toxins and dietary antigens) to permeate the epithelial barrier and enter the lamina propria where they trigger aberrant inflammatory responses. Moreover, pyroptosis also plays a role in the damage to intercellular connections through different mechanisms. In an autocrine and paracrine manner, pro-inflammatory cytokines decrease the expression of the major components of tight junctions, such as occludin and ZO-1, leading to barrier impairment [13, 14]. On the other hand, cytoskeleton organization that is impaired in pyroptosis itself weakens cell–cell contacts and reduces the mechanical integrity of the epithelial barrier.

Importantly, epithelial pyroptosis is not only a consequence of barrier disruption, but can also amplify inflammation. During pyroptosis, large quantities of DAMPs and inflammatory mediators are released to the extracellular environment. These molecules can trigger the inflammasome activation in adjacent cells and expand the pyroptosis response. Besides, specific signalling pathways have also been identified that trigger pyroptosis in intestinal epithelial cells, inhibiting repair of the mucosal barrier. Such findings clearly demonstrate that pyroptosis contributes not only to the barrier disruption but also affects the regeneration of the tissue, and thus expedites the course of diseases [15].

3.2. Impact of pyroptosis in goblet cells and paneth cells on the chemical and microbial barrier

Other intestinal cells, in particular specialized secretory cells in the gut, such as goblet and Paneth cells, also have crucial roles in maintaining the chemical and bacterial barrier. Increasing data now indicate that pyroptosis of these cells is also involved in the development of UC.

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Goblet cells produce and secrete mucin, mainly MUC2, to form the mucus layer at the top of the intestinal epithelium. This layer acts as a protection against intestinal luminal microorganisms and prevents direct contact between the two. Under inflammatory conditions of UC, pyroptosis of goblet cells is induced; goblet cell number is reduced and secretory function is impaired. Accordingly, mucus layer is thinned or can be locally completely lost. Loss of this protective barrier allows closer interaction between intestinal bacteria and the epithelium, immune activation and inflammatory process. In addition, inflammatory mediators produced in pyroptosis also inhibit mucin synthesis; thus, mucin depletion, bacterial translocation and inflammation aggravation form a vicious cycle leading to the progression of inflammation, that is, a feedforward process [16]. Although Paneth cells are mainly found in the small intestine, Paneth cell metaplasia can exist in colon in the presence of inflammation. Paneth cells give homeostasis to intestinal microbial composition by secretion of antimicrobial peptides. In chronic inflammation, Paneth cells can also be pyrotic or defective, resulting in reduced production of antimicrobial peptides and a reduced capacity to kill pathogenic bacteria [17].

Reduced antimicrobial capacity results in microbial imbalance in the intestine, including increased pathogens and reduction of health-promoting bacteria. Such imbalance not only impairs epithelial tissue integrity but also promotes pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs) and NOD-like receptors (NLRs), and ultimately triggers inflammasome and pyroptotic activation, establishing a vicious cycle of dysbiosis, pyroptosis and inflammation to aggravate the disease.

4. Pyroptosis drives immune–inflammatory cascades in ulcerative colitis

As well as triggering innate immune reactions via secretion of pro-inflammatory mediators, pyroptosis also remodels the local intestinal immune microenvironment and contributes to activation of adaptive immunity and maintenance of inflammatory cascades. This cell death-mediated inflammatory network is an important mechanism for chronic and relapsing phenotype in UC.

4.1. Release of pyroptosis-related factors and activation of innate immunity

During the progression of UC, pyroptotic death of epithelial and immune cells releases intracellular contents, which ultimately recruit and activate immune cells, including macrophages, dendritic cells and neutrophils. These recruited immune cells are activated and can produce a large variety of pro-inflammatory products, in turn leading to further local inflammation. IL-1β and interleukin-18 (IL-18) released via the pore created by GSDMD are the major effector cytokines that play an important role in the progression of inflammation.

IL-1β (interleukin 1β) is an important pro-inflammatory cytokine and may have various functions in UC. It facilitates recruitment of neutrophils to inflamed tissues, increasing their phagocytosis and antimicrobial activity. IL-1β induces Th17 cell differentiation via downstream signalling mechanisms and thereby increases IL-17 secretion, eventually intensifying mucosal inflammatory responses [18]. By contrast, IL-18 plays a part in inflammation mainly through induction of interferon-γ and enhances the Th1-type responses. IL-18 has a twofold effect on UC: it can prevent diseases during the acute stage of UC, whereas its long-term continuous expression exacerbates tissue damage and disease progression in the chronic phase of UC [19].

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4.2. Dysregulated adaptive immune responses

Chronic inflammation in UC is associated with abnormal activation of adaptive immunity and has an important effect on disease development. Pyroptosis participates in this by reshaping local intestinal immune microenvironment and shaping T cell differentiation and function. Pro-inflammatory cytokines secreted by pyroptosis, such as interleukin-1β, interleukin-18 and interleukin-6, can substantially influence cytokine dynamics in gut-associated lymphoid tissue (GALT) and thus directly influence T cell skewing. Th17 cells are abundant in the colonic mucosa of patients with UC and a higher level of Th17 activity is associated with greater severity of disease [20]. Constant stimulation of Th17 responses by IL-1β and other inflammatory factors secreted by pyroptosis maintains Th17 responses and mediates the chronicity of inflammation [18]. In contrast, IL-18 boosts T helper 1 (Th1) immune responses by inducing interferon-γ, resulting in an immune imbalance. Combined activation of Th1 and Th17 pathways brings up a chronic and complicated inflammatory condition in UC.

In addition, the inflammatory microenvironment mediated by pyroptosis can further directly damage Treg function, leading to reduced immune control. Breakdown of balance between Treg cells and Th17 cells has an important role in UC occurrence, whereas pyroptosis may be one of the factors responsible for the imbalance of immune function in UC pathogenesis [21]. Importantly, pyroptosis is not limited to epithelial cells but also exists in immune cells, thereby also enhancing inflammatory signalling. For example, pyroptotic macrophages further secrete more pro-inflammatory mediators and recruit other immune cells, forming an "inflammatory amplification loop" to maintain immune activation and maintain the progression of disease [22].

5. Conclusion

Pyroptosis is mediated by members of the Gasdermin family. Pyroptosis is a form of inflammatory programmed cell death contributing to the initiation and development of UC. Pyroptosis promotes formation of membrane pores and lysis of epithelial cells, disrupting the integrity of the intestinal barrier. This disruption results in luminal bacteria and antigens accessing the barrier and then triggers induction of innate immune responses. Also in parallel, pyroptosis releases pro-inflammatory mediators, exacerbating the inflammatory responses and driving adaptive immune dysregulation, thus forming a self-amplifying loop. At the level of the molecular pathology, the pyroptotic pathway of the GSDMD-centric mechanism that links inflammasome activation to membrane lysis has become a therapeutic target of great interest. Modulation of elements of this pathway has shown promise in experimental studies of anti-inflammatory and barrier protective effects. However, these challenges still exist, including the cell-type–specific roles of pyroptosis, its reciprocal role with gut microbiota and the balance between efficacy and safety in therapeutic clinical outcomes. Future research study using multi-omics study is needed to unravel the regulatory network of pyroptosis and its functional crosstalk with immunity, metabolism and the microbial ecosystem to meet the needs of highly specific and low-toxicity therapeutic means for precision therapy of UC.

References

[1] Le Berre C, Honap S, Peyrin-Biroulet L. Ulcerative colitis [J]. Lancet, 2023, 402(10401): 571-584.
[2] Sandborn W J, Vermeire S, Peyrin-Biroulet L, et al. Etrasimod as induction and maintenance therapy for ulcerative colitis (ELEVATE): two randomised, double-blind, placebo-controlled, phase 3 studies [J]. Lancet, 2023, 401(10383): 1159-1171.

DOI: 10.54254/2753-8818/2026.34121

[3] Vasudevan S O, Behl B, Rathinam V A. Pyroptosis-induced inflammation and tissue damage [J]. Seminars in Immunology, 2023, 69: 101781.
[4] Chai R, Li Y, Shui L, et al. The role of pyroptosis in inflammatory diseases [J]. Frontiers in Cell and Developmental Biology, 2023, 11: 1173235.
[5] Lu X, Sun Y, Zhang Z, et al. Regulation of pyroptosis by natural products in ulcerative colitis: mechanisms and therapeutic potential [J]. Frontiers in Pharmacology, 2025, 16: 1573684.
[6] Bai Y, Pan Y, Liu X. Mechanistic insights into gasdermin-mediated pyroptosis [J]. Nature Reviews. Molecular Cell Biology, 2025, 26(7): 501-521.
[7] Jiang M, Qi L, Li L, et al. The caspase-3/GSDME signal pathway as a switch between apoptosis and pyroptosis in cancer [J]. Cell Death Discovery, 2020, 6: 112.
[8] Xu Z, Chen Z-M, Wu X, et al. Distinct Molecular Mechanisms Underlying Potassium Efflux for NLRP3 Inflammasome Activation [J]. Frontiers in Immunology, 2020, 11: 609441.
[9] Huang D, Xu D, You C, et al. Caspase-8-driven NLRP3 inflammasome activation exacerbates bronchopulmonary dysplasia by increasing the apoptosis and pyroptosis crosstalk of alveolar epithelial cells [J]. International Immunopharmacology, 2025, 161: 115025.
[10] Bertheloot D, Latz E, Franklin B S. Necroptosis, pyroptosis and apoptosis: an intricate game of cell death [J]. Cellular & Molecular Immunology, 2021, 18(5): 1106-1121.
[11] Wu Y-Z, Xie Y, Chen L, et al. Gasdermin E-mediated intestinal epithelial pyroptosis promotes chemically induced colitis in mice [J/OL]. Gastroenterology Report, 2025, 13: goaf021 [2026-04-01].
[12] Li S, Chen M, Zheng S, et al. ZAKα Induces Pyroptosis of Colonic Epithelium Via the Caspase-11/GSDMD Pathway to Aggravate Colitis [J]. Inflammation, 2025, 48(5): 3235-3251.
[13] Chao L, Li Z, Zhou J, et al. Shen-Ling-Bai-Zhu-San Improves Dextran Sodium Sulfate-Induced Colitis by Inhibiting Caspase-1/Caspase-11-Mediated Pyroptosis [J]. Frontiers in Pharmacology, 2020, 11: 814.
[14] Zhang S, Wang T, Wu Z, et al. A mixed levan fructan from Rohdea japonica mitigates ulcerative colitis induced by dextran sulfate sodium via regulating intestinal microbiota mediated pyroptosis [J]. Carbohydrate Polymers, 2026, 376: 124838.
[15] Jena K K, Mambu J, Boehmer D, et al. Type III interferons induce pyroptosis in gut epithelial cells and impair mucosal repair [J]. Cell, 2024, 187(26): 7533-7550.e23.
[16] Liu F, Wang X, Cui Y, et al. Apple Polyphenols Extract (APE) Alleviated Dextran Sulfate Sodium Induced Acute Ulcerative Colitis and Accompanying Neuroinflammation via Inhibition of Apoptosis and Pyroptosis [J]. Foods, 2021, 10(11): 2711.
[17] Zheng Y, Qiao C, Xiao W, et al. Pregnane X receptor activation attenuates intestinal inflammation: The role of pyroptosis and necroptosis inhibition [J]. International Immunopharmacology, 2025, 166: 115620.
[18] Zhao Y, Luan H, Jiang H, et al. Gegen Qinlian decoction relieved DSS-induced ulcerative colitis in mice by modulating Th17/Treg cell homeostasis via suppressing IL-6/JAK2/STAT3 signaling [J]. Phytomedicine: International Journal of Phytotherapy and Phytopharmacology, 2021, 84: 153519.
[19] Guo L, Chen X, Zeng H, et al. Production of recombinant human long-acting IL-18 binding protein: inhibitory effect on ulcerative colitis in mice [J]. Applied Microbiology and Biotechnology, 2023, 107(23): 7135-7150.
[20] Gong Y, Lin Y, Zhao N, et al. The Th17/Treg Immune Imbalance in Ulcerative Colitis Disease in a Chinese Han Population [J]. Mediators of Inflammation, 2016, 2016: 7089137.
[21] Liu X, Zhou M, Dai Z, et al. Salidroside alleviates ulcerative colitis via inhibiting macrophage pyroptosis and repairing the dysbacteriosis-associated Th17/Treg imbalance [J]. Phytotherapy research: PTR, 2023, 37(2): 367-382.
[22] Chen K, Shang S, Yu S, et al. Identification and exploration of pharmacological pyroptosis-related biomarkers of ulcerative colitis [J]. Frontiers in Immunology, 2022, 13: 998470.