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REVIEW

The Mechanism of Pyroptosis and Its Application Prospect in Diabetic Wound Healing

Abdullah Al Mamun[1,2], Chuxiao Shao[1], Peiwu Geng[1], Shuanghu Wang[1], Jian Xiao[2,3]

[1]Central Laboratory of the Sixth Affiliated Hospital of Wenzhou Medical University, Lishui People's Hospital, Lishui City, Zhejiang, 323000, People's Republic of China; [2]Molecular Pharmacology Research Center, School of Pharmaceutical Sciences, Wenzhou Medical University, Wenzhou, 325000, People's Republic of China; [3]Department of Wound Healing, the First Affiliated Hospital of Wenzhou Medical University, Wenzhou, 325000, People's Republic of China

Correspondence: Jian Xiao, Email xfxj2000@126.com

Abstract: Pyroptosis defines a form of pro-inflammatory-dependent programmed cell death triggered by gasdermin proteins, which creates cytoplasmic pores and promotes the activation and accumulation of immune cells by releasing several pro-inflammatory mediators and immunogenic substances upon cell rupture. Pyroptosis comprises canonical (mediated by Caspase-1) and non-canonical (mediated by Caspase-4/5/11) molecular signaling pathways. Numerous studies have explored the contributory roles of inflammasome and pyroptosis in the progression of multiple pathological conditions such as tumors, nerve injury, inflammatory diseases and metabolic disorders. Accumulating evidence indicates that the activation of the NOD-like receptor thermal protein domain associated protein 3 (NLRP3) inflammasome results in the activation of pyroptosis and inflammation. Current evidence suggests that pyroptosis-dependent cell death plays a progressive role in the development of diabetic complications including diabetic wound healing (DWH) and diabetic foot ulcers (DFUs). This review presents a brief overview of the molecular mechanisms underlying pyroptosis and addresses the current research on pyroptosis-dependent signaling pathways in the context of DWH. In this review, we also present some prospective therapeutic compounds/agents that can target pyroptotic signaling pathways, which may serve as new strategies for the effective treatment and management of diabetic wounds.

Keywords: diabetes mellitus, diabetic wound healing, pyroptosis, NLRP3, caspase-1, GSDMD, inflammation, inflammasome

Introduction

Diabetes mellitus (DM) is a chronic glucose metabolism condition. However, chronic organ and tissue damage from elevated blood glucose levels in DM patients results in the development of retinopathy, nephropathy, neuropathy and diabetic wound healing (DWH). Accumulating evidence indicates that DWH is caused by chronic inflammation due to impaired tissue repair mechanisms in people with DM.[1,2] In addition, diabetic foot ulcers (DFUs) are a severe and common complication of DM that results in significant morbidity and mortality worldwide.[3] Mortality rates associated with the development of DFUs are estimated to be 5% in the first 12 months and 5-year mortality rates have been estimated at 42%.[4] The standard practices in DFU management include surgical debridement, dressings to facilitate a moist wound environment and exudate control, wound off-loading, vascular assessment and infection and glycemic control.[5] Treatment of DFUs accounts for approximately one-third of the total cost of diabetic care, which was estimated to be US $176 billion in direct healthcare expenditures in 2012.[6] Despite these high healthcare costs, about 20% of patients have unhealed DFUs at 1 year.[7] Although there are well-established principles for managing DFUs, the treatment of DFUs is often challenging. A broad spectrum of novel interventions is being studied to improve wound healing. Persistent wounds in DM typically result in chronic inflammatory responses and accumulate several pro-inflammatory mediators. Extensive studies have also indicated that the NLR family pyrin domain containing 3 (NLRP3) inflammasome is activated in patients with DM.[8–10] Inflammasome pathways can be triggered by several metabolic impairments including hyperglycemia, hyperlipidemia and hyperuricemia.[11–14] NACHT domains, leucine-rich repeats (LRRs) and NLRP3 may impair angiogenesis and ulcer healing in T2DM.[15,16] Pyroptosis, a specific type of cell death, functions as

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a wide-range immune system that defends against pathogenic microbial infections.[17] Numerous studies have shown that excessive pyroptosis can lead to the progression of neurological, cardiovascular and inflammatory diseases.[18–21] Pyroptosis exacerbates metabolic conditions including hyperglycemia by inducing persistent inflammation and insulin-resistant mediators.[22] Moreover, current studies suggest that pyroptosis plays a significant role in developing diabetes complications, particularly in DWH.[23,24]

Molecular Mechanisms of Pyroptosis

Pyroptosis is an alternative manifestation of programmed cell death distinguished by cytoplasmic swelling and denaturation, which further facilitates the secretion of intracellular components and triggers a robust inflammatory response. In addition, pyroptosis is a predominant cellular mechanism to harmful stimuli including pathogen ligands, excessive amounts of host substance and external stimuli.

Canonical Pyroptosis

Microbial infections, pathogen-associated molecular patterns (PAMPs) and endogenous damage-associated molecular patterns (DAMPs) activate inflammasome multiprotein complex. The innate immune system depends on the activation of inflammasomes.[25] Several intracellular sensor molecules including NOD-like receptors (NLRP1b, NLRC4 and NLRP3), a member of the HIN200/AIM2-like receptor family (AIM2) and a TRIM family member (Pyrin/TRIM20) sense exogenous pathogens and endogenous damage such as bacterial infection, cytosolic double-stranded DNA (dsDNA), crystals and toxins to assemble the canonical inflammasomes.[26] Sensor proteins aggregate and recognize the inflammasome apoptosis-associated speck-like protein containing CARD (ASC), which includes a CARD domain. This interaction further promotes the activation of inflammasome sensors and the stimulation of pro-caspase-1 through self-cleavage.[27,28] Gasdermin D (GSDMD) acts as a direct substrate of inflammatory Caspases in pyroptosis.[29] Gasdermin-N domains are released from the plasma membrane by the Caspase-1 complex, cleaving GSDMD at the connector protein. Active Caspase-1 splits the pro-inflammatory cytokines, resulting in the enzymatic maturation of interleukin-1β (IL-1β) and interleukin-18 (IL-18).[31] Rapid/excessive pore creation in the cytoplasmic membrane region releases several pro-inflammatory factors into the extracellular microenvironment, which further allows a variety of immune cells to penetrate and trigger inflammation.[32,33] The creation of GSDMD-mediated cytoplasmic pores facilitates ion penetration into cells, resulting in osmotic pressure alterations, cell enlargement, cellular component release and pyroptosis.[34] Accumulating evidence indicates that several factors such as potassium efflux, mitochondrial malfunction, ROS and mtDNA release, lysosome disruption, chloride efflux and calcium flux can trigger pyroptosis.[35–41] Recent research investigations have demonstrated that NLRP3 inflammasome activation involves thioredoxin interacting protein (TXNIP), NIMA-related kinase 7 (NEK7), pannexin-1 and P2X7 receptor (P2X7R).[28,42] Both pannexin-1 and P2X7R have been linked to the transport of potassium ions and fluctuations in adenosine triphosphate (ATP) levels.[43,44] Therefore, the activation of canonical inflammasome pathway is a key driver in inducing pyroptosis-dependent cell death.

Non-Canonical Pyroptosis

The non-canonical pyroptotic signaling pathway has been extensively investigated alongside the canonical pyroptotic signaling pathway. In 2011, Caspase-11-infected macrophages with *E. coli*, *Citrobacter corynii*, or *Vibrio cholera* triggered pyroptosis without inflammatory bodies.[45] Extracellular lipopolysaccharides (LPS) produced by Gram-negative bacteria can stimulate the transcription of cytokines via the toll-like receptor 4 (TLR-4).[46] Caspase-4/5/11 is activated by LPS in macrophages and is transported to the cytoplasm with cholera toxin B.[47] LPS induces Caspase-11 pathway activation in a TLR4-independent manner, indicating that Caspase-11 immediately responds to LPS.[47] Pyroptosis can be triggered by the activation of Caspase 11 and 4 pathways, which bind directly to LPS. However, the precise role and function of LPS in activating Caspase-11 and its human homologs is still unknown. Caspase-4/5/11 mediates pyroptosis in mouse macrophages through GSDMD.[48] According to Aglietti et al, p30 protein fragments from GSDMD splitting after Caspase-11 activation may attach to the membrane, resulting in pyroptosis and cellular rupture.[49] Therefore, the activation of Caspase-4/5/11 signaling pathway induces cell swelling and cytoplasmic membrane denaturation, leading to pyroptosis (Figure 1). Caspase-11 cleaves and lyses membrane channel protein pannexin-1, deteriorating the channel for membrane small molecule release, triggering intracellular ATP efflux, activating P2X7 and mediating macrophage pyroptosis.[50] Exogenous ATP activation of P2X7

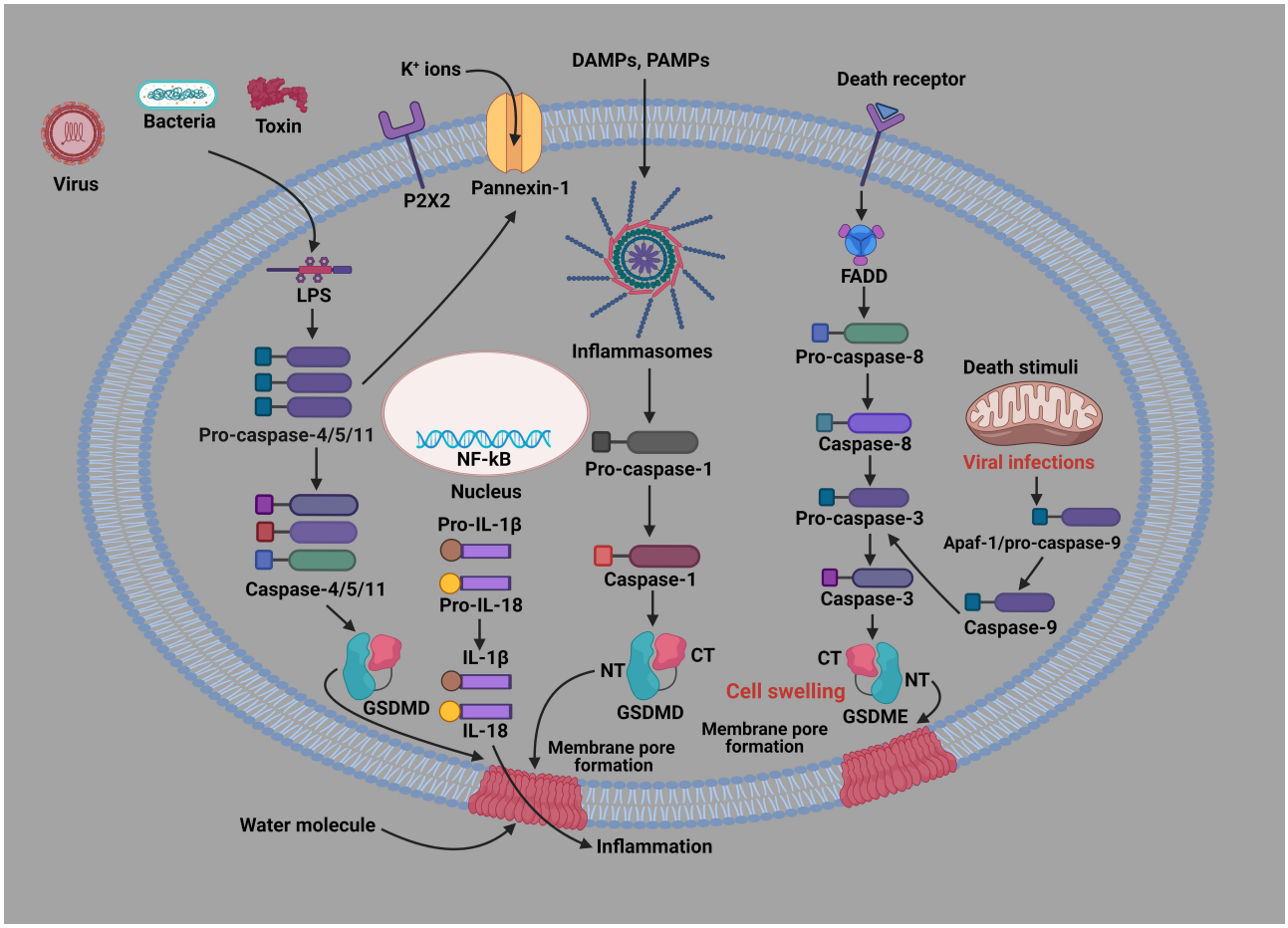

Figure 1 Cellular and molecular mechanisms of pyroptosis-related signaling pathways. Pyroptotic signaling pathways are mainly triggered by the stimulation of damage-associated molecular patterns (DAMPs) or pathogen-associated molecular patterns (PAMPs), leading to the activation of a variety of inflammasome components. The activated inflammasome proteins further activate the Caspase-1 pathway. Then, the activated Caspase-1 splits GSDMD to produce GSDMD N-fragment and plasma membrane pores, resulting in pyroptosis-dependent cell death. Furthermore, the Caspase-1 pathway triggers the formation and release of IL-1β and IL-18 inflammatory factors. In addition, LPS binds to the precursor of Caspase-4/5/11, inducing pyroptosis. Caspase-3/GSDME can also cause pyroptosis-mediated cell death. In addition, mitochondrial and death receptors can also trigger the Caspase-3 pathway. The activated Caspase-3 splits GSDME to produce GSDME N-fragment, creating cytoplasmic membrane pores, cell contraction and denaturation, resulting in pyroptosis-mediated cell death.

induces the K+ efflux channel, thereby promoting the activation ofNLRP3 inflammasome complex.[51] The Caspase-11-mediated non-canonical inflammasome can increase the efflux of potassium ions through pannexin-1, which facilitates the activation of NLRP3 inflammasome and Caspase-1, resulting in pyroptosis, maturation and outflow of several inflammatory mediators.[35]

Other Signaling Pathways

Caspase-3/8 and granzyme-mediated pathways are implicated in pyroptosis. Caspase-3/8 was once regarded as the primary trigger of apoptosis.[52] Caspase-3-mediated cleavage of gasdermin E (GSDME) in tumor cells induced by chemotherapy and Caspase-8-mediated cleavage of GSDMD in mouse macrophages after infection with *Yersinia* reinforced this theory.[53] Programmed cell death ligand 1 (PD-L1) modulates TNF-mediated apoptosis into pyroptosis in breast cancerous cells through the formation of GSDMCs.[54] Zhang and co-workers revealed that PD-L1 is transported to the nucleus and upregulated by gasdermin C (GSDMC) with p-Stat3 during hypoxia. Caspase-8 selectively cleaves GSDMC, leading to the activation of pyroptosis.[55] A combination of daunorubicin, actinomycin D, doxorubicin (DOX) and epirubicin activates Caspase-3/8-dependent signaling pathways and pyroptosis in breast cancer.[54] Previous studies have revealed that granzyme can trigger pyroptosis without inflammatory or pro-apoptotic caspases.[56,57] The research by Zhang et al showed that cytotoxic lymphocyte serine protease granzyme B (GzmB) directly cleaves GSDME in the

targeted cells.[58] In a further investigation, Zhou and his colleagues discovered that cytotoxic lymphocyte-released granzyme A (GzmA) could directly cleave GSDMB protein molecules and result in pyroptosis in the targeted cells.[59]

This review will discuss the molecular mechanisms and contributory role of pyroptotic signaling pathways in the pathogenesis and progression of DWH. This review also summarizes articles on the potential novel therapies for improving DWH by targeting pyroptosis-related signaling pathways.

Pyroptosis-Dependent Signaling Pathways in the Progression of DWH

Numerous research investigations indicate that reduced inflammatory response impairs skin wound healing in long-term wound healing models.[60–64] Pyroptosis is associated with an inflammatory reaction characterized by elevated expression level of inflammasomes, GSDMD pore-forming protein and pro-inflammatory cytokines including IL-18 and IL-1β.[65] The NLRP3 inflammasome, Caspase-1 multi-protein complex and ASC are the main regulatory pathways involved in triggering inflammation and pyroptosis following cellular injury. Recently, Yang et al showed that hyperglycemia (HG) activates NLRP3 inflammasome and increases the production of IL-1β in HaCaT cells.[24] The activation of Caspase-1, NLPR3, ILβ and IL18 can further induce pyroptosis-dependent cell death. NLPR3 inflammasome signaling is crucial to the natural healing process of wounds. Elevated pro-inflammatory cytokines including tumor necrosis factor-α (TNF-α), IL-1β and interleukin 6 (IL-6) further facilitate the process of wound healing. Numerous research investigations have shown that the NALP3 inflammasome signaling pathway is crucial to skin wound healing.[66,67] Moreover, robust inflammation significantly contributes to the development of chronic wounds.[68] The activation of intracellular inflammasomes triggers massive inflammatory responses, resulting in pyroptotic cell death and the extensive release of several pro-inflammatory mediators. Cytoplasmic LPS further activates the Caspase-11-dependent non-canonical inflammasome signaling pathways. Growing evidence suggests that Caspase-11 activates Caspase-1 via the NLRP3 inflammasome pathway, resulting in the proteolytic maturation of pro-IL-1β and IL-18.[45,47] Ao et al found elevated protein and mRNA expression level of GSDMD/Caspase-11/NLRP3/IL-1β in LPS-induced skin tissues.[69] The study conducted by Lu et al revealed that pyroptosis mediated by nucleotide-binding oligomerization domain 1 (NOD1), NOD2 and GSDMD-N impairs skin wound healing in diabetic rats.[70] Hyperglycemia disrupts injured skin tissue repair by the overactivation of NLRP1 inflammasome and pyroptosis-driven inflammation. The published work by Chen et al has indicated that the activation of canonical pyroptosis and excessive inflammatory reaction in fibroblasts impair wound healing of DFUs.[71] Accumulating evidence indicates that[72,73] the upregulation of mir-374a-5p reduces viability and activates apoptosis and pyroptosis of DFU fibroblasts.[71] Metastasis associated in lung adenocarcinoma transcript 1 (MALAT1) has been identified as a pyroptosis-related long non-coding RNA (lncRNA).[74–76] NLRP3 and NEK7 are involved in the assembly of inflammasomes and the pyroptotic process.[77] Reduced MALAT1 expression further activates NEK7/NLRP3/Caspase-1 signaling pathways, resulting in pyroptosis in fibroblast cells during DFUs. Gasdermin D (GSDMD) is a cytoplasmic protein that triggers inflammatory cell death through the formation of cytoplasmic pores.[78] The activation of canonical and non-canonical inflammasome in macrophages induces the cleavage of GSDMD, cytoplasmic membrane pores and pyroptosis, a lytic pro-inflammatory cell death phenomenon.[79] Pyroptosis is characterized by the excessive activation of NLRP3 cascade and Caspases, resulting in pore formation in the cytoplasmic membrane and the subsequent release of several pro-inflammatory factors such as IL-1β and IL-18. Current research indicates that the overactivation of NLRP3 inflammasome may play a contributory role in the development of DM and its related complications, particularly DWH.[80] Recently, Liu and colleagues have shown that NETs activate the NLRP3 inflammasome and trigger inflammatory reactions in diabetic wounds.[15] Yang et al reported that mice induced with diabetes by STZ exhibited increased activation of the NLRP3/Caspase-1/GSDMD signaling pathway in wound tissues.[23] The examination of wound healing at macroscopic level revealed a significant improvement in wound closure in Gsdmd−/− mice with STZ-induced diabetes compared to the delayed wound healing observed in the STZ-induced diabetic animal. Interestingly, the deficiency of NLRP3/Caspase-1 alleviated the release of NETs and accelerated the process of wound healing. Neutrophil extracellular traps (NETs) in DFUs impair wound healing through the activation of GSDMD. Previous studies found that AIM2 and Casp-11-gene knockout mice did not exhibit significant protection against impaired diabetes-induced wound healing. To explore the process of GSDMD activation in neutrophils during the healing of DFU, the authors investigated both canonical (AIM2/NLRP3/Caspase-1) and non-canonical pathways for inflammasome activation (Caspase-11).[23] The authors showed that hyperglycemia promotes the formation of neutrophil extracellular traps (NETs) and activates the NLRP3/Caspase-1/GSDMD signaling pathway in wounds of both humans and mice. Xu et al revealed that downregulated

expression level of NLRP3, GSDMD, GSDMD-N, pro-caspase-1 and pro-IL-1β proteins contributes to the impairment of wound healing in hyperglycemic rats.[81] A prominent study by Bitto and co-workers has demonstrated that NLRP3 inflammasome activation impairs the process of wound healing in diabetic mice.[9] Prior research has also demonstrated that the persistent activation of the NLRP3 inflammasome in macrophages has a detrimental effect on the process of wound repair in T2D patients and mouse models.[11] In addition to Caspase-1, the enzyme NE cleaves GSDMD to produce an active fragment.[82] NE mediates the activation of GSDMD and the formation of NET. Hyperglycemia provides an inflammatory environment, which increases the expression of protein kinase R (PKR) and NALP3 in diabetic wounds.[11] Diabetic wounds and macrophages treated with LPS and high glucose showed elevated levels of NALP3 and PKR.[83] Caspase-1 and NALP3 gene-knockout mice exhibited diminished inflammatory response during the early stages of injury, resulting in impaired healing.[84] PKR was activated by the Caspase-1 and NALP3 inflammasome signaling axis in mice with diabetes and delayed wound healing. The activated NLRP3 inflammasome in diabetic wounds induces elevated pro-inflammatory cytokines, which further contribute to local hyperglycemia, accumulation of AGEs and the formation of reactive oxygen species (ROS).[85,86] ROS formation can induce premature senescence in endothelial progenitor cells (EPCs) in hyperglycemic conditions, which further disrupts the repair of damaged tissues and inhibits angiogenesis.[87] Previous studies have revealed that inflammasome activation in macrophages impairs insulin sensitivity and angiogenesis, resulting in delayed DFUs healing.[2,88,89] Emerging evidence also indicates that exogenous irritants significantly reduce the activity of NLRP3 inflammasome in diabetic wounds, which further inhibits the proliferation and migration of keratinocytes.[90,91] Innate immune response to infections and tissue injury relies on the NLRP3 inflammasome, which triggers extensive inflammation.[92] Recently, Koh and colleagues have revealed that NLRP3 inflammasome activation may also contribute to the progression of chronic wound inflammation and low skin wound healing in DM.[93] Moreover, NLRP3 inflammasome activity at sustained levels leads to impaired epidermal and dermal healing. Koh et al also showed that deficient NLRP3 and Caspase-1 animals showed lower levels of IL-1β, TNF-a and neutrophils (Np) and macrophages (Mp) in wound healing.[84] Therefore, the activation of canonical pyroptosis plays a contributory role in the progression of DWH (Figure 2).

Oxidative stress (OS) is a significant contributor to the pathogenesis of DM.[94] TXNIP is an endogenous negative modulator of TXN, which regulates cellular redox homeostasis.[95] Several studies have revealed that TXNIP has a dual effect of exacerbating OS and triggering inflammation via activating the NLRP3 inflammasome.[96–98] The activity of the TXNIP-NLRP3 inflammasome induces GSDMD-dependent pyroptosis, which may contribute to excessive inflammation. Dysregulation of TXNIP is implicated in the progression of diabetes and insulin resistance.[99] Increasing evidence indicates that high glucose and O_2 production and impaired nitric oxide (NO) signaling trigger inflammation via triggering TXNIP.[100–102] TXNIP interacts with NLRP3 protein molecules in a ROS-dependent manner. Previous research indicates that ROS overproduction leads to elevated TXNIP levels, NLRP3 activation, Caspase-1 activation and IL-1β generation.[103,104] Angiogenesis and vascular repair may be adversely affected by elevated IL-1β.[105] Deng et al observed a significant increase in the protein expression levels of TXNIP/NLRP3/Caspase-1 in diabetic mice and HG-stimulated endothelial progenitor cells (EPCs). Taken together, the above findings suggest that activation of the pyroptotic signaling pathway contributes to the progression of DWH.[106]

Hypoxia impairs angiogenesis, which further induces excessive cell death.[107,108] Apoptosis and necroptosis are classic mechanisms underlying this effect. Pyroptosis is an important type of cell death that is related to inflammation. Multiple studies have revealed that pyroptosis impairs cell proliferation and i*n vitro* functions such as migration and adhesion, whereas hypoxia can lead to pyroptosis.[109,110] Recently, Zhang et al reported that PCSK9 induces hypoxia-induced vascular EC pyroptosis via Smac mitochondrion-cytoplasm translocation in critical limb ischemia.[111] Even though ECs directly perceive changes in blood oxygen, few studies have focused on the contributory role of hypoxia-induced pyroptosis in the progression of DWH. In addition, the exact contributory role of ischemia-mediated pyroptosis in the progression of DWH is entirely elusive. Thus, further studies are highly warranted to explore the underlying molecular mechanisms of the impacts of hypoxia and ischemia on the activation of inflammasome and pyroptosis in DWH.

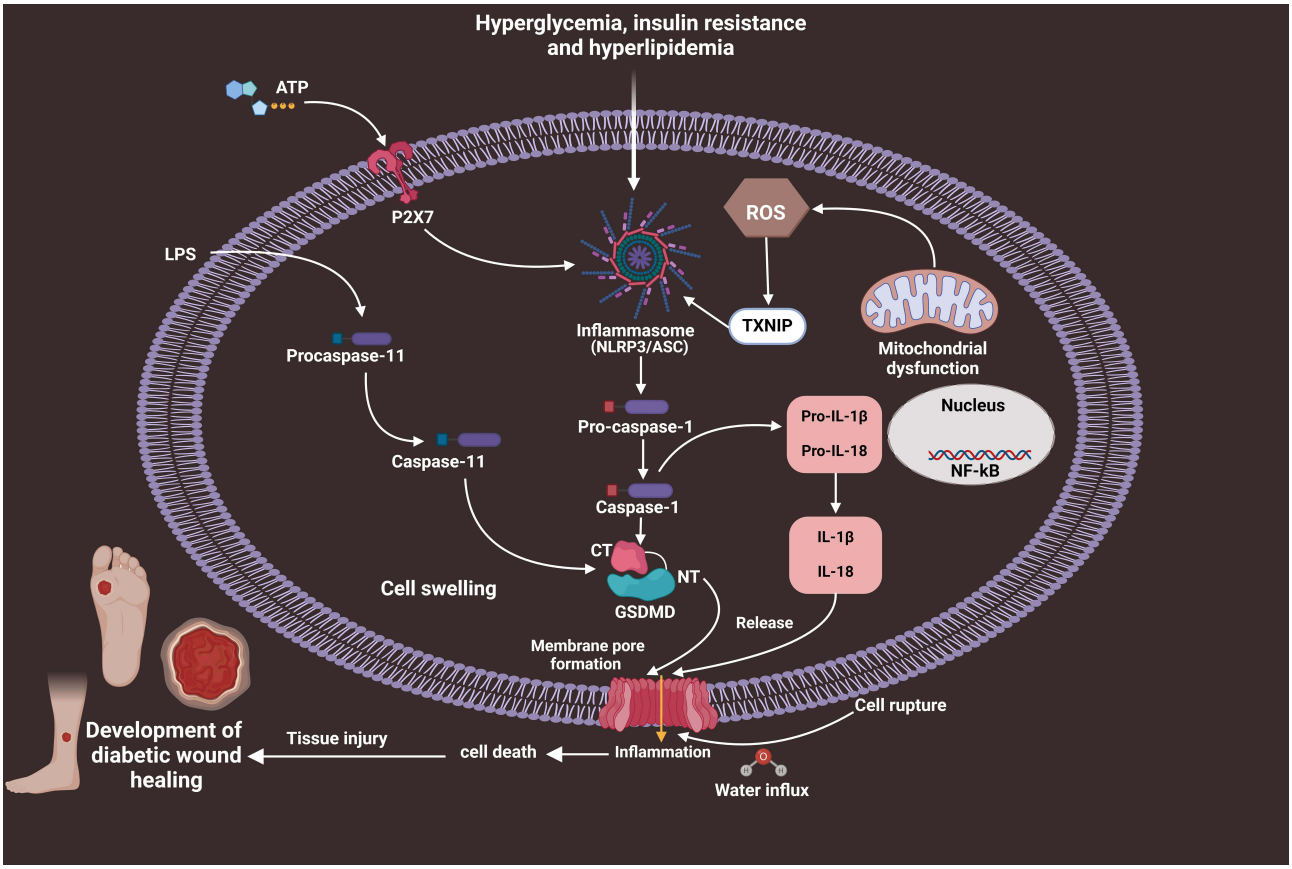

Figure 2 Schematic mechanisms of pyroptosis-dependent cell death in the course of the pathogenesis of DWH. Hyperglycemia, insulin resistance and hyperlipidemia stimulate NLRP3/ASC inflammasome signals, further activating pro-caspase-1 into Caspase-1 form. Then, activated Caspase-1 induces pyroptosis and the generation of inflammatory factors including IL-1β and IL-18, resulting in low-grade inflammation and extensive tissue damage, eventually advancing DWH.

Suppressing Pyroptosis-Dependent Signaling in Therapeutic Regulation of DWH

Disulfiram (DIS), developed in the 19th century, inhibits aldehyde dehydrogenase and is an effective therapeutic agent for the treatment and management of alcoholism.[112] A recent study has revealed that DIS is an effective inhibitor of GSDMD pore-forming protein.[113] Previous studies suggest that DIS mitigates robust inflammation and the formation of fibrosis by inhibiting the activation of canonical pyroptosis in a variety of diseases.[114–117] GSDMD is a well-established cytoplasmic pore-forming protein that induces pyroptosis-regulated cell death. This pore-forming protein in the cytoplasmic membrane allows the massive release of IL-1β, IL-18 and other inflammatory mediators. Yang et al recently found that the administration of DIS significantly accelerated wound healing in DFUs by lowering the release of NETs.[23] Mechanistically, DIS hinders the formation of NET by inhibiting the activation of NLRP3/Caspase-1/GSDMD signaling pathways in rat models of DFUs. GSDMD serves as the effector of NETosis, a process that forms neutrophil extracellular traps (NETs). Potential inhibitors can be used to treat immunopathological disorders involving NETs. Therefore, the GSDMD inhibitor DIS exhibits the therapeutic potential for improving wound healing in patients with DFUs and could be utilized in clinical applications.

Several stem cells derived from umbilical cords, bone marrow and hair follicles have garnered considerable attention in the field of regenerative medicine.[118] Numerous studies have confirmed that transplanted stem cells promote tissue repair through paracrine action.[119–121] In addition, exosomes produced by stem cells during the paracrine process have attracted considerable attention in the field of regenerative medicine.[122] Studies have revealed that exosomes produced by stem cells can facilitate kidney damage repair, attenuate myocardial infarction areas, modulate immune responses and accelerate the healing of skin woundss. Recent studies have identified a variety of long non-coding RNAs (lncRNAs) in exosomes.[123,124] Li et al have

indicated that mesenchymal stem cells-derived lncRNA H19 accelerates wound healing by enhancing PTEN via microRNA-152-3p in DFUs.[125] Yang et al also showed that HF-MSC-Exo markedly suppressed the production of IL-1β and IL-18 and activation of Caspase-1 and decreased the presence of the NLRP3 inflammasome in HaCaT cells.[125] The previous work also demonstrated that HF-MSC exosomal lncRNA H19 facilitates fibroblast proliferation and migration and attenuates pyroptosis, which further accelerates wound healing and DFU-induced tissue damage. Based on a mechanistic analysis, HF-MSC-Exo-expressing lncRNA H19 accelerates the healing of skin wounds by inhibiting the canonical pyroptotic signaling pathway in vitro and in vivo. Therefore, H19-overexpressing exosomes derived from HFMSCs could be considered a potential component in therapeutic approaches aimed at alleviating pyroptosis and enhancing the healing of skin wounds in the treatment of diabetic complications. However, the underlying molecular mechanism of HF-MCSs targeting non-canonical pyroptosis remains unknown. Thus, further studies must be executed to analyze the therapeutic efficacy of HF-MCSs in improving wound healing of diabetic patients.

Mesenchymal stem cells (MSCs) are a distinct type of cells that can undergo self-renewal and differentiate into a variety of bone cells.[126] Bone marrow-derived MSCs have been widely utilized in the field of regenerative medicine.[127,128] Numerous research studies have been executed to explore the application of MSC-CM in the treatment and management of skin wounds.[129–131] BM concentrate-induced MSCs conditioned medium accelerates wound healing and attenuates the formation of hypertrophic scarring.[132] A study showed that the application of concentrated hypoxia-preconditioned adipose mesenchymal stem cell-conditioned medium accelerated skin wound healing in a rat model with full-thickness skin defects.[133] Moreover, bone marrow-derived mesenchymal stem cell-conditioned medium (BMMSC-CM) in rats improved keratinocyte proliferation and migration in a diabetes-induced microenvironment by suppressing ROS overproduction and reversing MEK 1/2 and Erk 1/2 phosphorylation.[134] A new study has revealed that the application of adipose-derived stem cell conditioned medium (CM) can enhance wound healing and promote hair growth in SD rats with burn wounds on their dorsal region.[135] Pioneering research by Xu et al indicated that the application of BMMSC-CM mitigates inflammation, enhances autophagy and alleviates NLRP3/Caspase-1/GSDMD-dependent pyroptosis in DFUs (Table 1).[81] Therefore, BMMSC-CM can be used as a new cell-free therapeutic approach in suppressing pyroptosis-dependent cell death to accelerate the healing process of DFUs.

Histone deacetylase (HDAC6) may deacetylate substrates such as α-tubulin, peroxiredoxin-1 and 2 and HSP90. Past research has indicated that inhibition of HDAC6 possesses promising anti-oxidant and anti-inflammatory actions without acetylating

Table 1 Compounds/Agents Targeting Pyroptosis-Related Signaling Pathways for the Therapeutic Regulation of DWH

Compounds/Agents	Targeting of Inhibiting Pyroptosis-Related Signaling Pathways	References
Disulfiram	NLRP3/Caspase-1/GSDMD/IL-1β and IL-18	[23]
HF-MCSs	NLRP3/ Caspase-1/IL-18/IL-1β	[125]
BMMSC-CM	NLRP3/Caspase-1/GSDMD/IL-1β and IL-18	[81]
Tubastatin A	NLRP3/Caspase-1/ IL-1β	[136]
PKR inhibitor C16	NLRP3/IL-1β	[83]
Calcitriol	NLRP3/IL-1β	[137]
MF-094	NLRP3/ Caspase-1/IL-18/IL-1β	[138]
Metformin	NOXS/ROS/NLRP3	[139]
Bletilla striata polysaccharide	NLRP3/IL-1β	[140]
Heparin sulfate	NLRP3/IL-1β and IL-18	[141]
Sanguisorba officinalis extract	NF-κB/NLRP3/ Caspase-1/IL-1β and IL-18	[142]
Genistein	NF-κB/ASC/NLRP3/Caspase-1	[143]
UC-MSCs	NLRP3/Cleaved Caspase-1/GSDMD/IL-1β/IL-18	[144]
Rapamycin	ROS/NF-κB/NLRP3	[145]
Paeoniflorin	TLR2/ NF-κB/NLRP3/IL-1β	[146]
WB800N	TLR2/NLRP3/ASC/Caspase-1/IL-1β	[147]
Glyburide	ROS/ NLRP3/Caspase-1/	[11]
Ac-YVAD-cmk	Caspase-1/NLRP3/ IL-1β/ IL-1β	[11]
Bay 11–7082	ROS/TXNIP/NLRP3/Caspase-1/ IL-1β	[67]
MCC950	NLPR3/Caspase-1/IL-1β/18	[137]

histones or altering epigenetics.[148] TSA is a selective inhibitor of HDAC6, as compared to other HDACs. Xu et al reported that TSA suppressed the activation of NLRP3-mediated pyroptosis by enhancing the signaling of transcription factor EB.[149] Pioneering research conducted by Kulkarni and co-workers showed that topical application of HDAC6 inhibitor TSA accelerated wound healing through alleviating Caspase-1-dependent pyroptosis in diabetic mice.[136] Accumulating studies indicate that suppressing IL-1β and inflammasome components may accelerate wound healing by increasing the levels of IL-10.[11,15,150] In addition, the administration of TSA resulted in improved wound healing in diabetic mice through the suppression of pro-inflammatory cytokines and the promotion of pro-healing factors. Therefore, TSA gel could be a new therapeutic drug candidate for accelerating DWH via the regulation of pyroptosis-mediated cell death (Figure 3). More clinical studies are highly warranted to determine the therapeutic efficacy and explore the anti-pyroptotic targets of TSA in the treatment and management of DWH.

PKR is upregulated in metabolic conditions and mediates metabolic signaling and inflammation.[151] Multiple studies have elucidated the functions of PKR in modulating insulin signaling and enhancing glucose homeostasis in DM.[152–155] There is evidence that PKR interacts with NALP3 protein molecules and is necessary for assembling inflammasomes.[156] Kulkarni and colleagues evaluated the therapeutic potential of PKR inhibitors in delayed wound healing of diabetic patients using C16 hydrogel.[83] Selective PKR inhibition with C16 fostered faster wound healing, decreased levels of p-PKR and p-eIF2α, enhanced angiogenesis, alleviated inflammatory cell accumulation and improved wound strength.[83] Therefore, C16 can deliver a new therapeutic effect for treating DWH via the regulation of pyroptosis.

The pleiotropic vitamin D (VD) is derived from dietary supplements or produced endogenously in the skin by UV radiation (Baeke).[157] Growing evidence indicates that vitamin D deficiency impairs insulin synthesis and secretion, while vitamin D-supplemented diets remarkably improve insulin production.[158,159] In addition, vitamin D regulates plasma calcium and tissue inflammation during wound healing.[160] Lu et al reported that mice lacking the VD receptor (VDR− /-) exhibited impaired corneal epithelial wound healing and minimized tight junction integrity at the wound margin. Topically administered vitamin D impairs corneal epithelial wound healing in wild-type mice.[161] Calcium-rich diet

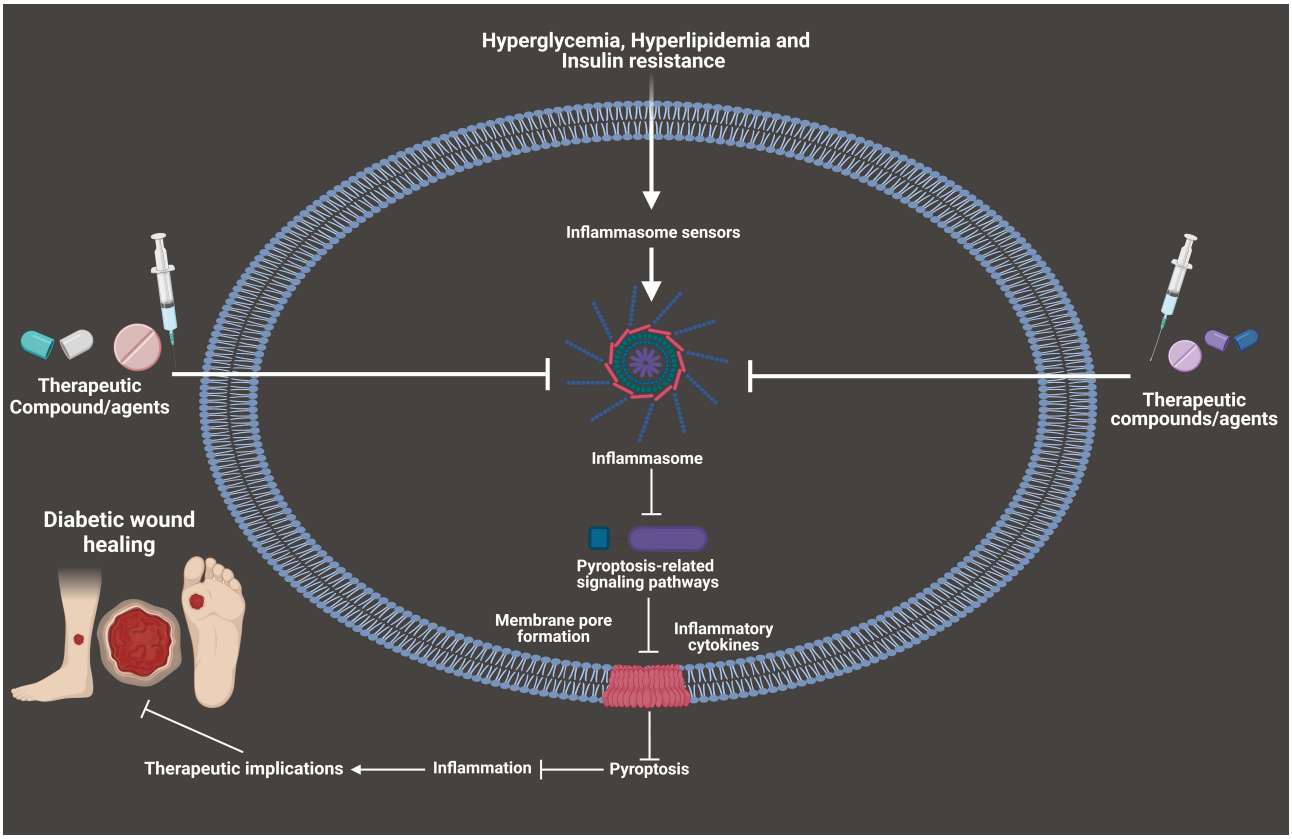

Figure 3 Compounds/agents targeting pyroptosis-related signaling pathways for the therapeutic regulation of DWH.

partially improves corneal wound healing in diabetic mice with VDR− /- and VD deficiency.[162] Vitamin D regulates the differentiation of epidermal and hair follicles. Recently, Zhou and co-workers have revealed that the topical application of calcitriol (CAL) enhances the healing of diabetic corneal wounds and the regeneration of peripheral nerves by impeding the activation of NLRP3 inflammasome.[137] It was also found that the inhibition of NLRP3/IL-1β accelerates diabetic corneal wound healing and reinnervation. Therefore, CAL may be an anti-pyroptotic agent that accelerates the process of wound healing in DM.[137] Therefore, the topical application of CAL provides a potentially effective administrative route in the treatment of DWH. However, further studies are highly required to analyze the pharmacological target of CAL alleviating GSDMD/GSDME-dependent pyroptosis in accelerating wound healing in patients with DM.

Current studies indicate that targeting inflammasome delivers a potential therapeutic avenue for improving DWH.[163] The consistent activation of NLRP3 has been considered to impede the process of wound healing in patients with DFUs.[164] USP30 regulates the viability and migration of skin fibroblasts by targeting the NLRP3 inflammasome. Furthermore, NLRP3 is implicated in the modulation of IL-1β/IL-18 and MMP-2/MMP-9 by USP30. The NLRP3 inflammasome modulates the level of Caspase-1 p20 protein by regulating USP30. Li et al showed that MF-094 is a strong and specific USP30 blocker, which modulates the NLRP3 inflammasome to promote DWH.[138] MF-094 inhibits USP30 and its downstream target Caspase-1 p20 in diabetic rats, accelerating wound healing and reducing the levels of NLRP3, demonstrating the physiological significance of USP30-NLRP3. Further studies are required to explore and confirm the physiological relevance of USP30-NLRP3 regulation by manipulating the NLRP3 inflammasome in vivo. In summary, these findings suggest that MF-094 could be a promising drug candidate for suppressing NLRP3 inflammasome-mediated pyroptosis in the treatment and management of DWH.

Inflammasomes regulate the innate immune response and trigger inflammatory reactions.[66] The NLRP3 inflammasome is well-recognized as the predominant inflammasome. It comprises three key components: NOD-like receptor protein 3, ASC and Caspase-1. Recent research indicates that the NLRP3 inflammasome plays a crucial role in the progression of wound healing.[165,166] Growing evidence suggests that inhibition of the NLRP3 inflammasome and cleaved IL-1β mitigates inflammation and accelerates wound healing.[141,166] Intriguingly, Chiu et al revealed that the modulation of NLRP3 inflammasome by the activation of autophagy resulted in the mitigation of burn wound development and enhancement of wound healing in a rat burn model.[167] The modulation of M2 macrophage polarization by inhibiting the activities of NLRP3 inflammasome might potentially serve as a novel therapeutic strategy to enhance the wound-healing process.[9] Topical pharmacological inhibitors suppressed the functions of the inflammasome in mice wounds, induced a switch from pro-inflammatory (M1 macrophage) to healing-associated (M2 macrophage) phenotypes and increased the levels of pro-healing growth factors.[168] Metformin (MTF), a biguanide, is widely prescribed for the treatment of T2DM. It is well known that MTF, an AMPK activator, inhibits wound healing in patients with diabetes.[169] MTF enhanced wound healing, promoted angiogenesis and elevated circulating endothelial progenitor cell (EPC) count.[170] Fatma et al suggest that MTF accelerates the healing of cutaneous wounds in STZ-induced diabetic rats.[139] Zhao and his colleagues found that MTF locally enhanced the epidermis, hair follicles and collagen deposition, accelerating the process of wound healing.[171] Many studies have shown that MTF can significantly inhibit pyroptosis-dependent cell death in alleviating the progression of multiple diseases including diabetic complications.[99,172–176] Intriguingly, Qing et al have suggested that MTF increases the polarization of M2 macrophage to accelerate wound healing by modulating the AMPK/mTOR/NLRP3 inflammasome pathways.[177] The aforementioned studies have contributed novel perspectives on the molecular mechanism behind MTF treatment and its prospective therapeutic applications in the context of wound healing.

Bletilla striata (Thunb.) Reichb. f. belongs to the group of plants commonly used in traditional Chinese medicine. *Bletilla striata* has been documented in Chinese historical literature as a folk medicine to stop bleeding and enhance tissue regeneration and wound healing in the skin.[178] *Bletilla striata* are primarily composed of polysaccharides.[179] *Bletilla striata* polysaccharide (BSP) has a wide range of pharmacological actions including anti-inflammatory, antioxidant, immunomodulatory, anti-aging and wound and ulcer healing.[180–184] Due to these promising properties, BSP is a viable material for wound dressing, hydrogel, tissue engineering scaffolds and drug delivery vehicles.[178,185–187] According to Yu et al, BSP promotes fibroblast infiltration and collagen formation in wounds in diabetes with DFUs.[188] Further research revealed that BSP mitigated the formation of angiotensin II–induced ROS and the release

of pro-inflammatory cytokines in human mesangial cells.[180] Recently, Zhao and co-workers showed that BSP intervention enhanced DWH in mouse models by reducing macrophage penetration, promoting angiogenesis, suppressing NLRP3 inflammasome overactivation, lowering IL-1β release and improving insulin sensitivity.[140] Therefore, BSP can be an effective therapeutic drug candidate for accelerating diabetic wounds via suppressing pyroptosis-mediated cell death. However, further research is required to explore the pharmacological target of BSP in GSDMD/GSDME-dependent pyroptosis as a potential treatment for DFUs.

Dynamic interactions between extracellular matrix (ECM) and growth factors have been associated with the process of wound healing.[189] Heparin sulfate (HS) glycosaminoglycan is essential to maintain the extracellular matrix (ECM), which consists of scaffold proteins. A series of studies have revealed that HS modulates the function of proteolytic enzymes, morphogens, chemokines and growth factors produced in the tissues.[190,191] However, Bame and co-workers have shown that local matrix metalloproteases and serine proteases eradicate the actions of HS.[192] In the early period of DWH, the normal balance of HS is disrupted. The research by Wang et al suggests that HS enhances wound healing in diabetic rats by mitigating inflammation.[141] The inflammasome represents the complex of multiple proteins that activate the immune system of the host in response to harmful stimuli. Mirza and colleagues have suggested that the NLRP3 inflammasome plays a crucial role in regulating the inflammatory response in wounds of diabetic mice.[11] Menini et al report that the accumulation of DAMPs stimulates the NLRP3 inflammasome, resulting in insulin resistance and organ dysfunction.[193] Glucotoxicity and chronic inflammation in diabetes are linked to the overactivation of the NLRP3 inflammasome axis.[193] Therefore, impeding the NLRP3 inflammasome accelerates DWH in glucotoxicity. Intriguingly, Wang et al found that HS mitigates inflammation and promotes tissue wound healing in diabetic rats by inhibiting the activation of NLRP3 inflammasome and IL-1β cleavage.[141] Therefore, HS could be a promising anti-pyroptotic drug for accelerating DWH.

Sanguisorba officinalis L., a traditional Chinese medicinal plant, is commonly applied for the treatment of burns and scalds.[194,195] Current research suggests that *S. officinalis L.* possesses promising anti-oxidant, anti-inflammatory, anti-infectious and anti-allergic effects.[196–198] Cheng et al indicated that oral supplementation *of Sanguisorba officinalis* extract resulted in faster wound contraction, reduced epithelialization timeline, increased hydroxyproline substances and elevated IL-1β and VEGF levels, promoting collagen synthesis and angiogenesis in experimental burn wounds.[199] Song and co-workers report that *Sanguisorba officinalis* L. facilitates diabetic wounds in rats by modulating the NLRP3/Caspase-1 canonical pyroptotic signaling pathways.[142] Intriguingly, the researchers found that ESO could markedly mitigate inflammation and enhance diabetic wound closure via modulating the NF-κB/NLRP3 signaling axis, obstructing M1-like polarization and increasing M2-like polarization of macrophages. Therefore, inflammasome-dependent pyroptosis and homeostasis in the immune system can be targeted with ESO in diabetic wounds to provide new insights into DWH processes.

Genistein (GST), a legume isoflavone, is recognized for its estrogen-like actions.[200] The administration of GST regulates the anti-oxidant defense system and pro-inflammatory factors to enhance the process of wound healing.[201] Current evidence suggests that NLRP3 accelerates wound healing in barrier tissues including skin and epithelial cells.[202,203] Further research revealed that GST enhances wound healing in hyperglycemic mice by regulating the ASC/NLRP3/Caspase-1 inflammasome, nuclear factor erythroid 2-related factor and associated indicators.[143] *In-vitro* analysis showed that ESO administration significantly suppressed the formation of NLRP3, Caspase-1 and IL-1β in RAW264.7 cells treated with LPS. Therefore, the administration of GST may be effective in preventing and treating delayed wound healing through the alleviation of inflammation and Caspase-1-dependent pyroptosis during the inflammatory phase.

Human umbilical cord mesenchymal stem cells (UCMSCs) are multipotent stem cells obtained and cultured from the umbilical cord.[204] Multiple studies suggest that UCMSCs exert significant proliferation efficiency compared to BM-derived MSCs, which may accelerate wound healing and tissue regeneration.[205–208] A study by Wang et al demonstrated that ApoEVs derived from UCMSCs improved wound healing in db/db mice by suppressing the level of pyroptosis-associated proteins such as NLRP3, cleaved caspase-1, GSDMD, IL-1 and IL-18.[144] The authors showed that NLRP3, Caspase-1, GSDMD and F4/80 co-localized in pyroptotic BMDMs and ApoEV treatment significantly reduced the number of positive cells and fluorescence intensity in LPS/ATP-induced macrophages. Research investigations have shown that higher blood sugar levels may result in macrophage oxidative stress through the generation of excessive ROS in oxidative phosphorylation.[209] Studies on humans and animals have revealed that oxidative stress-related enzymes and metabolites significantly impede wound healing.[210–214] Growing evidence indicates that excessive ROS formation may activate NLRP3 inflammasome axis, resulting in

pyroptosis.[215] ApoEVs derived from UCMSCs have been shown to effectively inhibit the accumulation of ROS, mitigate the generation of OS in macrophages and alleviate the occurrence of pyroptosis.[144] It has been demonstrated that the administration of ApoEVs is effective in modulating different types of cell death in a variety of cell types. Therefore, UCMSCs may provide a novel therapy for treating T2D-mediated wound healing and extend our understanding of the regulation of cell death. Regrettably, the existing evidence does not establish a definitive relationship between apoptosis and the prevention of pyroptosis. Several studies have indicated that apoptotic products can potentially affect pyroptosis, thereby providing information regarding the regulation of cell death.

Rapamycin (RAP), an mTOR inhibitor, is commonly used as an immunosuppressive drug following renal, liver and heart transplantation.[216] Xiao et al showed that RAP increased epidermal autophagy in a rat model of severe second-degree burn lesions.[217] Previous studies indicate that RAP impairs wound healing by inhibiting the activation of γδ T cells in skin tissues.[218] The mammalian target of rapamycin (mTOR) inhibits autophagy, which is necessary for the activation of NLRP3 and the release of IL-1β pro-inflammatory cytokine.[219,220] NF-κB is a significant nuclear transcription factor that regulates multiple cellular processes in the inflammatory response. Recent research suggests that RAP mitigates inflammation by modulating the activation of NF-κB pathway.[221] Chai and co-workers have reported that RAP suppresses HG-induced NLRP3 inflammasome activation by restricting the mTOR/NF-κB pathway in macrophages.[145] Elevated glucose levels promote the expression of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and the production of ROS, leading to the activation of redox-sensitive NF-κB. RAP blocks the NF-κB pathway by activating mTOR, resulting in the inhibition of the endogenous IKK. In the previous work, the authors also showed that a deficit of mTOR hinders the activation of NF-κB pathway and NLRP3 inflammasome.[145] Therefore, RAP may treat diabetes-induced inflammatory response in wound healing. The therapeutic significance of recent discoveries could be confirmed by in vivo studies exploring the regulation of inflammasome for the treatment of DWH.

Paeoniflorin (PAF) is a monoterpene glycoside that originated from the dried and peeled root of *Paeoniae albaradix*.[146] PAF is an anti-oxidant and anti-inflammatory compound found in *Paeonia alba radix*.[222] Shao et al discovered that PAF treatment efficaciously suppressed the secretion level of inflammatory factors and chemokines (specifically TNF-α, IL-1β and MCP-1) by blocking TLR2, resulting in the alleviation of diabetic nephropathy.[222] Past research has indicated that PAF mitigates LPS-induced inflammation in mice by inhibiting the activation of NLRP3 inflammasome.[223] It has been demonstrated that PAF accelerates wound healing in diabetic rats through the activation of the Nrf2 pathway.[224] Chemokines including chemokine (C-X-C) ligands 1 and 2 trigger C-X-C motif chemokine receptor 2 (CXCR2) in neutrophils. IL-1β activates the NF-κB signaling pathway, leading to the primary expression of these chemokines. TNF-α modulates the networks of chemokine in inflammation-induced disorders by activating the NF-κB signaling pathway. Previous studies have revealed that restricting CXCR2 mitigates and reverses the progression of T1DM in mouse models.[225] Moreover, inhibition or knockdown of CXCR2 improved islet transplant survival and function. Recently, PAF has been found to exert significant suppressory effects on the NLRP3 inflammasome and NF-κB-mediated inflammatory responses in DFUs through the inhibition of the chemokine receptor CXCR2.[146] Therefore, PAF may be a potential NLRP3-inflammasome-mediated pyroptotic inhibitor in alleviating the pathogenesis and progression of DWH.

Bacillus subtilis, a probiotic, modulates the immune response, remodels gut microbiota, extends fermentation and boosts the economy.[226] Past studies identified a new cyclic lipopeptide from *Bacillus subtilis* CAU21 and bacteriocin (BAC-IB17) from *Bacillus subtilis* KIB17.[227,228] *B. subtilis* (WB800N) can also modulate immunological responses.[229] Current research has shown that amoxicillin decreases microbiota alpha and beta diversities, disrupting gut microbiota and relieving diabetic wounds in mice.[230] *Bacillus subtilis* is an oral microbe that regulates gut diversity and composition (WB800N and DSM 32315).[231,232] A pioneering study performed by Li and co-workers showed that *Bacillus subtilis* WB800N accelerates wound healing in diabetic mice by regulating the function of TLR2.[147] TLR2 is the primary factor implicated in the innate immune response. Stimulating the immune response proved advantageous for the healing of wounds in patients with diabetes.[233] The TLR2/NLRP3/Caspase-1 axis plays a regulatory role in immune response.[234] The previous work showed that *Bacillus subtilis* WB800N upregulated the protein expression levels of TLR2, NLRP3, ASC and Caspase-1 in diabetic mice.[147] TLR2 is essential for pro-IL-1β induction, whereas NLRP3/ASC is indispensable for Caspase-1 activation and subsequent cleavage of pro-IL-1β, resulting in the production of mature IL-1β. IL-1β is a pro-inflammatory cytokine that plays a fundamental role in driving infection-mediated inflammation.[235] The combination of *Bacillus subtilis* and TLR2 antagonist abolished the suppressory effects

of SsnB on serum IL-1β, IL-37 and skin wound cell apoptosis.[147] *Bacillus subtilis* WB800N was found to induce inflammation and cell apoptosis through the activation of TLR2, leading to an expedited healing process for diabetic wounds. Thereofre, these findings imply that WB800N might be a canonical pyroptotic inhibitor in the pharmacological treatment and management of DWH.

Glyburide (GLD) is a popular sulfonylurea medication for T2DM, which can inhibit NLRP-3 inflammasome overactivation and enhance insulin production from pancreatic β-cells through a distinct mechanism.[236] A recent work by He et al suggests that GLD exhibits diverse anti-inflammatory actions including the inhibition of inflammasome assembly.[237] It has been reported that GLD inhibits the activation of inflammasomes by blocking ATP-sensitive potassium channels (KATP).[238] Previous research showed that GLD accelerates wound healing by anti-inflammation and RIP140 degradation.[239] Diabetic wounds promote the activation of inflammasomes in cultured macrophages through pathways mediated by ROS and IL-1β, contributing to a pro-inflammatory positive-feedback loop that perpetuates the inflammatory response.[85] To ascertain the potential enhancement of wound healing in *db/db* mice by the inhibition of inflammasome activity, Koh et al administered the NLRP-3 inflammasome blocker GLD and the irreversible Caspase-1 blocker YVAD directly into the wounds of the animals.[11] The application of pharmacological inhibitors or bone marrow transfer from mice lacking NLRP3 or Caspase-1 to *db/db* mice can inhibit the activation of inflammasomes and facilitate early healing in diabetic wounds. This is achieved by reducing the pro-inflammatory characteristics of macrophages and promoting factors that aid in wound healing. The application of GLD remarkably improved tissue healing in *db/db* mice via suppressing NLRP3/Caspase-1-dependent pyroptosis. Therefore, GLD could be a promising pyroptotic inhibitor to accelerate wound repair in patients with DM. However, more clinical research is highly required to clarify the potential therapeutic advantages of GLD in suppressing pyroptosis in various aspects of DWH.

NLRP3 inflammasomes are crucial pro-inflammatory mediators regulating host responses to diverse stresses.[240] Ac-YVAD-cmk is a selective, irreversible inhibitor of Caspase-1 that may inhibit the activation of pyroptosis and mitigate the release of the pro-inflammatory cytokines IL-1β and IL-18. In the prior study, the administration of YVAD was shown to downregulate the concentrations of IL-1β and IL-18 in the dermal wounds of diabetic db/db mice.[11] This finding aligns with the inhibitory effects of Ac-YVAD on the NLRP3 inflammasome, which ultimately resulted in enhanced reepithelialization and augmented collagen accumulation. Thus, Ac-YVAD-cmk could potentially serve as a promising therapeutic agent for improving DWH. Further research is required to examine the possible therapeutic benefits of Ac-YVAD-cmk in DWH.

The development of effective inhibitors of NLRP3 inflammasomes is currently in progress. BAY 11–7082 is an inhibitor of I-B kinase-I, which suppresses the ATPase activity required to activate NLRP3 and directly targets its inflammasome.[241] A work published by Sung and colleagues indicates that Bay11-7082 promotes wound healing by suppressing the expression of matrix metalloproteinases (MMPs) induced by mechanical injury and TNF-α in the posterior cruciate ligament.[242] Mechanistically, BAY 11–7082 impedes the activation of NLRP3 inflammasome-dependent inflammatory pathways and enhances angiogenesis. NF-kB and inflammasome blockage are difficult to distinguish in complicated biological processes including wound healing. The previous study by Bitto et al showed that the application of Bay 11–7082 to skin wounds in db/db mice resulted in an expedited healing process and increased reepithelialization.[9] Additionally, there was a reduction in the presence of NLRP3 inflammasome components and associated factors such as Caspase-1, IL-1β and IL-18. Current investigations have revealed that NLRP3 agonists promote the production of ROS, which further induces the activation of NLRP3 inflammasome through the ROS-sensitive NLRP3 ligand TXNIP.[243] Mitochondria and NADPH oxidase are the primary sources of ROS triggered by external stimuli. The mitochondrial respiratory chain primarily produces ROS in cells. ROS overproduction induces DNA damage, lipid peroxidation and protein oxidation in oxidative stress.[244] Dai et al showed that the application of Bay 11–7082 further accelerates wound healing in diabetic rats by attenuating the formation of ROS.[67] More importantly, Bay 11–7082 enhanced wound closure and suppressed the activation of NLRP3-inflammasome components including ASC, caspase-1 and IL-1β in STZ-induced diabetic rats.[67] Therefore, Bay 11–7082 may have potential therapeutic benefits in accelerating wound healing in diabetic patients.

A diaryl sulfonylurea-containing molecule MCC950, is a potent and specific NLRP3 inflammasome inhibitor.[245] Accumulating studies have indicated that MCC950 ameliorates diabetic complications including diabetic renal injury by suppressing NLRP3/Caspase-1-dependent pyroptosis.[246,247] It has also been reported that MCC950 obstructs the activation of NLRP3 but not AIM2, NLRC4 or NLRP1 inflammasomes.[248] Previous studies indicated that MCC950 inhibits the activation of canonical and non-canonical inflammasome signaling pathways and alleviates the production of pro-inflammatory mediator IL-

1β by hindering the oligomerization of ASC.[249] In addition, Wang and co-workers showed that MCC950 intervention promoted diabetic corneal wound healing and reinnervation by inhibiting the activation of the NLPR3/Caspase-1/IL-1β-dependent pyroptotic signaling axis.[137] The authors clearly showed that the application of MCC95O downregulated the pyroptosis-dependent protein and mRNA expression levels, resulting in the alleviation of diabetic wounds in mice. Therefore, these findings suggest that MCC950 could be a promising inflammasome-mediated pyroptotic inhibitor in accelerating diabetic wounds.

Conclusions and Perspectives

Specifically, the NLRP3-Caspase-1-GSDMD signaling axis has been identified as the principal mechanism underlying pyroptosis in the pathogeneiss and progression of DWH. Furthermore, long non-coding RNAs (lncRNAs) play a crucial role in regulating cell pyroptosis in DWH. Natural compounds and traditional medicines have been found to suppress pyroptosis-regulated cell death by inhibiting the activation of NLRP3 inflammasome. However, the current evidence is limited and does not establish strong directions of the contributory roles of pyroptosis in the progression of DWH. The majority of studies have been conducted using animal models. Therefore, further investigations are required to investigate the specific mechanisms and potential functions of pyroptosis-mediated cell death in the progression of DWH. Inflammatory pyroptosis may be able to serve as a biological marker for predicting the pathogenesis and progression of DWH. There is a limited understanding of effective strategies to modulate pyroptosis in order to prevent or treat DWH. The first and most important approach in treating diabetic complications including DWH is lowering blood glucose levels. Therefore, further investigations are highly required to explore the complex relationship between pyroptosis, diabetes and DWH. Increasing evidence indicates that some natural compounds/agents can be employed as therapeutic targets in inhibiting pyroptosis and alleviating inflammation for the treatment and management of DWH. In conclusion, research efforts to address these questions and other essential concerns would offer an innovative perspective for the effective treatment and management of DWH in the near future.

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Disclosure

The authors report no conflicts of interest in this work.

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