European Review for Medical and Pharmacological Sciences 2022; 26: 1156-1163

A narrative review of pyrolysis and its role in ulcerative colitis

J. LI[1], C.-M. MA[1], D.-L. DI[2]

[1]Department of Anatomy, Weifang Medical University, Weifang, Shandong, China
[2]Department of Immunology, Weifang Medical University, Weifang, Shandong, China

Abstract. – Cell death is one of the inevitable life activities of cells during the growth and development of the body. Regulated cell death (RCD) is a type of cell death mode that can be regulated and depends on specific molecular mechanisms which play an essential role in various pathophysiological environments. Pyrolysis is a newly discovered method of programmed cell death mediated by members of the Gasdermin protein family which is characterized by the activation of inflammatory factors and the formation of cell membrane pores. The specific manifestations are the swelling of cells, the appearance of plasma membrane bullae and the release of cell contents after cell rupture. A cascade of inflammation occurs after cell death. Activation of inflammasomes activates the classic pyrolysis pathway depending on caspase-1 or the non-classical pyrolysis pathway depending on Caspase-4/5 /11 and the subsequent inflammation reaction, excessive immune response caused by microbial infection and danger signals can lead to a variety of inflammatory diseases. In the inflammatory response, large numbers of inflammasomes activate the substrate protein GSDMD. GSDMD mediates pyrolysis by forming pores in the plasma membrane and mitochondria. Many studies have shown that pyrolysis plays an essential role in inflammatory bowel disease and other inflammatory diseases. This article aims to elaborate on the molecular mechanisms of pyroptosis in ulcerative colitis (UC) pathogenesis and provide new therapeutic ideas for UC.

Key Words:
Pyrolysis, Ulcerative colitis, Inflammasome, GSDMD.

Introduction

Ulcerative colitis (UC), which is caused by multiple factors, often occurs in chronic nonspecific inflammation of the colonic mucosa and submucosa, the main clinical manifestations of UC are diarrhea, abdominal pain, mucus pus and blood in the stool. UC has a long course of the disease and some cancer risks that seriously affect patients' quality of life. The incidence of UC has increased continually with the changes in people's lifestyles and eating habits in recent years. However, the etiology and pathogenesis of UC are still unclear. As a newly discovered method of programmed cell death, pyrolysis is widely involved in the occurrence and development of inflammatory diseases, the inflammatory factors released during pyrolysis can directly affect the body's physiology, morphology and pathology. Many studies have confirmed that pyrolysis plays an essential role in UC. An in-depth exploration of the relationship between pyrolysis and UC will help understand the role of pyrolysis in the occurrence and development of UC.

Discovery of Pyrolysis

Pyroptosis is a new type of programmed death of inflammatory cells that mainly activates Caspase through inflammasomes which causes shearing and multimerization of Gasdermin family members, including Gasdermin D or Gasdermin E, and then, perforate cells and causing cell death. Pyrolysis occurs faster and is often accompanied by the release of many inflammatory factors than apoptosis. Pyrolysis was first discovered in 1992. Aachoui et al[1] found in their research that macrophages infected by Shigella flexneri will die and they believe this cell death is caused by apoptosis. Further studies have shown that this is a new type of cell death mediated by Caspase-1, this type of cell death will no longer occur when Caspase-1 in macrophages is specifically blocked. In 1999, studies showed that Caspase-1 mediated programmed cell death occurred after macrophages were infected with Salmonella and many inflammatory cytokines, such as IL-1 and IL-18 will released[2]. In 2001, Cookson et al[3] recognized that this type of cell death caused by bacterial infection is a form of death that is entirely

Corresponding Author: Dalin Di, MD; e-mail: 642917492@qq.com

different from apoptosis and called this Caspase-1-dependent programmed cell death pyrolysis. Subsequent studies found that after macrophages were infected by pathogens, such as mycobacterium tuberculosis, this type of programmed cell death also occurred[4]. Similar to Caspase-1, Caspase-11 is also an inflammatory cysteine aspartase. The lipopolysaccharide of gram-negative bacteria can cause mouse macrophages' death and this process depends on Caspase-11[5]. In 2014, it was discovered for the first time that human-derived Caspase-4/5 has a biological function similar to Caspase-11. Caspase-4/-5/-11 can directly recognize bacterial lipopolysaccharide, cause the activation of downstream proteins, and trigger cell pyrolysis[6].

The Gasdermin family protein is the crucial molecule in cell pyrolysis, which is a protein family with a porogenic effect mainly composed of Gasdermin A (GSDMA), Gasdermin B (GSDMB), Gasdermin C (GSDMC), Gasdermin D (GSDMD), Gasdermin E (GSDME) and other members. The expression of different Gasdermin proteins has tissue specificity, Gasdermin D and Gasdermin E are the most well-known pyrolysis executive proteins. The Gasdermin proteins are usually in a state of self-inhibition at the beginning. When cell pyrolysis occurs, the activated Caspases cut Gasdermin D/E into N-terminal and C-terminal, the N-terminal has a pore-forming effect and the C-terminal has an inhibitory effect. The N-terminal causes cell membrane perforation and the release of inflammatory factors or other cellular contents that trigger cell pyroptosis[7]. In 2018, the Nomenclature Committee on Cell Death (NCCD) redefined pyroptosis as a provocative response-related programmed death method formed by the Gasdermin protein family, and this method of death is closely related to the inflammasome[8]. Inflammatory bodies are polymer protein complexes formed after the body recognizes pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs) of invading pathogens. Different inflammasomes can activate different Caspase and the different pyrolysis pathways. At present, pyrolysis can be divided into classic pathways that depend on Caspase-1 and non-classical pathways that depend on Caspase -4 /-5/-11[9].

Molecular Mechanism of Cell Pyrolysis

The body usually triggers an inflammatory response after infected by microorganisms. The host cell first recognizes the pathogen-associated molecular pattern ligand (PAMPs) on the pathogen's surface by the pattern recognition receptor (PRR). The common PRRs include Toll-like receptors (TLR), retinoic acid-inducible gene I-like receptors (RLR), Nod-like receptor (NLR), C-type lectin-like receptor (CLR) and melanoma deficiency factor 2 receptor (AIM2). After the PRR recognizes PAMP (bacteria, fungi or viruses), it will stimulate inflammatory response to form inflammasomes. The typical inflammasome complex comprises receptor protein, adaptor protein and effector protein. Four typical inflammasomes have been identified, including NLRP1, NLRP3, NLRC4 and AIM2. Human NLRP1 is the first discovered and the most studied inflammasome; it can be activated by crystal compounds, nucleic acids, hyaluronic acid, fungi or bacteria. NLRC4 inflammasome can be activated by bacterial lipopolysaccharide or gram-negative bacteria's type III secretion system. The PRR protein contains three domains, the C-terminus of the leucine-rich repeat sequence (LRR), the center of the nucleotide-binding homology (NACHT) domain and the Caspase recruitment domain (CARD) or pyrimidine domain (PYD) in the N-terminal. LRR recognizes the ligand and the NACHT domain is responsible for binding to ATP, the CARD/PYD domain is responsible for mediating homotypic protein interactions, the adaptor protein ASC contains the CARD domain or PYD domain which activates the downstream effector protein Caspase[10].

Classical Pyrolysis

For a long time, the classic pyrolysis has been considered a Caspase-1 mediated cell death program. The effector protein pro-caspase-1 contains the CARD domain which can bind to the CARD domain of the adaptor protein ASC through the homotypic interaction of CARD-CARD or PYD-PYD, triggering the formation of the kinase concentration zone and recruiting pro-Caspase-1, the zymogen undergoes autohydrolysis to produce two subunits of p10 and p20 and form a P10/P20 heterodimer, which further comprises a tetramer and finally becomes active Caspase-1. NLRC4 can directly recruit pro-Caspase-1 without ASC, promote the activation of Caspase-1 and cause pyrolysis. Activated Caspase-1 acts on GSDMD or GSDME and plays a crucial role in the host's defense against pathogen infection or danger signals. GSDMD is inactive before cutting. After sharing, it can produce active fragments of about

32kD which are combined with the membrane and punched on the cell surface. These pores can increase the osmotic pressure of the cell and cause a large amount of water to flow into the cell, which eventually leads to cell swelling and swelling, then triggers pyrolysis[11]. GSDME can permeate the mitochondrial membrane, release cytochrome C and activate apoptotic bodies, further enhancing the pyrolysis reaction. GSDME is highly expressed in normal tissues but is low in most tumor cells, closely related to the immune escape of tumor cells. In the process of oncogene generation, the GSDME gene undergoes DNA methylation, which leads to epigenetic gene silencing, thereby participating in the occurrence and development of tumors. The use of chemotherapy drugs can increase the expression level of GSDME in tumor cells and turn apoptosis into GSDME-dependent pyrolysis[12,13]. GSDME also plays a significant role in the cytotoxicity induced by chemotherapy drugs. The researchers exposed GSDME−/− mice to cisplatin and examined their small intestine, spleen, lung and other tissues, confirming that GSDME can promote anti-tumor immune cells' infiltration and enhance the toxicity of cisplatin to non-small cell lung cancer cells through cell pyrolysis[14]. The activation of Caspase-1 is a key factor in the classical pyrolysis pathway and an important defense mechanism against microbial infections. Caspase-1 can promote the maturation of inactive IL-1 or IL-18 precursors and subsequently release them into the extracellular environment, recruiting immune cell infiltration and causing the expansion of the inflammatory response[15]. Caspase-1 can cleave MyD88 linker-like (MAL) protein in the TIR domain, regulate the activity of the TLR/MyD88/NF-κB signaling pathway and promote the pyrolysis process. The activity of macrophages NF-κB signal pathway of Caspase-1 deficient mice were downregulated and resistant to shock induced by lipopolysaccharide[16].

Non-Classical Pyrolysis

Both human-derived Caspase-4/-5 and mouse-derived Caspase-11 can cause atypical pyrolysis. After the bacteria infect host cells, the lipid A component of LPS interacts with the CARD domain of Caspase-4/-5/-11 to cause the oligomerization and activation of caspase, the activated caspase cleaves GSDMD into GSDMD-N and GSDMD-C. GSDMD-N polymerizes in the cell membrane, causing swelling and scorching of cells. In addition, Caspase-11 also releases IL-1β and IL-18 through the NLRP3-ASC-caspase-1 pathway and recruits inflammatory cells to exacerbate the inflammatory response. GSDMD is a crucial target of Caspase-11 in the host's response to gram-negative bacteria. GSDMD gene knockout mice can avoid the lethal effect of heat shock caused by LPS, which is consistent with the phenotype of Caspase-11 knockout mice[6,17]. In Caspase-11-/- mice, Dextran Sodium Sulfate (DSS) induced intestinal tissue damage, and inflammatory cell infiltration was alleviated significantly, the release of pyrolysis/necroptosis marker HMGB1 was also significantly reduced[18].

Caspase-3 Mediated Pyrolysis

Caspase-3 has many activation mechanisms, the most common is that under the stimulation of chemotherapy drugs, mitochondria release mitochondrial-related inducing factors that will activate Caspase-3, which activates GSDME and induces pyroptosis process. It has been shown that the expression level of GSDME determines the mechanism of tumor cell death. When GSDME is highly expressed, Caspase-3 cleaves it and releases the N-terminal domain, punching holes in the cell membrane and causing the cell to undergo pyrosis. When GSDME is under low expression, it will cause tumor cells to undergo apoptosis. The Caspase-3/GSDME signaling pathway can regulate tumor cells to switch between apoptosis and pyrolysis that is expected to provide new ideas for tumor treatment. Researchers also found that GSDME can be located upstream of caspase-3, promote caspase-3 activation and form a self-amplified feedback loop. These new findings may change our understanding of programmed cell death[19]. Evidence[20] also showed that 293T cells stably express DFNA5 stimulated by chemotherapeutic drugs such as etoposide, Bax will activate caspase-3 and cleaved GSDMD-related protein DFNA5 at the Asp270 site to induce cell pyrolysis. Virus vesicular stomatitis virus (VSV) or encephalomyocarditis virus (ECMV) infection can also cause the lysis of DFNA5 and induce pyrolysis.

Pyrolysis and UC

Ulcerative colitis (UC) is a chronic non-specific inflammation of the colorectum which belongs to inflammatory bowel disease (IBD), it is listed as one of the most modern refractory diseases by the WHO. The lesions of UC mainly involve the colonic mucosa and submucosa, mainly starting

from the distal colon, affecting the entire colon and the terminal ileum. The clinical manifestations of UC are diarrhea, abdominal pain, mucus, pus and blood in the stool. This disease is long and often recurs and may induce UA-related colorectal cancer, which seriously threatens the life and health of the patient[21,22]. The evolution of IBD can be divided into four stages: emergence, acceleration in incidence, compounding prevalence, and prevalence equilibrium. In recent years, with the aging of the IBD population and the unexpected increase in patient mortality due to the COVID-19 pandemic, the incidence of IBD, especially UC, has gradually increased towards stability[23]. A survey[24] shows that UC incidence is closely related to the region's economic development. The survey shows that the incidence of UC is closely related to the region's economic development. With the development of the economy, the prevalence of UC in the world is (5.50~24.30)/10 000. The prevalence rates are the highest in developed regions, the prevalence in Asia and the Middle East is lower, which is about 6.30/10 000, the prevalence in mainland China is 11.30/10 000. The incidence rate of UC in Korea in 1997 was 7.57/10 000, by 2005, it had increased to 30.87/10 000. Although the fatality rate of UC is not very high, it has an unsatisfactory cure rate; if the patient does not receive adequate treatment, UC is likely to develop into colon cancer.

Pyrocytosis is a form of programmed cell death caused by inflammasomes. Caspase -1 or Caspase-4/-5/-11 cleaves GSDMD or GSDME and small holes are formed, which will drive the cell ruptures and releases various cytokines. These cytokines have a variety of biological functions and a wide range of target cells which play an essential role in intestinal inflammation. Pyroptosis plays a vital role in the host's resistance to microbial infections and is closely related to an inflammatory immune response. The excessive inflammatory reaction may lead to many diseases. Many scholars[25] have shown that cytokines play an essential role in inflammatory conditions such as UC. In UC animal models, almost all inflammatory cytokines can be found to increase. Once pyrolysis occurs, inflammatory cytokines, such as IL-1β and IL-18 will be released and cause various pathological damages to the intestine. IL-1β is a potent inflammatory cytokine that promotes the recruitment of immune cells to inflammation sites by inducing the expression of adhesion molecules. It can also activate dendritic cells, macrophages and neutrophils and the release of IL-1β is strictly regulated due to its highly pro-inflammatory properties. IL-1RA is a natural antagonist of IL-1β receptors that can inhibit the release of IL-1β. Several clinical studies[26,27] have reported that colonic lamina propria monocytes in patients with UC secrete high levels of IL-1β, which is closely related to the occurrence of the disease. IL-1β in the patient's intestine can play a crucial role in activating pathogenic CD4(+) T and Th17 cells through the IL-1 receptor on the surface of T cells, targeted inhibition of IL-1β can effectively alleviate clinical symptoms. The symptoms of UC are related to IL-1β in animal models. For example, NOD2 mutant mice are prone to UC and macrophages in these mice secrete high levels of IL-1β after being stimulated by DSS. Recombinant IL-1RA can significantly inhibit these symptoms[28]. IL-18 was first discovered as an inducer of INF-γ and its role in intestinal diseases is related mainly to its pro-inflammatory response. The structure and intracellular signal transduction pathway of IL-18 is similar to IL-12, IL-18 has a more vital ability to induce INF-γ production than IL-12. Intestinal epithelial cell (IEC) is the main source of IL-18 in the intestine through various inflammasomes[29]. After intestinal cells are infected with Salmonella typhimurium, IL-18 can promote NK cells to create perforin to kill pathogens, suggesting that IEC is in the intestine and also suggesting that IEC plays an essential role in an intestinal inflammatory response and mucosal defense response[30].

UC is a disease characterized by excessive inflammation and dysregulated IL-18 plays an important role in UC. Genome-wide association studies have linked IL-18RAP/IL-18R1/IL-1R1 site mutations with susceptibility of UC[31]. An increased level of IL-18 often accompanies UC patients. The results of the immunohistochemical analysis show that IL-18 is abundantly expressed in intestinal epithelial cells in non-inflammatory areas, and macrophages express a lot of IL-18 in diseased areas[32]. In addition, the dysregulated IL-18 can affect the intestinal Th1/Th2 balance and promote the occurrence of UC, which may be a key pathogenic factor in patients with UC[33]. The onset of UC patients is related to the intestinal microbial ecological disturbance. The butyrate-producing bacteria Roseburia infantis (RI) in the patient's intestines can inhibit inflammation and plays an anti-inflammatory effect in colitis induced by dextran sodium sulfate (DSS). The flagellin of RI can inhibit the formation of NLRP3 inflammasomes through the miR-223-3p/NLRP3 signal in macrophages, thereby inhibiting

pyrolysis[34]. Different types of macrophages, such as M1 and M2 have entirely different biological functions and play an important role in the pathogenesis of UC. There is evidence that targeting macrophage polarization is beneficial to UC treatment; lactic acid-producing probiotic saccharomyces cerevisiae can inhibit the polarization of M1 macrophages and inhibit the production of NLRP3 inflammasomes which play an essential role in regulating the balance of intestinal flora and alleviate the symptoms of UC[35]. The expression level of GSDME protein in the colonic mucosa of UC patients is significantly increased. GSDME protein mainly accumulates in colonic mucosal epithelial cells at the site of inflammation and is rarely expressed in normal colonic mucosa tissue. In the AOM/DSS-induced colorectal cancer mouse model, a large number of adenocarcinomas were found in the mucosa of wild-type mice, and many malignant cells penetrated the submucosa. In contrast, only a few adenomas were found in GSDME-/- mice. Further studies[36] confirmed that GSDME-mediated pyrolysis could release HMGB1 through IECs cells to promote the occurrence of intestinal mucosal inflammation, and HMGB1 can induce colon cancer cell proliferation and PCNA expression through the ERK1/2 signaling pathway and promote tumor development. Using LPS to stimulate peripheral blood mononuclear cells from UC patients, NLRP3 was activated. The concentrations of IL-1β, IL-6 and TNFα in the cell supernatant also increased, confirming that the NLRP3 inflammasome plays an important role in UC[37].The interaction between integrin receptors on the surface of IEC infected by Yersinia bacteria and bacterial adhesin activates NLRP3, which then releases IL-18 and causes inflammation in the intestinal mucosa[38]. In the DSS-induced mouse model, NLRP3 activates pro-Caspase, thereby inducing pyrolysis. In UC mice, NLRP3 can promote the differentiation of Th cells to T1 type and cause inflammation in the mouse intestine, the release of IL-1β and IL-18 mediated by NLRP3 inflammasomes is a core participant in UC pathogenesis. Both cytokines promote the occurrence of UC through the activation of NLRP3. Compared with wild-type mice, NLRP3-/-, ASC-/- or Caspase-1-/- mice have milder colitis symptoms, inhibition of Caspase-1 activity can reach a similar protection level compared with NLRP3-/- mouse[39,40].

Many experiments have confirmed that inhibiting pyrolysis can effectively alleviate UC symptoms. MCC950 is a specific small molecule NLRP3 inflammasome inhibitor that can inhibit the activation of NLRP3, which has been proven to be effective in treating inflammatory diseases. It can effectively relieve the clinical symptoms of asthma and ulcerative colitis, atherosclerosis, heart failure, and neurodegeneration[41]. It has been confirmed[42] that the combined treatment of metformin and MCC950 has a synergistic therapeutic effect on the DSS-induced mouse model. Metformin/MCC950 can effectively alleviate colonic inflammation, disease activity index (DAI) and macroscopic injury index (MDI). In addition, it can also attenuate the activity of yeloperoxidase (MPO) and the release of cytokines, such as TNF-α and IL-6 through TLR4/NF-κB signaling pathway, inhibit the production of caspase-1 and cell pyrolysis; this may be a promising candidate for the treatment of human UC in the future. The hypoglycemic drug dapagliflozin (DPZ) can reduce the infiltration of neutrophils in the colon tissue of UC rats, inhibit the secretion of IL-1β and upregulate the secretion of the anti-inflammatory cytokine IL-10. It also effectively relieves clinical symptoms of UC rats, prolong the survival period of UC rats. These protective effects are closely related to DPZ preventing NLRP3 inflammasome activation through the NF-κB/AMPK/NLRP3 axis, inhibiting caspase-1 activity and inhibiting pyrolysis[43]. The latest research confirms that NEK7 protein plays a vital role in forming NLRP3 inflammasomes. Targeted inhibition of NEK7 activity in macrophages can significantly inhibit the formation of NLRP3, suggesting that NEK7 protein may be a new target for the treatment of UC[44]. The complement component C3a/C3aR also plays a vital role in the pathogenesis of UC. Moreover, C3a/C3aR can promote the activation of caspase-11, induce cell pyrolysis and promote the occurrence of UC. C3aR relieves intestinal injury symptoms through inhibitors of the activation of caspase-11 and the production of TNF-α and IL-6 in UC rats[45]. MEG3 is an imprinted gene located at the DLK1-MEG3 locus of human chromosome 14q32.3, a long non-coding RNA. LncRNA MEG3 is highly expressed in various normal tissues and low in tumor tissues. LncRNA MEG3 also plays a protective role in UC development. It can effectively alleviate the colon's oxidative stress, apoptosis, and pyrolysis in UC rats. It can also upregulate miR-98-5p and inhibitory cytokine IL-10 production, providing a potential UC treatment target[46].

Traditional Chinese medicine has a specific effect on UC treatment. Kuijieling (KJL) is a traditional Chinese medicine that has been proven to be effective in the treatment of UC patients. It

can effectively inhibit the activation of NLRP3, ASC, Caspase-1, GSDMD-N, GSDMD-N in colon tissue of DSS-induced UC mouse model by inhibiting pyrolysis[47].

Another traditional Chinese medicine Huangqin Decoction (Huangqin) cam also significantly relieves clinical symptoms of UC which can inhibit the NLRP3/Caspase-1 signaling pathway in UC rats' cells and inhibit LDH, IL-1β and IL-18 production[48]. Shen-Ling-Bai-Zhu-San (SLBZS) is a traditional Chinese medicine that significantly affects many gastrointestinal diseases which can reduce the production of IL-1β, IL-18 and TNF-α in the UC mouse model by inhibiting MAPK and NF-κB signaling pathways. It can also increase the expression levels of colon tight junction proteins ZO-1 and Occludin and play an essential role in protecting the integrity of the colon barrier and improving the inflammatory response[49].

Conclusions

Pyroptosis is a new type of programmed inflammatory necrosis closely related to UC. Blocking pyroptosis can relieve UC symptoms effectively, and traditional Chinese medicine has demonstrated certain advantages in UC treatment. Therefore, it is of great clinical significance to study the role of pyroptosis in UC, which may provide new ideas for the clinical treatment of UC patients in the future.

Conflict of Interest

The authors declare that they have no conflict of interest.

Funding

This project is financially supported by the Shandong Province Health Department (Grant Number: 2019WS589) and Science and Technology Development Project of Weifang City (Grant Number: 2019YX025).

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