

Pyroptosis in Diabetic Peripheral Neuropathy and its Therapeutic Regulation

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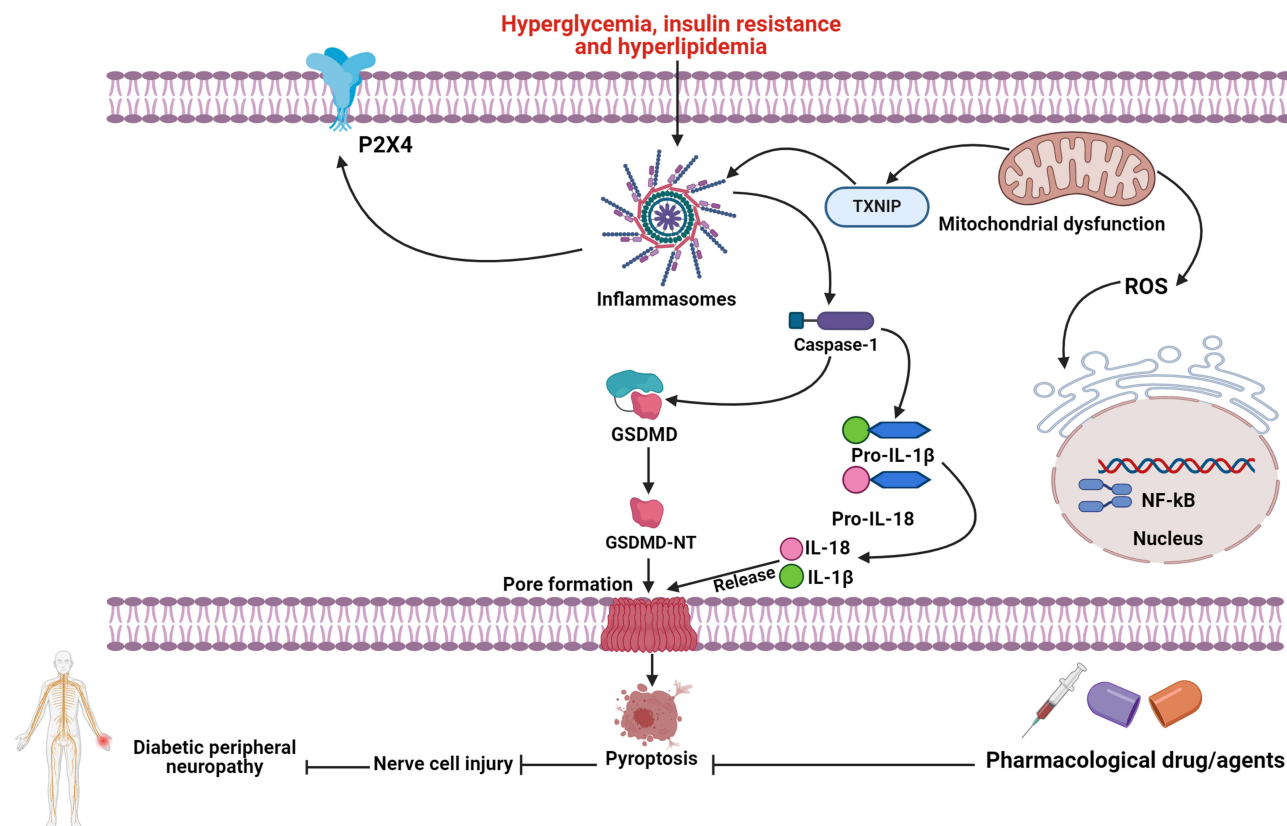
Abstract: Pyroptosis is a pro-inflammatory form of cell death resulting from the activation of gasdermins (GSDMs) pore-forming proteins and the release of several pro-inflammatory factors. However, inflammasomes are the intracellular protein complexes that cleave gasdermin D (GSDMD), leading to the formation of robust cell membrane pores and the initiation of pyroptosis. Inflammasome activation and gasdermin-mediated membrane pore formation are the important intrinsic processes in the classical pyroptotic signaling pathway. Overactivation of the NOD-like receptor thermal protein domain associated protein 3 (NLRP3) inflammasome triggers pyroptosis and amplifies inflammation. Current evidence suggests that the overactivation of inflammasomes and pyroptosis may further induce the progression of cancers, nerve injury, inflammatory disorders and metabolic dysfunctions. Current evidence also indicates that pyroptosis-dependent cell death accelerates the progression of diabetes and its frequent consequences including diabetic peripheral neuropathy (DPN). Pyroptosis-mediated inflammatory reaction further exacerbates DPN-mediated CNS injury. Accumulating evidence shows that several molecular signaling mechanisms trigger pyroptosis in insulin-producing cells, further leading to the development of DPN. Numerous studies have suggested that certain natural compounds or drugs may possess promising pharmacological properties by modulating inflammasomes and pyroptosis, thereby offering potential preventive and practical therapeutic approaches for the treatment and management of DPN. This review elaborates on the underlying molecular mechanisms of pyroptosis and explores possible therapeutic strategies for regulating pyroptosis-regulated cell death in the pharmacological treatment of DPN.

Keywords: Diabetes mellitus, Diabetic peripheral neuropathy, Inflammation, Pyroptosis, NLRP3, Caspase-1, GSDMD, IL-1 β and IL-18

Introduction

The World Health Organization (WHO) states that diabetes mellitus (DM) is growing, especially in low and middle-income countries. In contrast, more DM deaths occur in those under 70 age than in high-income countries.^{1,2} The seventh most common cause of mortality worldwide was DM, which affected 422 million people in 2014 and 1.6 million in 2016. Current data indicate that the prevalence of DM is anticipated to reach 642 million by 2040.^{3,4} Type 2 diabetes mellitus (T2DM) is mainly characterized by increased chronic inflammation burden.^{5,6} In addition, diabetic microvascular complications including diabetic peripheral neuropathy (DPN) are also characterized by a high inflammatory burden.^{7,8} It is widely believed that DPN is a devastating complication of DM characterized by complex molecular pathogenesis.⁹ DPN is closely related to a variety of clinical symptoms including nerve damage, paraesthesia and sensory loss and affects around 50% of adults diagnosed with diabetes.¹⁰ However, effective therapies lack specificity and are not currently available. Thus, it is necessary to find efficient approaches against DPN based on the exact molecular mechanisms implicated in the pathogenesis. Therefore, effective therapies to alleviate DPN must be developed based on the underlying mechanisms. The pathogenesis of DPN is complex, involving chronic inflammation and dysfunction of Schwann cells as major contributing factors.¹¹ In addition, environmental and genetic factors including lifestyle factors

Graphical Abstract



such as detrimental nutrition, physical inactivity/sedentary lifestyle, obesity or overweight and alcohol and smoking consumption, have been proven to increase the risk of DPN and its complications. Numerous investigations indicate that hyperglycemia promotes AGEs and ROS overproduction, which further stimulate oxidative stress and chronic inflammation, resulting in a variety of complications.^{12,13} Current research shows that activation of pyroptosis-mediated cell death mediates the advancement of diabetic complications including DPN.^{14–19}

Cell death is typically classified as programmed cell death (PCD) or non-programmed cell death (non-PCD). Specific genes encode signals or actions that eliminate functionally dispensable, infected, or possibly malignant cells and characterize the types of PCD. The most common forms of PCD are pyroptosis, apoptosis and necroptosis.²⁰ Pyroptosis is a form of cell death that involves the creation of pores in the cytoplasmic membrane, cellular contraction, membrane denaturation and the release of inflammatory molecules.²¹ Pyroptosis, also called gasdermins (GSDMs)-dependent programmed necrosis, is the most recently characterized form of PCD triggered by the disruption of extracellular and intracellular homeostasis that deteriorates the innate immunity system.^{22–24} Emerging evidence indicates that pyroptosis, a form of PCD with hyperinflammation, typically leads to a significant infection and induces the progression of multiple diseases.^{25,26} Numerous studies have shown that excessive pyroptosis activation can lead to the progression of several neurological, cardiovascular and inflammatory diseases.^{27–42} Pyroptosis exacerbates metabolic conditions including hyperglycemia by inducing persistent inflammation and insulin-resistant mediators.^{43–46} Current studies indicate that the activation of inflammasome and pyroptosis plays contributory roles in developing diabetes complications, particularly in DPN.^{15,47–55} In addition, pyroptosis-mediated prolonged inflammation induces the development of depression, neurodegenerative disorders, ischemic strokes and intracranial hemorrhages and⁵⁶ promotes neuroinflammatory injury and pain and disrupts the regeneration and repair of peripheral nerves.^{57–59}

In this review, we first covered the underlying molecular mechanisms of pyroptosis and addressed various signaling pathways that may activate pyroptosis and their impact on the progression of DPN. This review finally presents an overview of prospective therapeutic compounds/drugs for targeting inflammasome and pyroptosis in the treatment and management of DPN.

Biological Features of Pyroptosis

Pyroptosis is mainly derived from the Greek roots “pyro” and “ptosis”, signifying fever and falling, respectively.^{60,61} This nomenclature is used to characterize a recently discovered form of programmed cell death (PCD) with inflammatory properties. Since 1990, scientists have identified that *Shigella flexneri* or *Salmonella* infection eradicates mouse macrophages or human monocytes.⁶² *Shigella dysenteriae* was reported by Arturo Zychlinsky in 1997 to activate caspase-1 in host cells.⁶³ The Arturo Zychlinsky lab discovered in 1999 that restricting caspase-1 suppressed *Salmonella*-induced cell death.⁶⁴ The research teams of Lawrence H. Boise and Brad Cookson found in 2001 that bacterial infection resulted in macrophage death through the activation of Caspase-1-dependent programmed necrosis, a death mechanism distinct from apoptosis.^{65,66} Pyroptosis and apoptosis have common biological characteristics and functions such as DNA fragmentation and chromatin. Pyroptotic cells show swelling and the formation of bubble-like bulges on their cell membranes prior to rupture.⁶⁷ Apoptosis involves Caspase-3 for membrane blebbing. Pyroptosis features specific cellular characteristics that distinguish it from other forms of apoptosis.^{68–70} Apoptosis is commonly regarded as a non-inflammatory form of cell death, while pyroptosis may trigger low-grade inflammation.⁷¹ Pyroptosis is induced by extracellular and intracellular signals including bacterial and viral infections, exposure to toxins and specific chemotherapeutic agents/drugs.^{72–74} Compared to necrosis, pyroptosis produces cytoplasmic flattening resulting from plasma membrane rupture against explosive rupture. Caspase activation or granzyme release induces gasdermin N-terminal oligomerization and pore creation (1–2 μm) in plasma membrane, facilitating a mature form of IL-1 β /IL-18 (4.5 nm) and caspase-1 (7.5 nm) permeability.⁷⁵ The water infiltrating through pores promotes cell enlargement, osmotic lysis, plasma membrane rupture and IL-1 β and IL-18 release.^{25,76} The low molecular weight of 7-amino actinomycin (7-AAD), propidium iodide (PI) and ethidium bromide (EtBr) allows pyroptotic cell permeability. In contrast to pyroptotic cells, apoptotic cells maintain the integrity of the membrane, eliminating the formation of these dyes.⁷⁷ Surprisingly comparable to apoptotic cells, Annexin V indicates pyroptotic cells and attaches to phosphatidyl serine (PS). Thus, Annexin V cannot distinguish between apoptotic and pyroptotic cells. Apoptotic bodies are produced in apoptosis, whereas pyroptotic bodies are produced in pyroptosis.⁷⁸ Pyroptotic bodies are 1–5 μm in diameter, similar to apoptotic bodies.⁷⁹ However, a novel gasdermin-D (GSDMD) protein has been identified and characterized, which is typically in an auto-inhibitory state.⁸⁰ Following caspase splitting, GSDMD produces the N-terminal fragment (GSDMD-NT), which further inflates and ruptures cells. Therefore, GSDMD serves as the effector molecule that regulates the execution of pyroptosis-dependent cell death. Similar to the GSDMD pore-forming protein, GSDMA, GSDMB, GSDMC, DFNA5/GSDME and DFNB59 induce pyroptosis and membrane denaturation.^{81,82} Recently, Wang and colleagues proved that the mechanism of pyroptosis induced by the GSDMD-NT is consistent with the N-terminal domain of GSDME interacting with 4, 5-diphosphate phosphatidylinositol [PI (4,5) P₂], resulting in the perforation of liposomes and elimination of their phospholipid components.⁷⁴ In an article published in 1994 by Feng Shao and colleagues, pyroptosis was renamed gasdermin family-driven programmed necrosis in cells.²⁵ Recently, Chauhan and co-workers also observed that neutrophil elastase (NE) hydrolyzed GSDMD and triggered neutrophil pyroptosis.⁸³ Therefore, pyroptosis is another form of regulated cell death (RCD) that extensively depends on gasdermin protein family members for creating plasma membrane pores, often (but not typically) as a result of inflammatory caspase activation, according to the Nomenclature Committee on Cell Death (NCCD) in 2018.²¹

Molecular Mechanisms of Pyroptosis

Classical and non-classical inflammasome pathways, apoptotic caspases-dependent and granzymes-dependent pathways have been recognized as the primary signaling pathways that induce pyroptosis-dependent cell death.⁷⁹ Gasdermin proteins are the end mediators in these signaling pathways and are required to be cleaved by precursor caspases or granzymes.⁸⁴ Caspases are classified into inflammatory and apoptotic bodies, depending on their specific role and

function.⁸⁵ Caspases-1/4/5/11 are inflammatory caspases that trigger pyroptosis, inhibit the proliferation of pathogens and regulate the maturation and secretion of a variety of pro-inflammatory factors.⁸⁶ Activation of inflammatory caspases serves as the primary defense mechanism against infectious pathogens. Inflammasome is a multiprotein complex that initiates Caspase-1 activity downstream of the cell membrane.^{87–90} The activation of inflammatory Caspase-4/5/11 does not require a molecular complex and has been demonstrated to bind LPS directly.⁹¹ Apoptotic caspases primarily initiate and regulate the cellular mechanisms of apoptosis. Current investigations have shown the ability of proteases to cleave gasdermins, which results in triggering pyroptosis-driven cell death.⁹²

Classical Signaling Pathways

Classical pyroptotic cell death can be triggered by the formation of inflammasomes, leading to the cleavage of GSDMD and extensive release of pro-inflammatory factors including IL-1 β and IL-18.^{93,94} Inflammasomes are multi-molecular complexes that stimulate the adaptive immune response and protect the host against microbial infections.^{95–99} Inflammasomes can cause non-microbial diseases. Many studies indicate that inflammasomes and their cytokines are essential in oncogenesis including proliferation, metastasis and invasion.^{100–103} Activated cytosolic PRRs recognize pathogen- and danger-associated molecular patterns (PAMPs and DAMPs) to form the inflammasome.^{104,105} The activation of PRRs further triggers the downstream signaling pathways, leading to the production of type I interferons and the release of several pro-inflammatory cytokines. PRRs interact with pro-caspase-1 and ASC to produce inflammasomes upon cellular stimulation by signal molecules including bacteria and viruses.^{106–108} Nucleotide-binding oligomerization domain-like receptors (NLRs including NLRP1, NLRP3 and NLRC4), absent in melanoma 2 (AIM2) and pyrin are the most common PRRs.^{109,110} The N-terminal pyrin domain (PYD), nucleotide-binding oligomerization domain (NOD), LRR and CARD are components of NLRP1.¹¹¹ The PYD is essential for interacting with the ASC protein. NOD activates the signal by regulating the generation of ATP. LRR identifies and auto-inhibits ligands. CARD proteins then participate in the recruitment of pro-caspase-1. The anthrax fatal toxin, muramyl dipeptide and *Toxoplasma gondii* elements may trigger the activation of NLRP1.¹¹² NLRP3 includes N-terminal PYD, NOD and LRR without CRAD. Multiple factors including bacteria, viruses, fungi, uric acid, ROS, ATP and intrinsic damage signals activate the NLRP3 inflammasome axis.^{113,114} Extracellular ATP triggers the release of IL-1 β and activation of Caspase-1 through the stimulation of the P2X7 receptor, which further increases the efflux of K⁺ ions.¹¹⁵ The NLRC4 protein has an N-terminal caspase activation and recruitment domain (CARD), a central nucleotide-binding domain (NBD) and a C-terminal LRR domain. Flagellin and proteins of the type III endocrine system elicit a response from NLRC4.¹¹⁶ PYD and HIN-200 domains in AIM2 may recognize bacterial- or virus-derived double-stranded nucleotides.¹¹⁷ Pyrin protein comprises a PYD domain, two B-box domains and a C-terminal SPRY/PRY region. Pyrin mainly specifies bacterial toxins or effectors that inactivate host Rho guanosine triphosphatases.¹¹⁸ PRRs recruit pro-caspase-1 directly or indirectly through ASC to form Caspase-1-dependent inflammasome, which self-cleaves to stimulate Caspase-1. Active Caspase-1 splits IL-1 β and IL-18 precursors, releasing GSDMD-NT protein for pore creation and inducing inflammation and pyroptosis (Figure 1).¹⁰⁷ The host protects against pathogens by regulating classical inflammasome-mediated pyroptosis in immune cells.

Non-Classical Signaling Pathways

Human Caspase-4/5 (mouse ortholog Caspase-11) is not associated with the downstream sensory complexes in the non-classical pyroptotic signaling pathway. Human Caspase-4/5 (mouse orthologs Caspase-11) can be triggered by attaching directly to intracellular LPS via the N-terminal CARD in the non-classical pyroptotic signaling pathway, which excludes upstream sensory complexes.¹¹⁹ In contrast to dendritic cells, macrophages are sensitive to the oxidized phospholipid 1-palmitoyl-2-arachidonoyl-sn-glycero-3-phosphorylcholine (oxPAPC, a TLR4 agonist), which inhibits the non-classical inflammasome.¹²⁰ Caspase-4/5/11 may also split GSDMD into GSDMD-NT, which further polymerizes and creates pores on the cytoplasmic membrane region.^{90,121} The NLRP3/Caspase-1 pathway is required for the maturation and secretion of IL-1/IL-18, while Caspase-4/5/11 cannot cleave pro-IL-1/pro-IL-18.^{122,123} In addition, Caspase-4/5/11 splits GSDMD pore-forming protein, effluxing K⁺ and triggering NLRP3 inflammasome activation and pyroptosis.^{124,125} Yang et al revealed that pannexin-1 is another essential protein that stimulates Caspase-11-dependent non-classical pyroptotic cell death.¹²⁴ LPS stimulates Caspase-11 to cleave and alter Pannexin-1, releasing cellular ATP and initiating pyroptosis

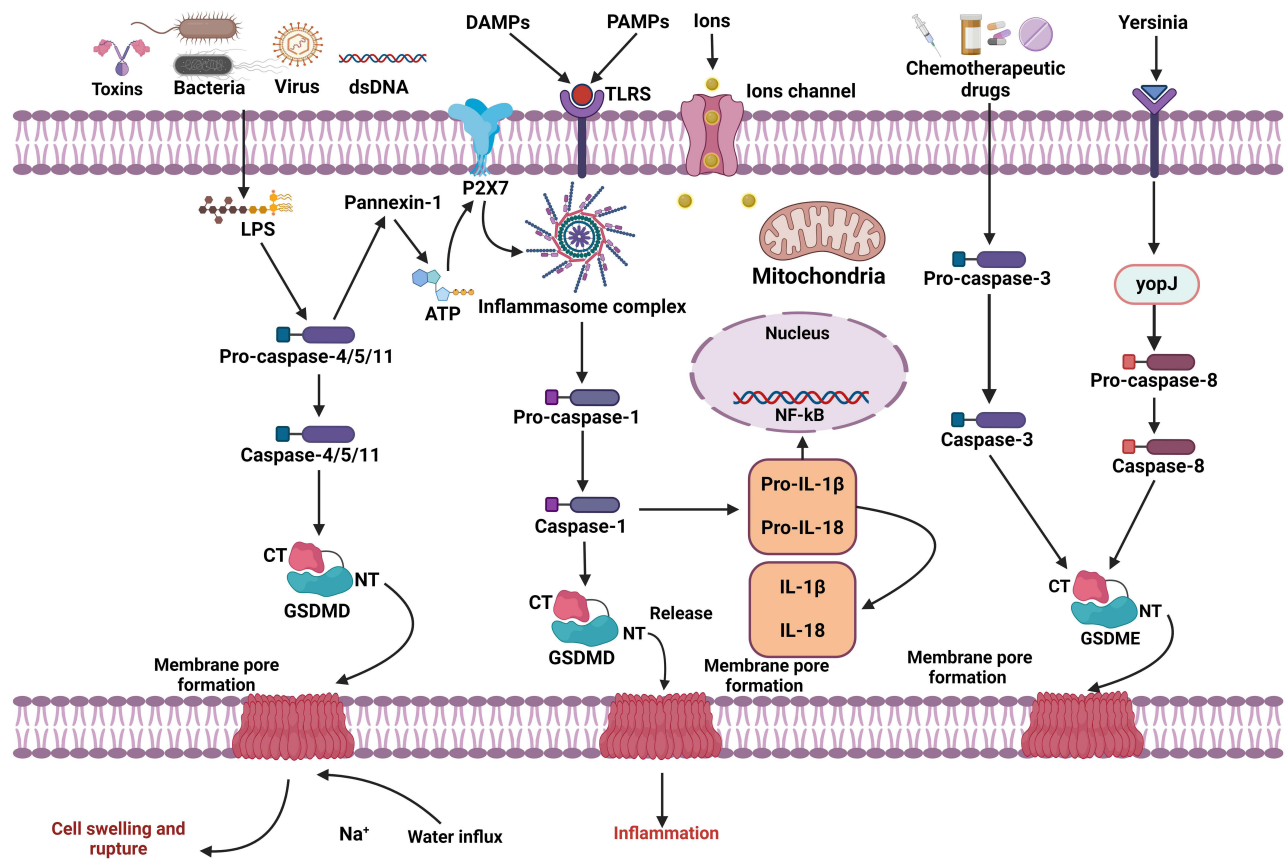


Figure 1 Cellular and molecular mechanisms of pyroptosis-related signaling pathways. Pyroptotic signaling pathways are mainly activated by the stimulation of damage-associated molecular patterns (DAMPs) or pathogen-associated molecular patterns (PAMPs), leading to the activation of a variety of inflammasome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

through the activation of the P2X7 receptor.¹²⁶ Interestingly, pannexin-1-deficient murine BMDMs may also induce K⁺ efflux and NLRP3 inflammasome-driven Caspase-1 activation with P2X7 independence, as reported in 2011.¹²⁷ Furthermore, eradicating pannexin-1 in mice protects against endotoxin shock, indicating that specific potassium (K⁺) ion channels regulate the non-classical NLRP3 inflammasome pathway.¹²⁴ The activation of the Caspase-11 pathway stimulates the NLRP3 inflammasome in non-classical pyroptotic signaling.¹²⁸

Alternative Signaling Pathways

Gasdermin proteins exhibit a high degree of structural conservation within their family. All gasdermins, excluding DFNB59, incorporate C-terminal and N-terminal domains and the N-terminus results in the activation of pyroptosis.⁸⁴ Researchers have found that chemotherapeutic drugs can significantly induce Caspase-3-mediated cleavage of GSDME with elevated GSDME expression, resulting in the generation of N-GSDME termini in tumor cells.^{74,129} Apoptosis-mediated caspases *Yersinia* infection in mouse macrophages have been shown to impede TGF- β -activated kinase 1 (TAK1) and trigger Caspase-8-driven GSDMD cleavage.^{130,131} Caspases-3/8 were believed to be incapable of generating gasdermin to induce pyroptosis. Further research found that *Yersinia* infection releases YopJ, which restricts TAK1 and triggers Caspase-8-mediated GSDMD cleavage in mouse macrophages.¹³² These findings contribute to the progress and expanding knowledge of pyroptosis-regulated cell death. Surprisingly, PD-L1 modulates TNF-induced apoptosis into pyroptosis in breast cancer cells.¹³³ In hypoxia, p-Stat3 enhances PD-L1 nuclear translocation and GSDMC transcription.

LPS commonly triggers pyroptosis by activating the Caspase-4/5/11 signaling pathways.¹³⁴ Researchers have discovered that macrophages activated by LPS undergo Caspase-8-mediated pyroptosis.¹³³ TNF- α activation induces the stimulation of Caspase-8 to lyse GSDMC, generate N-GSDMC and create membrane pores, leading to pyroptosis.¹³³ Nuclear PD-L1, Caspase-8 and GSDMC are required for TNF-induced pyroptosis in macrophages. Furthermore, antibiotics and chemotherapeutics can significantly promote pyroptotic death of breast cancer cells through the activation of the Caspase-8/GSDMC signaling axis.¹³³ The regulation of the NLRP3/Caspase-1-dependent pyroptotic signaling axis involves Caspase-6, which facilitates the interaction between receptor-interacting serine/threonine protein kinase 3 and Z-DNA protein 1.¹³⁵ However, the specific roles and functions of the other caspases involved in pyroptosis must be further investigated.

It was reported in 2020 that CAR T cells release GzmB, which activates the Caspase-3 signaling pathway in target cells.¹³⁶ Subsequently, the pyroptotic mechanism was mediated by Caspase-3 and GSDME, resulting in extensive pyroptosis. Recent findings show that GzmB directly cleaves GSDME molecules and triggers pyroptosis, promoting the anti-tumor immune response and restricting tumor formation.¹³⁷ It was subsequently demonstrated that Cytotoxic T lymphocytes (CTLs) and natural killer cells (NK) eliminated GSDMB-positive cells through the activation of pyroptosis. The fatal effects were triggered by the cleavage of GSDMB at the Lys229/Lys244 site by GzmA, which is derived from lymphocytes. Some tissues, especially the epithelium of the digestive tract and tumors express high levels of GSDMB.¹³⁸ The work by Zhou et al presented novel findings indicating that gasdermin may undergo hydrolysis by GzmA at a place other than aspartic acid, resulting in the creation of cytoplasmic pores.¹³⁹ These findings challenge the prevailing notion that Caspases can only initiate pyroptosis.

Role of Pyroptosis-Related Signaling Pathways in the Progression of DPN

DPN is a prevalent and devastating complication of DM.^{140–142} Extracellular matrix protein accumulation, excessive inflammation, axonal deterioration and unmyelinated fiber degeneration result in sensory conduction delays and long-term nerve injury in patients with DPN.¹⁴³ Multiple studies have indicated that the activation of pyroptosis and inflammasome are closely implicated in the pathogenesis and development of DPN.^{144–146} GSDMD is a recently discovered pore-forming protein belonging to the NLRP3 inflammasome family.^{76,147–150} Mastrocola et al found that the activation of the Caspase-1 pathway requires the cleavage of GSDMD1 in the inflammasome complex.¹⁵¹ Recently, Sun and colleagues performed Western blot assay to detect the protein expression level of GSDMD1 in SN tissue under chronic hyperglycemia conditions.¹⁴⁴ It was found that the diabetic group exhibited elevated GSDMD1 protein expression compared to the standard control group. More importantly, the authors indicated that GSDMD-dependent pyroptosis plays a progressive role in DPN. Thus, GSDMD-dependent pyroptosis induces peripheral neuropathy and nerve damage, leading to the development of DPN. GSDMD could be a pathophysiological biomarker for detecting the progression of DPN. However, further studies are extensively required to explore the contributory roles and functions of GSDMD-dependent pyroptosis in the pathogenesis and progression of DPN.

Inflammasomes are complexes comprising a sensor protein, an adaptor protein and an effector protein pro-caspase -1.^{95,152} Inflammasomes are categorized into two families such as the nucleotide-binding domain, leucine-rich repeat-containing proteins (NLRs) and the absence in melanoma 2 (AIM2)-like receptors (ALRs).¹⁵³ The activation of pro-caspase-1 results in the creation of cleaved-caspase-1, which cleaves pro-IL-1 β into IL-1 β , causing abnormal pain.¹⁵⁴ NLRP3 is a key molecule within the inflammasome, which can be activated by thioredoxin-interacting protein (TXNIP) and has attracted much attention in the field of pain.^{155–157} Upregulation of NLRP3 inflammasome in the sciatic nerve and dorsal root ganglion (DRG) is reportedly implicated in the pathogenesis and progression of DPN.¹⁵⁸ However, the epigenetic regulatory mechanisms underlying the modulation of NLRP3-dependent pyroptosis remain to be elucidated.

TXNIP is a multifunctional protein commonly called Vitamin D3 enhancing protein 1 or protein 2.^{159,160} Growing evidence indicates that TXNIP regulates cell proliferation, apoptosis, glucose and lipid metabolism.^{159–162} In addition, TXNIP regulates oxidative stress in the TRX system.¹⁶³ Elevated oxidative stress decreases the activity of TRX and promotes the expression and activation of TXNIP. Zhou et al observed the relationship between the NLRP3 and TXNIP.¹⁶⁴ ROS triggered TXNIP to dissociate from TRX and attach to the NLRP3 protein. TXNIP facilitates NLRP3 inflammasome activation and IL-1 β generation in T2DM progression.¹⁶⁵ P2RX7 is a purinergic type 2 receptor, which

regulates ligand-gated ion channels in the membrane region. High levels of millimolar ATP further activate the P2RX7 receptor during pathological conditions. Inflammasome activation is triggered by P2RX7 stimulation that facilitates membrane K⁺ efflux. Activation of P2RX7 by ATP leads to a prolonged elevation in intracellular Ca²⁺, resulting in the assembly of the inflammasome and subsequent activation of Caspase-1 signaling.¹⁶⁶ Excessive P2RX7 and NLRP3 inflammasome activation promote IL-1 β release in depression and diabetic complications including DPN.¹⁶⁷ Mustofa et al discovered that IL-1 β maturation and release are required to stimulate P2RX7 in LPS-primed mouse Schwann cells.¹⁶⁸ Caspase-1 splits GSDMD into the N-terminal proteolytic fragment (GSDMD-NT), creating cell membrane pores and inducing cell death by producing pro-inflammatory cytokines including IL-1 β and IL-18 that trigger an extensive inflammatory reaction. Caspase-1 pathway activation promotes GSDMD cleavage, GSDMD-NT production and IL-1 β release, leading to pyroptosis in high glucose-stimulated Schwann cells.¹⁹ Rogers et al discovered that Caspase-3 effectively triggered apoptosis and cleaved GSDME, resulting in the generation of N-terminal fragments (N-GSDME) and the initiation of pyroptosis.¹⁶⁹ Wang et al found that Caspase-3 cleavage formed N-GSDME, which interacted with 4, 5-diphosphate phosphatidylinositol (PI[4,5]P2) and perforated liposomes to release their contents.^{74,170} GSDME cleavage generates N-GSDME, which leads to the creation of membrane pores and pyroptosis. Moreover, GSDME-NT induces the permeabilization of the mitochondrial membrane, resulting in apoptosis through the mitochondrial intrinsic signaling pathways. Recent evidence explores that Caspase-3-dependent apoptosis can turn into pyroptosis-regulated cell death by cleaving the GSDME protein molecule.¹⁷¹ The GSDME-dependent pyroptosis signaling pathway is implicated in a variety of physiological and pathological processes.^{18,172–178} Li and colleagues have reported that GSDME-dependent pyroptosis contributes to inducing renal cell death and prolonged inflammation in diabetic neuropathy.⁵² The actual function and molecular mechanism of GSDME-dependent pyroptosis in neuropathic pain during DPN have remained unknown. Therefore, further studies are highly required to explore the pathophysiological roles of apoptosis-driven pyroptosis in DPN. However, SH-3 and WW domains interact with NLRP3 inflammasome.⁷² The NLRP3 inflammasome comprises three proteins: ASC, NLRP3 and pro-caspase-1. The NLRP3 inflammasome activates pro-Caspase-1, which further facilitates the generation of pro-inflammatory cytokines IL-1 β and IL-18 and triggers pyroptosis.¹⁷⁹

Inflammation exceeds the capacity of the hosts to combat pathogens effectively and hyperglycemia frequently results in sterile inflammation, which occurs with viral or bacterial pathogens. Recent studies indicate that inflammation significantly affects metabolic and hemodynamic dysfunction associated with diabetes.^{180,181} The activation of NLRP3 inflammasome further aggravates this perturbation, consistent with mounting evidence that OS induces prolonged inflammation.^{182–184} Metabolic disorders such as obesity induce the activation of NLRP3 by creating high amounts of glucose, palmitate and ceramide, which activate Caspase-1 and cause the cleavage of IL-1 β molecules.^{185,186} Inflammatory reactions such as IL-1 β release from the NLRP3 inflammasome, lead to the advancement of neuropathic pain. Therefore, NLRP3 inflammasome-mediated pyroptosis and inflammation induce the progression of DPN. A growing body of research suggests that decreasing the NLRP3 inflammasome provides a promising therapeutic approach for the treatment and management of DPN and pain.^{157,187,188}

P2X4 regulates endogenous DAMPs and stimulates NLRP3 inflammasome, which promotes the production and secretion of several pro-inflammatory cytokines including IL-1 β and IL-18. P2X4 receptors and downstream inflammatory cytokines trigger neuropathic pain in gliocytes. Interestingly, Kang and co-workers revealed that elevated P2X4 and NLRP3 expression further induces the progression of diabetic neuropathic pain in rat models.¹⁸⁷ NF- κ B pathway modulates cell proliferation and differentiation, morphogenesis, apoptosis and inflammasome activation, thereby triggering inflammation via enhancing the release of several cytokines, chemokines and adhesion molecules.¹⁸⁹ Several stimuli trigger NF- κ B and plays a regulatory role in the inflammatory response, stress response, pyroptosis and apoptosis. NF- κ B/NLRP3 inflammasome activation is a key factor in the development of DM.² The correlation between NLRP3 inflammasome activation and pyroptosis in DPN, which offered a theoretical foundation for regulating pyroptosis and exerting a protective effect by inhibiting the NF- κ B/NLRP3 signaling axis. NLRP3 inflammasomes have been profoundly attributed to the pathogenic mechanisms that induce T2DM and its related complications.⁴⁹ Ding et al revealed that NLRP3 inflammasome modulates endoplasmic reticulum stress, which regulates glucose tolerance, insulin resistance, inflammation and apoptosis in adipose tissue in DM.¹⁹⁰ It seems that the activation of NLRP3 inflammasome leads

to the maturation and the release of pro-inflammatory mediator IL-1 β in the sciatic nerve of diabetic rats. Furthermore, blood biochemistry demonstrates an increase in K⁺ and a decrease in Ca²⁺ in the plasma. The change in K⁺ concentration is considered an essential factor in NLRP3 inflammasome activation, because K⁺ efflux alone can potentiate IL-1 β maturation.^{191,192} The trends indicate a reduction in the Tnfr and CX3CR1 expression, although the effects were not significant in the sciatic nerve, probably due to the interindividual variability. Therefore, NLRP3-dependent pyroptosis and inflammation are a key player in inducing the progression of diabetic complications including DPN.

NF- κ B is a key regulator of HDAC2, which is implicated in triggering neuropathic pain.¹⁹³ Furthermore, HDAC2 significantly affects dorsal horn development after peripheral nerve injury.¹⁹⁴ Previous research has revealed that miR-183 mediates CCI-induced neuropathic pain.¹⁹⁵ Further microarray study indicated that miR-183 activates the TXNIP/NLRP3 inflammasome axis in peripheral nerve injury, further triggering neuropathic pain. The upregulation of the NLRP3 inflammasome has been reported to further aggravate neuropathic pain.¹⁸⁸ Mechanistically, Miao and colleagues investigated the contribution of NF- κ B p65-induced HDAC2 inflammatory response in neuropathic pain through the miR-183/TXNIP/NLRP3 signaling axis, which may aid in comprehending the pathophysiology of neuropathic pain in DM.¹⁹⁶ Zhou et al found that TXNIP/NLRP3 inflammasome activation may contribute to insulin resistance and hyperglycemic progression and regulate neurological pain through miR-23a in spinal glial cells.¹⁹⁷ Hao and colleagues proposed that the elevated TXNIP/NLRP3 complex may further promote the up-regulation of IL-1 β levels and accelerate inflammation.¹⁹⁸ In addition, Chen and colleagues have revealed that the TET2-TXNIP-NLRP3 inflammasome axis contributes to the progression of DNP.¹⁹⁹ The authors also showed that the secretion of Caspase-1-mediated IL-1 β pro-inflammatory cytokine triggers neuroinflammation during diabetic conditions in mouse models.¹⁹⁹ Therefore, TXNIP may produce a promising therapeutic target for the prevention and management of peripheral neuropathy in patients with diabetes. Zhang et al aimed to explore the presence of brain microglia activation in neuropathic pain and to analyze the effectiveness and underlying molecular mechanisms of glucagon-like peptide-1 receptor agonist (GLP-RA) on DPN through regulating microglia.¹⁹⁷ The authors revealed that downregulation of GLP-1RA could significantly induce inflammation by the activation of NLRP3 inflammasome in DPN, suggesting that NLRP3-dependent pyroptosis is a key contributor to the progression of DPN. Interestingly, a pioneering research reports that the GLP-1RA agonist mitigates the progression of diabetic neuropathic pain by obstructing the activation of NLRP3 inflammasome in brain microglia.¹⁹⁷

The inflammatory response is one of the essential pathologic features that link to the onset and progression of DPN.^{200,201} Inflammasome-driven inflammation contributes to a wide range of inflammatory reactions and targeting the NLRP3 inflammasome pathway is vital for the treatment of inflammation-associated diseases such as pulmonary disease, asthma, coronavirus disease 2019 and DPN.^{73,202–204} NLRP3 inflammasome is activated after stimulation, followed by a series of immune responses such as NLRP3 inflammasome proteins (molecule NLRP3, the adaptor molecule ASC and Caspase-1) production, Caspase 1-dependent release of the pro-inflammatory cytokines and pyroptotic cell death.²⁰⁵ Additionally, Schwann cell loss or apoptosis commonly occurred in both clinic DPN patients and experimental animals and inhibition of Schwann cell dysfunction ameliorated the progression of DPN. Therefore, the suppression of inflammasome activation and Schwann cell apoptosis might be a potential therapeutic approach for the treatment and management of DPN.

CXC motif chemokines have been implicated in neuronal injury and inflammatory reactions.²⁰⁶ Zhang et al performed a bioinformatics analysis utilizing data from the Gene Expression Omnibus (GEO) database to identify chemokine ligands (CXCLs) motifs associated with DPN.²⁰⁷ It was found that the expression level of CXCL2 was remarkably elevated in STZ-induced DPN rat sciatic nerve and HG-stimulated RSC96 cells.²⁰⁷ CXCL2 knockdown alleviates hyperglycemia-induced pyroptosis and inflammation by decreasing Caspase-3 activity in vitro and in vivo. In HG-treated RSC96 cells, CXCL2 knockdown increased cell viability and reduced apoptosis due to cleaved Caspase 3–9 expression. Furthermore, CXCL2 knockdown restricted the activation of NLRP3 inflammasome and mitigated the release of pro-inflammatory cytokines such as IL-1 β and IL-18. Under the HG condition, NLRP3 inflammasome activator nigericin enhances inflammasome activation by abolishing the inhibitory effects of CXCL2 knockdown. Therefore, NLRP3 inflammasome activation and prolonged inflammation further induce the pathogenesis and progression of DPN.

Glycogen synthesis kinase-3 β (GSK3 β) is a serine/threonine kinase that is consistently active and primarily regulated through phosphorylation at the serine residue.^{208–210} The activity of GSK3 β is elevated in the spinal cord of an animal model of neuropathic pain.²¹¹ Accumulating studies have revealed that inhibiting the activation of GSK3 β alleviates the generation of pro-inflammatory cytokines and triggers the production of anti-inflammatory cytokines in cortical microglia stimulated with LPS in vitro.^{209,210,212} GSK3 β can play an important role in activating NLRP3 inflammasome-mediated pyroptosis. Therefore, GSK3 β /NLRP3-dependent pyroptosis further induces the development of diabetic neuropathic pain (DNP). NLRP3 inflammasome may recognize ROS generated by normal or malfunctioning mitochondria in the same cell. It has been suggested that elevated levels of ROS are detected by a complex containing TRX and TXNIP, which results in the complex dissociation.²¹³ Accumulating evidence has shown that ROS generation stimulates tissue inflammation and induces NLRP3 inflammasome overactivation, leading to the progression of a variety of diseases.^{214,215} Recently, Wang et al showed that ROS overproduction further contributes to the progression of DNP by activating the TXNIP-NLRP3-NR2B signaling axis.²¹⁶ In summary, these findings suggest that the activation of pyroptosis-regulated signaling pathways plays a contributory role in the pathogenesis and progression of DPN (Figure 2). Therefore, a more comprehensive investigation of the role and underlying molecular mechanisms of the pyroptosis-driven signaling pathway in the progression and pathogenesis of DPN is highly warranted.

ROS is known to play a prominent role in the pathogenesis of a variety of diseases including DM.²¹⁷ Hyperglycemia, metabolic disorders, increased oxidative stress and mitochondrial dysfunction may exacerbate peripheral nerve damage in people with diabetes. NLRP3 is an inflammasome activated by ROS, which acts as a second messenger in the activation of the inflammasome and is believed to stimulate pyroptosis by activating the NLR/Caspase-1 signaling complex.^{192,218} Under normal conditions, the anti-oxidant enzymes can eliminate ROS during cell metabolism to

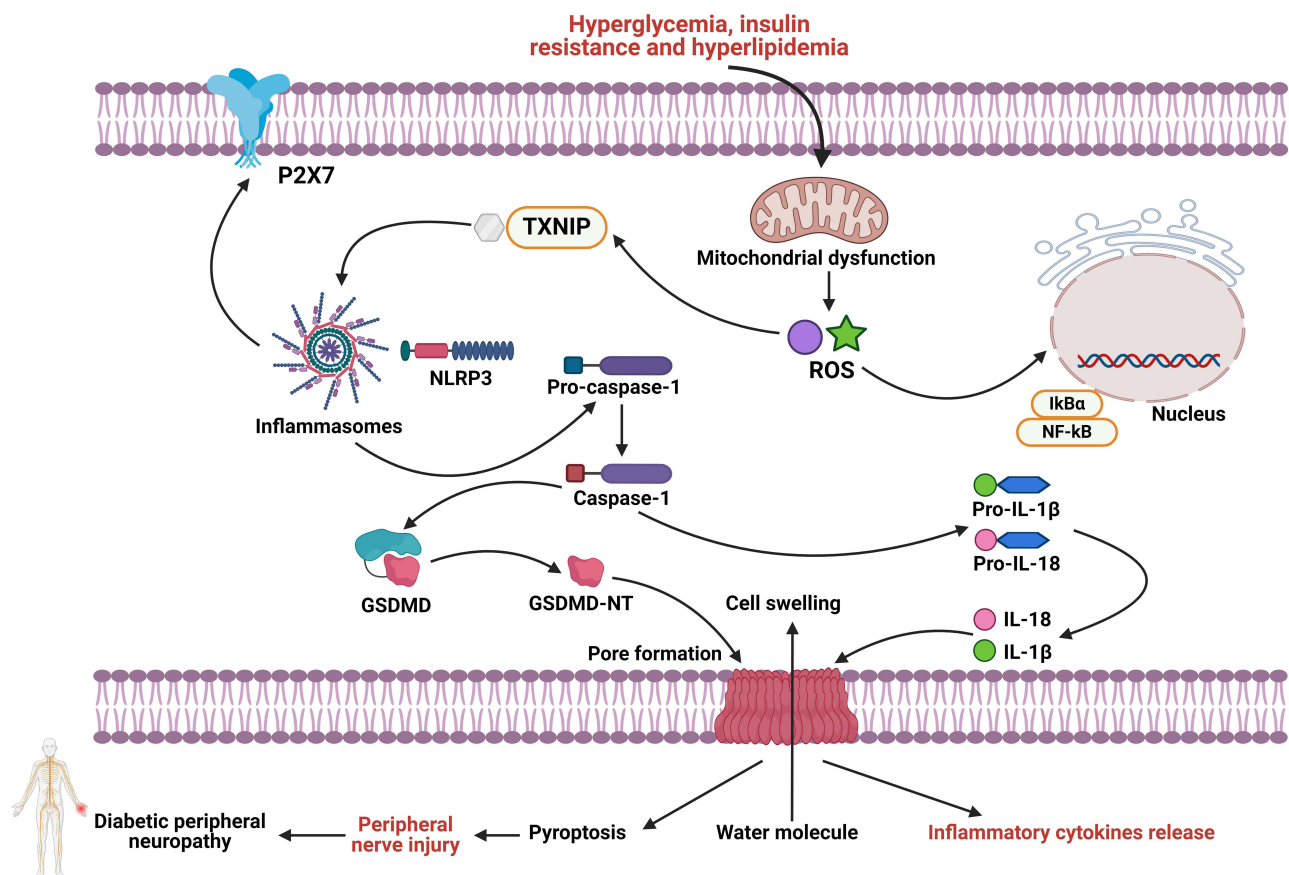


Figure 2 Pathophysiological roles of pyroptosis-dependent cell death in the course of the pathogenesis of DPN. Hyperglycemia, insulin resistance and hyperlipidemia stimulate NLRP3/ASC inflammasome signals, further activating pro-caspase-1 into Caspase-1 form. Then, activated Caspase-1 induces the generation and maturation of inflammatory factors including IL-1 β and IL-18, resulting in low-grade inflammation and peripheral nerve injury, eventually advancing DPN.

maintain the balance of ROS generation and elimination.²¹⁹ The accumulation of ROS results in oxidative stress and cellular disorders such as upregulation of lipid peroxidation and cell apoptosis when endogenous anti-oxidant defense cannot eliminate it in time.²¹⁹ The overproduction of ROS can further activate the expression of NF- κ B, which is a crucial transcription factor in inflammation, stress response and cell growth and survival.²²⁰ The hyperglycemia, hyperinsulinemia and insulin resistance of diabetes enhanced oxidative stress, leading to excessive cytokine generation in DPN.²²¹ It has been found that ROS-dependent NLRP3 inflammasome activation induces downstream pro-inflammatory responses, aggravating chronic inflammatory nerve damage.²²² Emerging studies have shown that inflammatory factors infiltrate peripheral nerves and chronic inflammatory reactions impair the normal function of peripheral nerves.^{223,224} Under inflammatory conditions, the cascade release of pro-inflammatory factors such as IL-6, IL-1 and TNF- α activates glial cells, which further express receptors for pro-inflammatory mediators and participate in inflammatory immune responses. Second, pro-inflammatory factors produce a cascade-like reaction, resulting in inflammation. Finally, the release of substance P and excitatory amino acids continues to depolarize dorsal horn neurons, leading to pain sensitivity and persistent pain.^{225–227} Therefore, ROS-dependent inflammasome activation and inflammatory reactions may further contribute to the pathogenesis and progression of DPN.

Inhibition of Pyroptosis-Dependent Signaling Pathways for the Therapeutic Regulation of DPN

Jinmaitong (JMT) is a traditional Chinese compound with a long history of use and has shown significant clinical effectiveness in the prevention and treatment of DPN.²²⁸ Previous studies have indicated that JMT lowers blood glucose and lipid metabolism, reduces nerve conduction velocity in DPN patients, alleviates numbness, cold and pain and enhances nerve transmission.²²⁹ Further studies reveal that JMT inhibits oxidative stress and alleviates DNA damage to sciatic nerves (SNs) in STZ-induced diabetic rats.²³⁰ Prior research has demonstrated that JMT targets peripheral neuronal apoptotic genes such as Bcl-2 and Caspase-3.²³¹ Xie et al reported that JMT exerts promising anti-oxidative effects to protect against SNs injury in STZ-induced diabetes.²³² Recent evidence suggests that overactivation of NLRP3 inflammasome plays an essential role in the pathogenesis of DM and its complications.^{49,123,190,233,234} The NLRP3 inflammasome includes the apoptosis-associated speck-like adaptor protein (ASC), NLRP3 and pro-caspase-1. Upon activation, NLRP3 becomes ligated to ASC and then binds to pro-caspase-1. This binding promotes cleavage and transformation of pro-caspase-1 to Caspase-1, which further facilitates the generation and maturation of pro-inflammatory factors IL-1 β and IL-18 and activates pyroptosis.^{73,235} TXNIP has been reported to be upstream of NLRP3 and the complexes of these two proteins are necessary for inflammasome activation.¹⁶⁴ Intriguingly, Sun et al demonstrated that JMT alleviates the pathogenesis and progression of DPN by inhibiting the activation of the TXNIP/NLRP3 inflammasome axis and mitigating pyroptosis-mediated inflammatory reactions in STZ-induced diabetic rats.¹⁴⁴ JMT could suppress the expression level of TXNIP and NLRP3 inflammasome proteins, as demonstrated by immunostaining and Western blot analysis of SNs in diabetic rats. In addition, the protein expression Cleaved-Caspase-1 was higher and the Caspase-1 precursor level was downregulated in the diabetic rats compared to the control rats, indicating the activation of the Caspase-1-dependent pyroptosis is a key contributor to the progression of DPN. It was also demonstrated that JMT decreased the protein expression level of GSDMD1 and suppressed the activation of the Caspase-1 signaling pathway in the STZ-induced diabetic rat model. Therefore, JMT could be a new ant-pyroptotic drug candidate for alleviating DPN (Figure 3). This research supports the therapeutic application of JMT as a traditional Chinese medicine in DPN treatment. However, further studies are highly required to investigate the primary active components of JMT targeting other pyroptosis-related signaling pathways in future research endeavors.

Loganin (LGN) is an iridoid glycoside obtained from the fruit of *Cornus officinalis*. A number of investigations have confirmed the promising anti-oxidant, anti-inflammatory and hypoglycemic actions of LGN, a compound traditionally applied in the treatment of DN.^{236–238} Past research indicates that LGN can remarkably alleviate diabetes-mediated anxiety and depression by lowering blood glucose and mitigating pro-inflammatory cytokines.²³⁹ Further investigation revealed that LGN stimulates the release of neurotrophic factors, which reduce mesencephalic neuronal death, ameliorate neurite damage and inhibit the activation of oxidative stress.²⁴⁰ Wang and co-workers have shown that LGN exerts

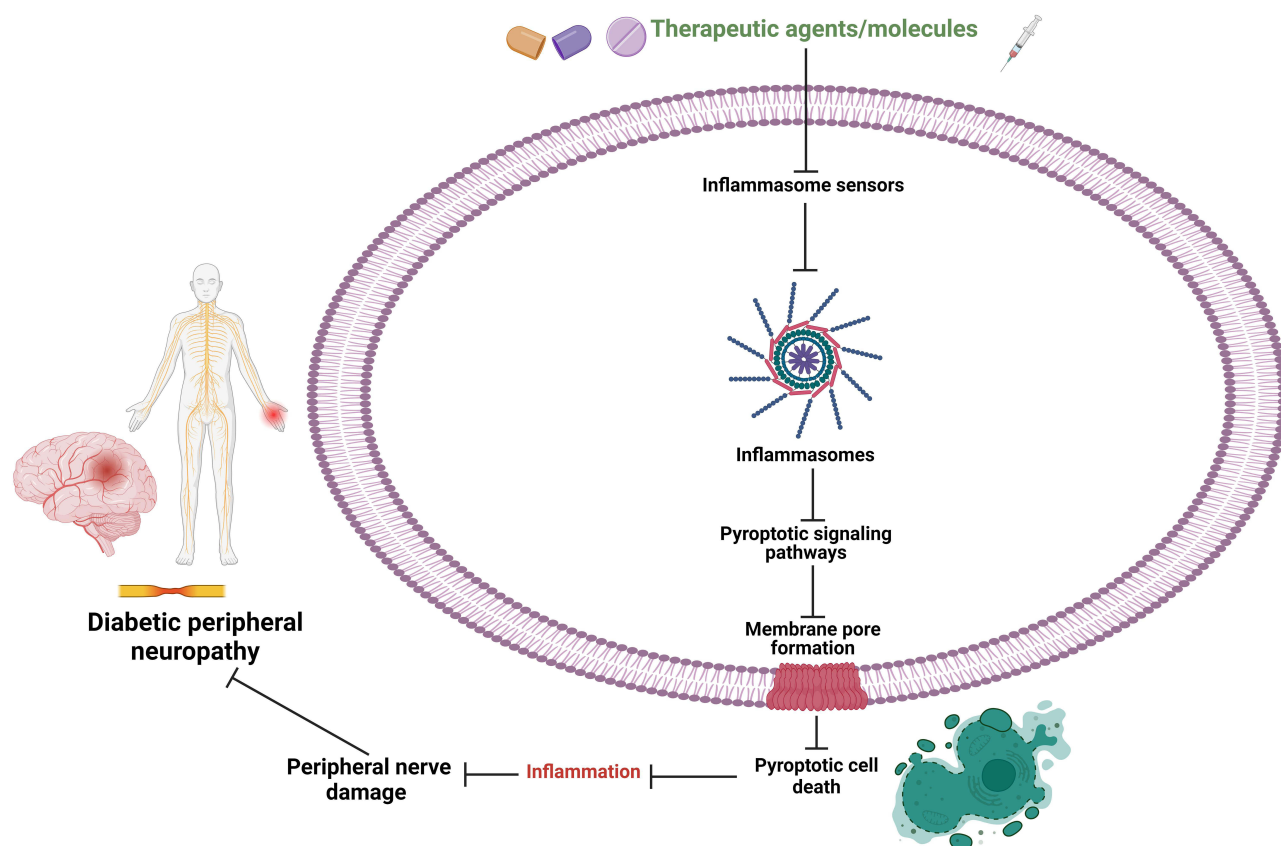


Figure 3 Schematic illustration of therapeutic implications by several experimental compounds/drugs targeting inflammasome and pyroptosis-related signaling pathways for novel therapeutic strategies in the treatment and management of DPN.

remarkable neuroprotective actions by alleviating neuronal pyroptosis in rats with cerebral hemorrhage.²⁴¹ Recently, Kong et al reported that LGN ameliorates diabetic renal injury by obstructing the activation of NLRP3 inflammasome-dependent pyroptosis.²⁴² Li and co-workers also indicated that LGN treatment attenuated OGD/R-induced cardiomyocyte pyroptosis by alleviating cell membrane damage and inhibiting the pyroptosis-related protein expression level of Cleaved Caspase-1, IL-1 β and IL-18.²⁴³ Furthermore, LG intervention blocked GLP-1R/NLRP3 pathway activation in OGD/R-stimulated H9C2 cardiomyocytes by promoting GLP-1R expression and obstructing NLRP3 inflammasome stimulation.²⁴³ Intriguingly, LGN treatment mitigates ROS production, inhibits NF- κ B-P2RX7-TNXIP protein expression and alleviates NLRP3 inflammasome-mediated RSC96 cell damage. Previous research has indicated that LGN mitigates the generation of inflammatory mediators including IL-1 β by restricting the activation of NF- κ B signaling pathway in the spinal cord tissue of PDN rat models.²⁴⁴ In terms of neuroprotection, LGN attenuates mesencephalic neuronal apoptosis, neurite nerve damage and oxidative stress through the enhancement of neurotrophic factors.²⁴⁰ Furthermore, LGN has been demonstrated to mitigate neuropathic pain by ameliorating Schwann cell demyelination in rats with chronic contraction injury.²⁴⁵ High glucose levels adversely affect apoptosis, metabolism, proliferation and migration of Schwann cells.²⁴⁶ Accumulating evidence suggests that the overproduction of ROS caused by high glucose induces the activation of oxidative stress and inflammation, a recognized mechanism in the molecular pathogenesis of DPN.^{168,247} The study by Cheng and colleagues provides the first evidence that LGN treatment inhibits the activation of NLRP3 inflammasomes and subsequent pyroptosis by inhibiting the formation of ROS in high-glucose-treated RSC96 Schwann cells.¹⁹ Intriguingly, the authors revealed that LG treatment attenuates pyroptosis-driven inflammatory reactions and downregulates NF- κ B-P2RX7-TNXIP protein expression, protecting RSC96 cells against NLRP3 inflammasome overactivation.¹⁹ More importantly, the authors showed that LGN treatment could significantly suppress the mRNA and protein expression level of NLRP3, ASC, Caspase-1 and GSDMD and pro-inflammatory factors IL-1 β and IL-18 in high-

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

Compounds/Agents	Targeting of Inhibiting Pyroptosis-Related Signaling Pathways	References
Jinmaitong	TXNIP/NLRP3/Caspase-1/GSDMC1/IL-1 β and IL-18	[144]
Loganin IL-18	ROS/NF-kB/P2RX7/TNXIP/NLRP3/ASC/Caspase-1/IL-1 β and	[15]
nCurcumin	Caspase-1/GSDMD/IL-1 β and IL-18	[248]
Vincamine	ROS/NF-kB/NLRP3	[249]
GLP-1R antagonist	NLRP3/Cleaved Caspase-1/IL-1 β	[250]
Açai berry	NLRP3/ASC/Caspase-1/IL-1 β	[251]
Swertiamarin	NOX5/ROS/NLRP3/ IL-1 β and IL-18	[252]
Dexmedetomidine	ROS/P2X4/NLRP3/IL-1 β	[187,253]
Salidroside	P2X7/TXNIP/NLRP3/IL-1 β and IL-18	[254,255]

glucose-stimulated Schwann RSC96 cells.¹⁹ It was proved that LGN can alleviate hyperglycemia-induced peripheral nerve injury by suppressing pyroptosis-dependent cell death (Table 1). Therefore, LGN could be a novel pharmacological drug candidate for suppressing NLRP3 inflammasome-dependent pyroptosis and inflammation in the treatment of DPN.

Curcumin (CUR), a bioactive compound found in turmeric, exhibits wide-ranging therapeutic actions in the treatment of a variety of diseases.^{256–260} Numerous pieces of evidence indicate that CUR possesses promising anti-inflammatory, anti-oxidant and neuroprotective properties that attenuate the pathogenesis and progression of diabetic complications including DPN.^{261–264} Recently, Zhang and co-workers explored that CUR alleviates the progression of DPN by enhancing the expression of NGF in rat models.²⁶⁵ Dwivedi et al evaluated the pharmacological effects of nCUR combined with long-acting subcutaneous insulin (INS) in STZ-induced rats.²⁴⁸ Current studies have explored that apoptosis-regulated signaling pathways further lead to the activation of pyroptosis.^{71,171,266} Pioneering research performed by Elsayed and co-workers showed that CUR alleviated apoptosis and inhibited glial activation with modulation of Nrf2/HO-1 and NF-kB signaling in STZ-induced diabetic spinal cord central neuropathy. Therefore, CUR has possible therapeutic targets attenuating Caspase-3-dependent pyroptosis to alleviate and treat DPN. More specifically, the authors revealed that nCUR alone or in combination with insulin alleviates neuropathic pain by obstructing the activation of NLRP3 inflammasome and mitigating the release of inflammatory factors, indicating that nCUR exerts promising pharmacological targets suppressing inflammasome-mediated cell death for ameliorating the progression of DPN. Therefore, CUR could be a potent anti-pyroptotic drug candidate in alleviating DPN. However, the pharmacological effects and underpinning molecular mechanisms of CUR targeting Caspase-1/GSDMD-dependent pyroptosis and inflammation in ameliorating DPN remain elusive. Further studies must be executed to explore the pharmacological target of CUR in other pyroptosis-related signaling pathways in the pharmacological treatment of DPN.

Vincamine (VIN) is a monoterpenoid indole alkaloid obtained from *Catharanthus roseus*, commonly called *Vinca rosea*. Growing evidence suggests that VIN exerts multiple biological functions including anti-coagulant, memory-enhancing, nootropic, hypoglycemic, hypolipidemic, vasodilatory and anti-oxidant properties.²⁶⁷ Previous studies have shown that VIN possesses practical antidiabetic activities by elevating serum insulin and C-peptide levels in streptozotocin (STZ)-induced diabetic rats.^{267–269} Du et al report that GPR40 agonist VIN enhances glucose homeostasis in T2 diabetic mice.²⁷⁰ The author and co-workers found that VIN could protect the function of INS-832/13 cells by regulating G-protein-coupled receptor 40 (GPR40)/cAMP/Ca²⁺/IRS2/PI3K/Akt signaling pathways, while increasing glucose-stimulated insulin secretion (GSIS) by modulating GPR40/cAMP/Ca²⁺/CaMKII signaling pathway, which reveals a novel mechanism underlying GPR40-mediated cell protection and GSIS in INS-832/13 cells.²⁷⁰ Xu and colleagues found that VIN intervention impeded sciatic nerve myelin sheath injury and improved foot skin IENF density in DPN mice.²⁴⁹ The authors showed that VIN administration significantly ameliorated neurological dysfunctions in DPN mice.

The authors showed that VIN administration improved the blood flow velocities and perfusion areas of foot pads and sciatic nerve tissues in DPN mice.²⁴⁹ Moreover, VIN administration suppressed NLRP3 inflammasome activation through either β -Arrestin2 or β -Arrestin2/I κ B α /NF- κ B signaling, improved mitochondrial dysfunction through CaMKK β /AMPK/SIRT1/PGC-1 α signaling and alleviated oxidative stress through Nrf2 signaling pathway in the sciatic nerve tissues of DPN mice and LPS/ATP-treated RSC96 cells.²⁴⁹ The beneficial effects of VIN were abolished by GPR40-specific knockdown in dorsal root ganglia and sciatic nerve tissues. This pioneering review supports that VIN could treat DPN by pharmacologically activating GPR40. A pharmacological treatment for DPN may be achieved by targeting GPR40 activation through the suppression of the NLRP3 inflammasome. Therefore, VIN may be an effective pharmacological drug candidate in inhibiting the activation of NLRP3 inflammasome-dependent pyroptosis for the alleviation of DPN. However, further research is highly warranted to explore the anti-pyroptotic effects of VIN in the treatment and management of DPN.

Glucagon-like peptide-1 (GLP-1) is an incretin hormone that regulates a wide range of biological functions through a specific receptor named the GLP-1 receptor (GLP-1R).²⁷¹ GLP-1RAs such as exendin-4 and liraglutide are common drugs used for the treatment of T2D.^{272,273} GLP-1RA administration has been demonstrated to alleviate diverse CNS disorders including Alzheimer's disease, Parkinson's disease and cerebral ischemia by attenuating microglial activation.^{274–276} New research by Wang and colleagues found that activating microglial GLP-1R in the spinal cord alleviates inflammatory reactions, neuropathic pain and bone cancer.²⁷⁷ Pioneering research also showed that intracerebroventricular GLP-1RA administration suppressed Iba-1 expression and microglia activation in the brain and thalamus of DNP rats.²⁵⁰ A previous study by Mohiuddin et al showed that GLP-1 signaling protects peripheral nervous system neurons from oxidative insult in DPN. The therapeutic potential of GLP-1RAs on DPN was investigated in depth using the cellular oxidative insult model applied to the dorsal root ganglion (DRG) neuronal cell line. Interestingly, Zhang et al. GLP-1RA administration suppressed the classical pyroptosis-regulated mRNA and protein expression levels of IL-1 β , NLRP3 and Cleaved Caspase-1 in LPS-stimulated BV2 microglia.²⁵⁰ The authors showed that microglia were activated in the cortex and thalamus of diabetic rats.²⁵⁰ Intracerebral administration of GLP-1RA or minocycline alleviated heat and mechanical allodynia in rats.²⁵⁰ Moreover, the activation of brain microglia was attenuated in DNP rats by intracerebroventricular administration of GLP-1RA. The expression of NLRP3 in brain microglia, found by RNA sequencing, was reduced in DNP rats by administration of GLP-1RA. These findings suggest that GLP-1RAs have neuroprotective potential, which is achieved by their direct actions on DRG neurons by inhibiting the activation of inflammasome signaling pathways. Therefore, GLP-1RA could be a potential therapeutic avenue for attenuating diabetic neuropathic pain via suppressing the activation of NLRP3 inflammasome.

The fruit of the South American acai palm (*Euterpe oleracea* Mart), which is abundant in anti-oxidants, has recently gained interest as a functional diet. Açai berry has been applied in several studies as a potential anti-hyperglycemic and anti-inflammatory agent that prevents various injuries to physiological systems.^{278–282} Multiple evidence indicates that açai berries consist of a variety of polyphenolic compounds including pelargonidin, cyanidin, malvidin, delphinidin, peonidin, dihydrokaempferol, quercetin, luteolin and chrysoeriol.^{283,284} Many studies reveal that carotenoids such as carotene, lycopene, astaxanthin, lutein and zeaxanthin are also enriched in açai fruit pulp.^{283,285,286} Açai extract also presented beneficial effects against age-related oxidative stress in a d-Gal-induced aging model in human erythrocytes. Since aging of these cells is related to oxidative stress and *E. oleracea* presents anti-oxidant properties, this functional food could improve the functions of erythrocytes. The homeostasis of the organism as a whole counteracts age-related changes.²⁸⁷ The bioactive components of açai berry extract possess multiple beneficial effects through modulation of OS, inflammation, autophagy, Nrf2 activity in the hippocampus and frontal brain and NLRP3 inflammasome activation.^{288,289} Cadona et al report that açai extract exerts remarkable anti-neuroinflammatory actions by modulating the ROS/NLRP3/Caspase-1 inflammasome signaling axis.²⁹⁰ Pioneering research by Impellizzeri and co-workers suggests that administration of 500 mg/kg dose of açai berry extract ameliorates cognitive impairment by restricting the activation of NLRP3/ASC/CASP signaling axis in both sciatic nerve and spinal cord tissues of STZ-induced DPN mouse models.²⁵¹ The authors clearly showed that açai berry reduces mast cell degranulation and histological damage in diabetic neuropathy, improves physiological defense against ROS, modulates the NLRP3/ASC/CASP signaling axis, mitigates inflammation and inhibits oxidative stress. Thus, suppressing the NLRP3/ASC/CASP signaling pathway could be a potential

therapeutic target in the treatment of DPN. Therefore, açai berry could be a novel therapeutic agent suppressing pyroptosis-dependent cell death for the treatment and management of DPN.

Swertiamarin (SWN) is an iridoid compound mainly derived from *Enicostemma littorale* Blume, a plant with decades of traditional application in the treatment of diabetes, swelling, rheumatism and abdominal ulcers.²⁹¹ A growing body of evidence indicates that SWN exerts promising anti-oxidant, hepatoprotective, anti-hyperlipidaemic, anti-nociceptive, anti-edematogenic and free radical scavenging properties.²⁹² SWN has recently been shown to decrease hyperinsulinemia and hyperglycemia in rat models of diabetes and obesity.^{293,294} Previous studies have indicated that SWN can significantly improve the insulin resistance effect of patients with T2DM by activating the AMPK pathway, thereby restoring and enhancing the insulin sensitivity of hepatocytes.²⁹⁵ Furthermore, SWN significantly mitigates NF- κ B-driven inflammation in arthritis animal models.²⁹⁵ Saravanan et al demonstrated that SWN suppresses inflammation in adjuvant-induced arthritis by restricting NF- κ B/I κ B and JAK2/STAT3 transcription factors.²⁹⁶ Recently, Wang and co-workers have revealed that SWN effectively attenuated DPN in rats by restricting the NOXS/ROS/NLRP3 signaling pathway.²⁵² The expressions of NOXS, ROS, NLRP3 and inflammatory factors in DPN rats were detected using ELISA and the protein expressions of NOXS, ROS and NLRP3 were also detected with Western blotting.²⁵² It was shown that SWN downregulated the protein expressions of NOXS, ROS and NLRP3, maintained the balance of inflammatory factors, increased the pain threshold and nourished nerves to treat DPN in the rat models.²⁵² Therefore, SWN could be a promising therapeutic drug candidate for attenuating the pathogenesis and progression of DPN by suppressing the activation of NLRP3-dependent pyroptosis. However, further investigations are highly required to clarify the pharmacological targets of other pyroptosis-driven signaling pathways that alleviate DPN. Additional studies are also needed to explore the advantages and disadvantages of the two based on equivalent efficacy and the underlying molecular mechanisms to provide active and effective prevention and treatment and new low-toxic and harmless drug targets for DPN patients.

The P2X4 receptor and pro-inflammatory cytokines in gliocyte-mediated signaling pathways contribute to the progression of neuropathic pain.²⁹⁷ DAMPs downstream of P2X4 activate the NLRP3 inflammasome, which further matures and secretes cytokines, disrupting cells and tissues.^{298,299} P2X4 could modulate the production of proinflammatory cytokines such as IL-1 β by activating NLRP3 inflammasome via endogenous DAMPs. Dexmedetomidine (DEX) is a recently developed α 2-adrenergic receptor agonist that selectively ameliorates sympathetic nervous system functions and delivers significant anxiolytic effects.³⁰⁰ Past studies have indicated that DEX alleviates pain and slightly reduces breathing rate.^{301,302} Recently, pioneering research by Lin and co-workers has shown that administration of DEX mitigates DPN by suppressing the activation of oxidative stress and dysfunction of the mitochondria via regulating the microRNA-34a/SIRT2/S1PR1 axis.³⁰³ DEX has been revealed to alleviate spinal nerve damage by modulating the activation of the P2X4 receptor.³⁰⁴ In addition, Zhang and co-workers have demonstrated that the administration of DEX can effectively DPN-related behaviors and nerve cell damage by suppressing Caspase-3/9-dependent cell death and ROS production in diabetic rats.²⁵³ Previous studies have demonstrated that DEX exhibits potential anti-inflammatory activity, suggesting its potential to alleviate diabetes-induced inflammation.^{305,306} Inflammatory cytokines play an important role in neuronal damage, especially in painful neuropathy. The elevated levels of P2X4 and NLRP3 in STZ-treated rats suggested that cytokines are involved in the pathogenesis and progression of neuropathy.³⁰⁷ The exact mechanism of high glucose-induced P2X4 expression is not fully understood. It has been reported that hyperglycemic stimulation can activate the JAK/STAT signaling pathway by promoting the activity of transcription factor STAT1, thereby increasing the expression of P2X4.³⁰⁸ Numerous evidence indicates that overactivation of NLRP3 inflammasome may regulate the inflammation process of DM and related complications.^{49,309} In addition, P2X4 receptors could mediate the secretion of pro-inflammatory cytokine IL-1 β .³¹⁰ Kang et al investigated the impacts of P2X4/NLRP3 signaling on the development of DNP in rats.¹⁸⁷ The authors showed that the expression of P2X4 and NLRP3 in DNP rats was markedly reduced after treatment with DEX.¹⁸⁷ This finding is consistent with the involvement of the P2X4 receptor in the development of DNP. The NLRP3 and IL-1 β upregulation findings suggest they intervene in inflammatory factor activation. The authors revealed that DEX administration suppressed the expression levels of P2X4, NLRP3 and IL-1 β , suggesting that DEX modulates inflammasome overactivation and mitigates inflammation by blocking the activation of P2X4 receptor.¹⁸⁷ Therefore, DEX is more likely to target P2X4/NLRP3-dependent pyroptosis in alleviating DNP.

However, the pharmacological target and underlying molecular mechanisms of DEX suppressing the Caspase-1/4/5/11 inflammasome-dependent pyroptosis are unknown. Therefore, more studies are highly required to analyze the pharmacological targets of DEX in suppressing pyroptosis-dependent cell death for promising therapeutic avenues in the treatment of DPN.

Salidroside (SLD), a phenylpropanoid glycoside molecule, is the active component in the root of *Rhodiola rosea*, which has been employed to alleviate high-altitude sickness for decades.^{311,312} Previous studies have shown that SLD exerts significant anti-oxidant, anti-inflammation and stress reducer and anti-cancer, cardioprotection and immune enhancer properties.^{313,314} Accumulating studies have demonstrated that SLD significantly improves glucose homeostasis in diabetic animals by alleviating inflammation and increasing cellular metabolic flux.^{314,315} Current research indicates that SLD exerts remarkable anti-pyroptotic effects in the treatment of multiple disorders including Parkinson's diseases, Alzheimer's diseases, etc.^{46,316–320} Prior investigation suggests that SLD alleviates neural injury in STZ-induced T2D in rats.³²¹ Moreover, Hu and co-workers have shown that SLD alleviates chronic constriction injury-induced neuropathic pain and inhibits the activation of TXNIP/NLRP3 signaling pathway.²⁵⁴ Recently, Liu et al reported that SLD mitigates ulcerative colitis by suppressing macrophage pyroptosis and restoring Th17/Treg balance.³²² Chai et al also demonstrated that SLD ameliorates depression by suppressing NLRP3-mediated pyroptosis via inhibiting the activation of P2X7/NF- κ B/NLRP3 signaling axis.³¹⁸ In addition, Wang and colleagues have revealed that SLD mitigates neuroinflammation and enhances functional recovery following spinal cord injury by regulating microglia polarization.³²³ Intriguingly, Zheng and co-workers also demonstrated that SLD administration remarkably improved hyperglycemia, reduced insulin resistance and mitigated peripheral nerve injury and neuropathic pain in diabetic rats.³²⁴ Mechanistically, it was shown that SLD mediated AMPK pathway activation and restricted NLRP3 inflammasome activation in DRGs.³²⁴

Numerous studies have revealed the relevance of several ATP receptor subtypes to inflammation and neuropathic pain.^{325–329} In particular, P2X7 receptors (P2X7Rs) are important cell surface regulators of several key inflammatory molecules including TNF- α , IL-1 β , IL-18 and IL-6. Moreover, P2X7Rs are upregulated in inflammation and neuropathic pain states.³²⁵ Therefore, antagonists or modulators of P2X7Rs may have therapeutic potential as novel anti-inflammatory and anti-nociceptive agents. P2X7Rs could be among the pivotal targets of SLD for its anti-nociceptive and anti-inflammatory actions. Ni and colleagues have found that the effects of SLD on the altered pain behaviors, pro-inflammatory cytokines and the levels of P2X7 receptors in DM rats had a similar dose-response relationship, showing significant effects.²⁵⁵ The notion that inhibition of P2X7 Rs may play an important role in conveying antinociceptive and anti-inflammatory effects of SLD is strongly bolstered by previous studies, demonstrating the crucial roles of P2X7 receptors in triggering inflammation and neuropathic pain. Knocking out the P2X7 gene in mice results in the absence of inflammatory and neuropathic behavioral hypersensitivities.³²⁶ P2X7 Rs are up-regulated in injured nerves in patients with neuropathic pain and the gain-of-function in the P2X7 receptors is associated with pain hypersensitivity in osteoarthritis, post-mastectomy pain and diabetic neuropathic patients.³²⁹ Past studies confirmed that selective P2X7R antagonists have therapeutic potential for the treatment of both inflammation and peripheral pain.³³⁰ Therefore, SLD attenuated nociception in diabetes probably through inhibiting both expression and activation of P2X7Rs and subsequently reducing the release of pro-inflammatory cytokines. These findings suggest that SLD could be an effective pharmacological drug suppressing pyroptosis for a novel therapeutic avenue in the treatment and management of DPN.

Conclusions, Current Challenges and Future Prospectives

Understanding the regulatory mechanisms of inflammasome activation is essential to regulate the prolonged inflammatory response following nerve injury, enhance peripheral nerve regeneration and alleviate inflammatory reactions in the patients with DM. Numerous research investigations have revealed that NLRP3 inflammasome activation results in peripheral nerve injury-induced pain in peripheral nerve injury models. The comprehension of the function and regulatory mechanisms of NLRP3 inflammasome in peripheral nerve regeneration during DM is currently constrained. The underlying molecular mechanisms of Schwann cell-macrophage coordination in the inflammatory response, nerve development and regeneration are also undefined. Further investigation must be conducted to analyze the contributory role of pyroptosis in Schwann cells and macrophages. Inhibiting excessive activation of the NLRP3 inflammasome and

pyroptosis can enhance peripheral nerve injury repair based on its roles and regulatory mechanisms in the central and peripheral nervous systems. Several existing inhibitors have unanticipated adverse effects due to non-specificity. Therefore, further research is necessary to improve the selectivity of pyroptotic inhibitors. Researchers have recently concentrated on the effective experimental compounds/drugs targeting inflammasomes and pyroptotic signaling pathways. Natural bioactive compounds, traditional medicines and other natural products may present new therapeutic perspectives and guidance for the treatment and management of DPN. The therapeutic effects of these compounds/drugs are currently confined to the pre-clinical and clinical research stages. More pharmacological agents, particularly non-coding RNAs, require immediate investigation to evaluate and confirm their effectiveness and pharmacological actions for the treatment and management of DPN. Therefore, further research is necessary for a deeper comprehension of the mechanisms underpinning pyroptosis, which will contribute to our understanding of the role of pyroptosis-mediated cell death in the pathogenesis of DPN and facilitate the development of effective therapeutic agents that target pyroptotic signaling pathways.

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Disclosure

The authors declare no competing interests in this work.

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