DOI: 10.53469/jcmp.2025.07(03).15

Research Progress of Traditional Chinese Medicine Monomer in the Treatment of Psoriasis by Targeting Pyroptosis

Qin Sun[1], Xiaoning Yan[2,*]

[1]Shaanxi University of Chinese Medicine, Xianyang 712046, Shaanxi, China
[2]Shaanxi Provincial Hospital of Chinese Medicine, Xi'an 710003, Shaanxi, China
**Correspondence Author*

Abstract: ***As a chronic, recurrent and inflammatory skin disease, psoriasis is a difficult and urgent problem to be solved in clinic. In recent years, researchers have found that pyrodeath plays an important role in the occurrence and development of psoriasis, and psoriatic drugs targeting pyrodeath have also been extensively studied. This paper reviews the research on the treatment of psoriasis by targeting pyrodeath of traditional Chinese medicine monomers, in order to provide ideas for the development of new drugs for psoriasis***

Keywords: Psoriasis, Pyroptosis, Chinese medicine monomer**.**

1. Introduction

Psoriasis is an inflammatory skin disease involving multiple factors such as genetics, environment, infection and lifestyle. The global incidence of psoriasis is reported to be between 0.6% and 6.5%, with about 125 million people worldwide suffering from psoriasis [1] The disease has traditionally been considered a skin disease, but there is sufficient evidence that psoriasis is a systemic disease accompanied by other organ and system diseases, often accompanied by psoriatic arthritis, metabolic syndrome, cardiovascular disease, non-alcoholic fatty liver disease, inflammatory bowel disease and mental illness [2], which has a serious impact on the quality of life and physical and mental health of patients. At present, the existing psoriasis treatment methods (biologics, glucocorticoids, immunosuppressants, retinoids, vitamin D3 derivatives, phototherapy) have significantly improved the skin symptoms of patients, but due to side effects, expensive and other defects, there are certain limitations in clinical use. Therefore, the search for safe and effective psoriasis treatment drugs is the focus of future research.

At present, the pathogenesis of psoriasis has not been fully elucidated. Studies have shown that GSDMD-mediated pyroptosis plays an important role in the pathogenesis of psoriasis [3]. However, psoriatic drugs targeting pyroptosis have not been applied clinically due to their safety. The effective monomer components of traditional Chinese medicine selected from traditional Chinese medicine show a good prospect in the treatment of psoriasis, with the unique advantages of good efficacy, few side effects and high safety. This paper reviews the research progress of cell pyroptosis, cell pyroptosis and psoriasis, and the treatment of psoriasis by traditional Chinese medicine monomer targeting cell pyroptosis, in order to provide new ideas for clinical treatment of psoriasis.

2. Pyroptosis

Pyroptosis is an inflammatory programmed cell death mode mediated by Gasdermin. In humans, the Gasdermin family consists of six members GSDMA, GSDMB, GSDMC, GSDMD, GSDME, and GSDMF (PJVK/ DFNB59) [4]. In the presence of a large number of microorganisms and stimuli, Gasdermin is cleaved by activated caspase into n-terminal pore-forming domain (PFD) and C-terminal repressor domain (RD). The N-terminal pore-forming domain acts on the cell membrane to form pores with a diameter of 10 to 16 nm, thereby releasing intracellular inflammatory factors and performing pyroptosis. The pathways of pyroptosis include the classical pathway dependent on caspase-1, the non-classical pathway dependent on caspase-4/5/11, the apoptotic caspase-mediated pyroptosis pathway and the granzyme mediated pathway.

3. Four Signaling Pathways of Cell Pyroptosis

3.1 Caspase-1-mediated Classical Pathway

When the host is stimulated by pathogenic microorganisms, Intracellular pattern recognition receptors (PRRs) including NLR pyrin domain containing 1(NLRP1), NLR pyrin domain containing 3(NLR pyrin domain) containing 3, NLRP3), NLR containing a caspase recruitment domain 4(NLRC4), melanoma deficiency factor 2(absent in melanoma 2, AIM2 and Pyrin proteins contain a apoptosis-associated speck-like protein CARD, ASC) binds, thereby indirectly connecting the precursor of Caspase-1 to further assemble into inflammatory complex, namely inflammasome. The assembled inflammasome promotes the activation of the precursor of Caspase-1, and the activated Caspase-1 further cuts pro-IL-1β and pro-IL-18. At the same time, Caspase-1 splits executive protein GSDMD into N-terminal and C-terminal, and the N-terminal acts on the cell membrane to promote the formation of cell membrane pores, the release of inflammatory factors such as IL-1β and IL-18, and the cell death [5].

3.2 Non-classical Pathway Mediated by Caspase-4/5/11

During infection, lipopolysaccharides (LPS) of Gram-negative bacteria released into the cytoplasm activate caspase-11 in mice and caspase-4 and -5 in humans [6]. Although activated caspase-4/5/11 cannot cut pro-IL-1β and

pro-IL-18, it can split GSDMD protein into N-terminal and C-terminal. The N-terminal of GSDMD protein activates Caspase-1 by mediating the formation of cell membrane pores and activating the NLRP3 inflammassome. Eventually leading to the release of IL-1β and IL-18 [7] In addition, activated caspase-4/5/11 opens the cell membrane channel P2X7 by activating the Pannexin-1 channel to release ATP and promote the formation of pores in the cell membrane. Activated Pannexin-1 can also activate NLRP3 and Caspase-1 through K+ efflux, and finally induce pyroptosis of cells [8].

3.3 Apoptotic Caspase-mediated Pyroptosis Pathway

In addition to cell pyroptosis dependent on caspase-1/4/5/11, some apoptotic caspases can also trigger pyroptosis. Studies have shown that when a cell is infected by a virus or DNA damage, in order to prevent adjacent cells from being damaged or infected, caspase-3 is activated to split GSDME into N-terminal and C-terminal, and the N-terminal of GSDME protein induces the formation of cell membrane pores, thereby promoting the entry of extracellular water and ions into the cell, and finally the cell is swollen and broken. Intracellular content release [9] [10] In addition, during Yersinia infection, Yersinia inhibits transforming growth factor β-activated kinase 1 (TAK1) through the outer membrane protein effector YopJ. Thus, receptor interacting protein kinase 1 (RIPK1) and Caspase-8 were activated, and the activated Caspase-8 triggered pyroptosis by inducing the cleavage of GSDMD [11]. It has also been found that caspase-8 can also trigger pyroptosis by cutting GSDMC under hypoxia conditions [12]. In addition, caspase-3/6/7 can delete the C-terminal repressor domain of GSDMB protein by cracking GSDMB, prompting the release of the N-terminal pore-forming domain, and ultimately triggering pyroptosis [13].

3.4 Granzyme Mediated Pathway

In recent years, Granzyme -mediated pyroptosis of cancer cells has been widely studied. Granzyme A (GZMA), as the most abundant serine protease in the granzyme family, is considered to be the mediator of cell death. Studies have shown that GZMA derived from cytotoxic T lymphocytes can release the N-terminal pore-forming domain of GSDMB protein by lyzing GSDMB, and ultimately promote the pyroptosis of cancer cells expressing GSDMB [14] In addition, GZMB can induce pyroptosis by activating caspase-3 in target cells, and GZMB derived from natural killer cells can directly cleat GSDME at the same site as caspase-3 cleavage, thus triggering pyroptosis [15].

4. The Relationship between Pyroptosis and Psoriasis

Psoriasis is an immune-mediated chronic, recurrent and inflammatory skin disease, which involves many factors such as genetics, environment and immunity. The exact pathogenesis of this disease has not been fully elucidated, but the IL-23/Th17 cell axis has been considered to be a key link in the pathogenesis of psoriasis. Il-1β and IL-18 released during pyroptosis are inflammatory factors with strong pro-inflammatory effects among IL-1 family members. They can activate dendritic cells to produce inflammatory cytokines IL-12 and IL-23, and then promote Th17 cell differentiation and proliferation. Th17 cells further produce Th17 cytokines such as IL-17, IL-21 and IL-22, thus playing a pro-inflammatory role. Some studies have found that serum or plasma IL-18 levels are positively correlated with psoriasis area and severity index (PASI) [16].

GSDM acts as an executive protein of cell pyrosis. Studies have found that GSDM family genes are expressed in skin and gastrointestinal epithelial cells in a highly tissue-specific manner [17]. The protein levels of GSDMD-N and IL-1β were significantly increased in the epidermis of psoriasis patients. Animal experiments have shown that psoriasis symptoms in GSDMD conditioned knockout mice are reduced compared to mice with normal psoriasis induced by imiquimod [3]. Studies have also shown that GSDME-mediated keratinocyte pyroptosis is involved in the development of psoriasis through its pro-inflammatory effect [18].

5. TCM Monomers Treat Psoriasis by Targeting Pyroptosis

Wogonin is a kind of flavonoids extracted from scutellaria baicalensis, which has antioxidant, anti-inflammatory, anti-tumor, immunomodulatory and neuroprotective effects. In vitro studies have shown that Wogonin can significantly inhibit the proliferation of HaCaT cells induced by M5, and reduce the levels of inflammatory factors such as IL-6, TNF-α, IL-1β, IL-23, IL-17, IL-22, CXCL1, CXCL8 and CCL20 in HaCaT cells. Its anti-inflammatory mechanism is related to the inhibitory effect of baicalin on NLRP3 inflammasome and thus on the pyrodeath of HaCaT cells [19].

Cycloastragenol (CAG) is a triterpenoid saponin derived from Astragalus, which has anti-inflammatory, anti-tumor, anti-aging and other pharmacological effects. Studies have shown that CAG inhibits macrophage NLRP3 inflammation by inhibiting its assembly, thereby effectively alleviating skin symptoms of IMQ-induced psoriasis model mice, and inhibiting the expression of TNF-α, Il-1β, IL-6, IL-17a, IL-23a and other inflammatory factors in model mice [20].

Tectorigenin is a kind of flavonoid compound with anti-inflammatory, antibacterial, anti-tumor and other pharmacological effects, which comes from Pueraria lobata, Shegan, and Iris nigra. Tectorigenin reduces the levels of ASC, caspase-1 and IL-1β in M5-induced HaCaT cells by inhibiting the assembly of NLRP3 inflammasome [21].

Rosmarinic acid is a simple phenylpropyl with anti-inflammatory and antioxidant properties. In polyinosinate-polycytidylate (I:C) -induced keratinocytes, rosmarinic acid inhibits the activation of caspase-1 and down-regulates the secretion of IL-1β by inhibiting the activation of the NLRP3 inflammasome [22].

The main active component of pomegranate peel, Punicalagin, is a kind of compound with anti-inflammatory, antibacterial, antioxidant and anti-tumor activities. Studies have shown that Punicalagin can not only down-regulate the transcription of IL-1β by inhibiting the activation of NF-κB, but also inhibit the maturation and secretion of IL-1β by inhibiting the expression of caspase-1, further effectively inhibit the

IL-1β-mediated inflammatory cascade, thus effectively treating psoriasis [23].

Ginsenoside Rg1 is a kind of compound with anti-inflammation, anti-oxidation, anti-apoptosis and other biological activities. In vitro and in vivo studies have shown that ginsenoside Rg1 inhibits the activation of NLRP3 bodies by inhibiting ROS/NLRP3 signaling pathway, and further inhibits the expression of caspase-1 and the levels of inflammatory factors IL-1β and IL-18, thus alleviating psoriasis symptoms in model mice [24].

Paeonia lactiflora Pallas extract (PE) contains effective ingredients such as paeoniflorin, paeonol and β-sitosterol. Studies have shown that Paeonia extract can effectively inhibit the expression of IL-1β and caspase-1 by inhibiting the activation of the NLRP3 inflammatome in human epidermal keratinocytes stimulated by poly (I:C) [25].

Mustard seed has anti-cancer, anti-aging, scavenging free radicals and other effects. Studies have found that mustard seed can inhibit the generation of NLRP3 inflammasome and the secretion of IL-1β and IL-18, so as to effectively alleviate the skin symptoms of psoriasis model mice induced by IMQ [26].

6. Discussion

Psoriasis, as an immune mediated chronic inflammatory skin disease, has not yet found a complete cure, and exploring drugs targeting different signaling pathways is helpful for the treatment of the disease. Pyroptosis, as an inflammatory cell death mode, plays an important role in the pathogenesis of psoriasis. Currently, a variety of TCM monomeric components have been proved to exert their anti-psoriasis effects by directly or indirectly affecting pyroptosis, providing a theoretical basis for the clinical use of TCM targeting pyroptosis in the treatment of psoriasis.

At present, researchers have conducted extensive studies on the treatment of psoriasis by targeting cell pyrodeath with traditional Chinese medicine monomer components, but some mechanisms have not been fully elucidated, and existing studies are still confined to animal and cell experiments, so more in-depth basic studies and large-scale multi-center randomized controlled trials with long-term follow-up are urgently needed in the future. To provide more perfect clinical evidence-based medical evidence for the treatment of psoriasis by targeting pyroptosis with traditional Chinese medicine, and provide new ideas for the research of new drugs for psoriasis.

References

[1] Griffiths C E M, Armstrong A W, Gudjonsson J E, et al. Psoriasis [J]. The Lancet, 2021, 397(10281): 1301-1315.

[2] González-Parra S, Daudén E. Psoriasis y depresión: el papel de la inflamación [J]. Actas dermo-sifiliograficas, 2019, 110(1): 12-19.

[3] Lian N, Chen Y, Chen S, et al. Gasdermin D-mediated keratinocyte pyroptosis as a key step in psoriasis pathogenesis [J]. Cell Death & Disease, 2023, 14(9): 595.

[4] Rao Z, Zhu Y, Yang P, et al. Pyroptosis in inflammatory diseases and cancer [J]. Theranostics, 2022, 12(9): 4310.

[5] Chen S, Mei S, Luo Y, et al. Gasdermin family: a promising therapeutic target for stroke [J]. Transl Stroke Res, 2018, 9 (6): 555-563.

[6] Man SM, Kanneganti TD. Gasdermin D: the long-awaited executioner of pyroptosis [J]. Cell Res, 2015, 25 (11): 1183-1184.

[7] Rühl S, Broz P. Caspase-11 activates a canonical NLRP3 inflammasome by promoting K+ efflux [J]. European journal of immunology, 2015, 45(10): 2927-2936.

[8] Yang D, He Y, Muñoz-Planillo R, et al. Caspase-11 requires the pannexin-1 channel and the purinergic P2X7 pore to mediate pyroptosis and endotoxic shock [J]. Immunity, 2015, 43(5): 923-932.

[9] An H, Heo J S, Kim P, et al. Tetraarsenic hexoxide enhances generation of mitochondrial ROS to promote pyroptosis by inducing the activation of caspase-3 / GSDME in triple-negative breast cancer cells [J]. Cell death & disease, 2021, 12(2): 159.

[10] Bhat A A, Thapa R, Afzal O, et al. The pyroptotic role of Caspase-3/GSDME signalling pathway among various cancer: A Review [J]. International journal of biological macromolecules, 2023, 242: 124832.

[11] Sarhan J, Liu B C, Muendlein H I, et al. Caspase-8 induces cleavage of gasdermin D to elicit pyroptosis during Yersinia infection [J]. Proceedings of the National Academy of Sciences, 2018, 115(46): E10888-E10897.

[12] Zheng Z, Deng W, Bai Y, et al. The lysosomal Rag-Ragulator complex licenses RIPK1–and caspase-8–mediated pyroptosis by Yersinia [J]. Science, 2021, 372(6549): eabg0269.

[13] Chao K L, Kulakova L, Herzberg O. Gene polymorphism linked to increased asthma and IBD risk alters gasdermin-B structure, a sulfatide and phosphoinositide binding protein [J]. Proceedings of the National Academy of Sciences, 2017, 114(7): E1128-E1137.

[14] Zhou Z, He H, Wang K, et al. Granzyme A from cytotoxic lymphocytes cleaves GSDMB to trigger pyroptosis in target cells [J]. Science, 2020, 368(6494): eaaz7548.

[15] Zhang Z, Zhang Y, **a S, et al. Gasdermin E suppresses tumour growth by activating anti-tumour immunity [J]. Nature, 2020, 579(7799): 415-420.

[16] Su F, Xia Y, Huang M, et al. Expression of NLPR3 inpsoriasis Is associated with enhancement of interleukin-1b and caspase-1 [J]. Med Sci Monit, 2018, 24: 7909-7913

[17] Feng S, Fox D, Man S M. Mechanisms of gasdermin family members in inflammasome signaling and cell death [J]. Journal of molecular biology, 2018, 430(18): 3068-3080.

[18] Li Y, He Y, Yang F, et al. GSDME-mediated keratinocyte pyroptosis participates in the pathogenesis of psoriasis by promoting skin inflammation [J]. British Journal of Dermatology, 2024: ljae179.

[19] Ma J, Ji C, Sun Y, et al. Wogonin ameliorates the proliferation, inflammatory response, and pyroptosis in keratinocytes via NOD-like receptor family pyrin domain containing 3/Caspase-1/Gasdermin-D pathway

[J]. Immunity, Inflammation and Disease, 2024, 12(7): e1303.
[20] Deng G, Chen W, Wang P, et al. Inhibition of NLRP3 inflammasome-mediated pyroptosis in macrophage by cycloastragenol contributes to amelioration of imiquimod-induced psoriasis-like skin inflammation in mice [J]. International Immunopharmacology, 2019, 74: 105682.
[21] Li J, Yan W, Ren F, et al. Tectorigenin inhibits inflammation in keratinocytes by inhibition of NLRP3 inflammasome regulated by the TLR4/NF-κB pathway [J]. Allergologia et immunopathologia, 2023, 51(2): 82-89.
[22] Zhou M W, Jiang R H, Kim K D, et al. Rosmarinic acid inhibits poly (I: C)-induced inflammatory reaction of epidermal keratinocytes [J]. Life sciences, 2016, 155: 189-194.
[23] Tang L, Li T, Zhang B, et al. Punicalagin alleviates psoriasis by inhibiting NF-κB-mediated IL-1β transcription and caspase-1-regulated IL-1β secretion [J]. Frontiers in Pharmacology, 2022, 13: 817526.
[24] Mao J, Ma X, Zhu J, et al. Ginsenoside Rg1 ameliorates psoriasis-like skin lesions by suppressing proliferation and NLRP3 inflammasomes in keratinocytes [J]. Journal of Food Biochemistry, 2022, 46(5): e14053.
[25] Choi M R, Choi D K, Sohn K C, et al. Inhibitory effect of Paeonia lactiflora Pallas extract (PE) on poly (I: C)-induced immune response of epidermal keratinocytes [J]. International Journal of Clinical and Experimental Pathology, 2015, 8(5): 5236.
[26] Hu Jian. The expression of NLRP3 inflammasome in imiquimod induced mouse psoriasis like model and the effect of mustard seed on it [D]. Chinese People's Liberation Army Medical College, 2013.