Advances in the Relationship Between Pyroptosis and Diabetic Neuropathy

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Pyroptosis is a novel programmed cell death process that promotes the release of interleukin-1β (IL-1β) and interleukin-18 (IL-18) by activating inflammasomes and gasdermin D (GSDMD), leading to cell swelling and rupture. Pyroptosis is involved in the regulation of the occurrence and development of cardiovascular and cerebrovascular diseases, tumors, and nerve injury. Diabetes is a metabolic disorder characterized by long-term hyperglycemia, insulin resistance, and chronic inflammation. The people have paid more and more attention to the relationship between pyroptosis, diabetes, and its complications, especially its important regulatory significance in diabetic neurological diseases, such as diabetic encephalopathy (DE) and diabetic peripheral neuropathy (DPN). This article will give an in-depth overview of the relationship between pyroptosis, diabetes, and its related neuropathy, and discuss the regulatory pathway and significance of pyroptosis in diabetes-associated neuropathy.

Keywords: diabetes, neuropathy, pyroptosis, neuroinflammation, oxidative stress

INTRODUCTION

Diabetes is a metabolic disorder characterized by hyperglycemia and insulin resistance. Under hyperglycemia condition, advanced glycosylation end products (AGEs) and reactive oxygen species (ROS) are significantly increased and promote a series of adverse reactions, such as chronic inflammation and oxidative stress, and eventually induce a series of complications. Pyroptosis is a newly discovered form of programmed cell necrosis. Different from the pathogenesis of apoptosis, pyroptosis is activated through the lysis of caspase-1/4/5/11 and activation of the gasdermin D (GSDMD) signaling pathway, as well as the release of inflammatory cytokines, interleukin-1β...
(IL-1β), and interleukin-18 (IL-18), which ultimately leads to the cell swelling and rupture. At present, a large number of studies showed that pyroptosis is an important regulatory mechanism of diabetic complications, especially in diabetic neuropathy (DN) (Zhan et al., 2020; Cheng et al., 2021). This article will systematically review the relationship between pyroptosis, diabetes, and DN, and provide the theoretical basis for further exploring the regulatory role of pyroptosis in DN.

**PYROPTOSIS**

The discovery of pyroptosis will be traced back to 1986. Friedlander (1986) firstly found that treatment of anthrax lethal toxin (ALT) for primary macrophages of mouse can induce a large area of cell death and quickly release the contents. In 1992, the mice infected with the Gram-negative bacterium *Shigella flexneri* were found to have severe death of macrophage (Zychlinsky et al., 1992). The death of macrophages caused by these bacterial infection is dependent on caspase-1, but not caspase-3, that is required for apoptosis (Hilbi et al., 1998). In order to distinguish the cell apoptosis caused by DNA degradation, the condition of caspase-1 activation, release of pro-inflammatory factor, and cell swelling, rupture, and death after bacterial infection was named as “Pyroptosis” (Shi et al., 2017; Cookson and Brennan, 2001). The pyroptosis can be commonly divided into classical pathway and non-classical pathway.

**Classical Pathway**

When the body is stimulated by danger signals, it will assemble caspase-1 and activate inflammasomes, then use GSDMD as a physiological substrate to promote the degradation of cell membranes (He et al., 2015), lastly lead to cell death and the release of mature IL-1β and IL-18 (Ali et al., 2017; Błażejewski et al., 2017). This caspase-1-dependent pyroptosis is known as the “classical pathway” (Figure 1). The assembly of inflammasomes is a key step in the process of pyroptosis. Inflammasome can recognize pathogen-associated molecular patterns (PAMPs), danger-associated molecular patterns (DAMPs), and homeostasis-altering molecular processes (HAMPs) through pattern recognition receptors (PRRs) (Liston and Masters, 2017; Silveira et al., 2017). After that, PRRs are activated and recruit the adaptor apoptosis-associated speck-like protein containing a caspase-recruitment domain (ASC) (Yu et al., 2020). ASC contains two domains: pyrin domain (PYD) and CARD (Xue et al., 2019). Therefore, recruitment of ASC can cause homotype CARD–CARD interaction to each other, which promotes PRRs to combine with pro-caspase-1 and become a mature caspase-1. In addition, PRRs containing CARD can directly bind to CARD of pro-caspase-1 to form an ASC-free inflammasome complex (Hoss et al., 2017). Now, a variety of PRRs have been found to exist in the composition of inflammasomes, such as nucleotide-binding oligomerization domain-like receptors (NLRs) protein family, Toll-like receptors (TLRs) and retinoic acid inducible gene I-like receptors (RLRs), etc. (Jaeger et al., 2015). Activation of inflammasomes will promote the accumulation of GSDMD. Subsequently, active caspase-1 will cleave GSDMD to form C-gasdermin domain and N-gasdermin domain (He et al., 2015). At the same time, caspase-1 secures pro-IL-1β and pro-IL-18 to become the mature IL-1β and IL-18, then secretes into the cell and promotes inflammatory response (Itani et al., 2016). The active N-gasdermin domain in mammalian cells aggregates on the cell membrane and combines with lipids to form a large number of pores with a diameter of about 10–21 nm (Chen et al., 2016; Liu et al., 2016; Sborgi et al., 2016). The formation of these pores destroys the intracellular osmotic pressure, leads to cells swelling and eventually dissolution, resulting in cell pyroptosis. Due to the N-gasdermin domain of GSDMD has a pore-forming activity on cell membrane (Kovacs and Miao, 2017), pyroptosis is also defined as gasdermin-mediated programmed necrosis (He et al., 2015).

**Non-classical Pathway**

Lipopolysaccharide (LPS) directly connects with caspase-11 to decompose GSDMD precursor form (pro-GSDMD) to form N-gasdermin, then induces the formation of membrane pore, which is named as “non-classical pathway” (Figure 1; Yokoyama et al., 2018). This may be because the intracytoplasmic PRRs are CARD-containing receptor proteins, which can recognize LPS, then recruit and aggregate the activated caspase-11 multi-protein complex (Kayagaki et al., 2011). In fact, caspase-11 itself can recognize LPS by binding to the specific and high-affinity lipid A of LPS (Knodler et al., 2014). This binding triggers the oligomerization of caspase-11, and activates its proteolytic activity. The caspase-4 and caspase-5 in human is homologous to caspase-11 in mice, which also directly binds to LPS (Casson et al., 2015; Viganò et al., 2015). Thus, LPS-induced activation of inflammasomes can also be happened in human innate immunity. There are studies showed that caspase-11 in mice or caspase-4/5 in human can combine with LPS and activate to cleave the GSDMD, result in the production of pores in the plasma membrane and K+ ion efflux, and ultimately triggering the activation of NLRP3 inflammasome (Baker et al., 2015; Rühl and Broz, 2015).

**THE REGULATORY ROLE OF DIABETES ON PYROPTOSIS DURING NEUROPATHY**

Pyroptosis is a double-edged sword to the homeostasis of body. On the one hand, it helps to protect the multicellular organisms from bacterial infections; on the other hand, excessive pyroptosis may also lead to chronic inflammation (Lu et al., 2020). It is found that excessive pyroptosis leads to rapid rupture of plasma membrane, and excessive release of pro-inflammatory cytokines and chemokines, such as tumor necrosis factor-α (TNF-α), IL-1β, and interleukin-6 (IL-6), leading to neuroinflammation (Ramesh et al., 2013). Neuroinflammation triggers a series of secondary injuries after neuropathy and eventually leads to neuronal death (Simon et al., 2017). The levels of IL-1β and IL-18 were significantly elevated in cerebrospinal fluid, brain tissue, and plasma of patients with the infection of central
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FIGURE 1 | Classical pathway and non-classical pathway of pyroptosis. PRRs, pattern recognition receptors; ASC, apoptosis-associated speck-like protein containing a caspase-recruitment domain; LPS, lipopolysaccharide; NLRS, nucleotide-binding oligomerization domain-like receptors; PAMPS, pathogen-associated molecular patterns; DAMPS, danger-associated molecular patterns; HAMPS, homeostasis-altering molecular processes.

Pyroptosis is also an important regulatory mechanism in the occurrence and development of diabetes and its complications (Mamun et al., 2021). Diabetes is accompanied by chronic inflammation. Pyroptosis happens to be an inflammatory-mediated programmed cell death. Diabetes with long-term inflammation can cause excessive pyroptosis in the body (Wang et al., 2020). It had been reported that hyperglycemia can activate PYD containing NLRP3 inflammasome, and promote the transformation of pro-caspase-1 to caspase-1, thereby expedite the development of pyroptosis (Schroder et al., 2010). It was demonstrated that hyperglycemia initiates caspase-11/4 and GSDMD-dependent pyroptosis, and then leads to podocyte loss during diabetic nephropathy (Cheng et al., 2021).

Pyroptosis may also be an important regulatory target of DN. Persistent inflammation caused by excessive secretion of pro-inflammatory factors and peroxides is an important pathological mechanism underlying DN. Therefore, pyroptosis is very likely to be a key factor during the occurrence and development of DN. Here, we will review the regulatory mechanism of pyroptosis in DN as following (Figure 2).

Mitochondrial Dysfunction-Induced Oxidative Stress

Normal mitochondrial function plays a crucial role in maintaining the cellular homeostasis of body (Sas et al., 2018). Mitochondrial dysfunction produces a large amount of ROS. ROS is considered to be a key regulator of inflammatory response, which significantly promotes the activation of NLRP3 inflammasome in neurological diseases (Zhou et al., 2016). Gao et al. (2019) found that echinacoside (ECH) significantly reduces ROS level, improves the potential of mitochondrial membrane,
blocks nuclear factor kappa-B (NF-κB) activation, then inhibits the activation of NLRP3 inflammasome, and lastly promotes locomotor functional recovery of rat after SCI. Additionally, diabetes-associated hyperglycemia, hyperinsulinemia, and insulin resistance results in mitochondrial damage, excessive production of ROS, and ultimately leads to redox imbalance in cells, which is the important pathological mechanism of diabetes-associated complications (Shi et al., 2020). It is reported that the co-treatment of high glucose and LPS can promote the production of ROS, aggravate NLRP3 inflammasome and caspase-1-dependent pyroptosis in H9C2 cardiomyocyte (Qiu et al., 2019). Moreover, excessive ROS may cause the dissociation of thioredoxin-interacting protein (TXNIP) and thioredoxin (TRX) (Strowig et al., 2012). Then, TXNIP combines with NLRP3 through a leucine-rich repeat domain (LRR) to form an active inflammasome complex (Han et al., 2018). The overexpression of TXNIP induces the activation of NLRP3 inflammasome in the injured spinal cord and triggers the neuronal cell death dependent on pyroptosis (Yanagisawa et al., 2019). It has been proposed that galectin-3 (Gal-3) can promote the neuroinflammatory response in SCI model by regulating the ROS/TXNIP/NLRP3 signaling pathway (Ren et al., 2019). It has also been found that Loganin inhibits the formation and activation of NLRP3 inflammasome and reduces pyroptosis by inhibiting oxidative stress and NF-κB–P2X7–R–TXNIP signaling pathway in diabetic peripheral neuropathy.
and their secreted proinflammatory factors (TNF-α and neuronal dysfunction (Nayak et al., 2014). Our previous studies have found that mitochondrial damage-induced excessive ROS level is an important induction mechanism of diabetes-induced nerve damage, such as diabetes-associated cognitive dysfunction (Wang B. N. et al., 2021), diabetic embryonic neural tube malformation (Wang F. et al., 2017), and DPN (Li et al., 2021). Thus, the improvement of mitochondrial function and inhibition of oxidative stress are of great significance to the reduction of pyroptosis, the survival of nerve cells, and the recovery of nerve injury under diabetic condition.

Microglial Activation
During the occurrence and development of neurological diseases, a variety of cells in the nervous system participate in the regulation of pyroptosis, such as macrophages/microglia and astrocytes. Microglial activation is found to initiate and maintain the inflammatory response during brain diseases, such as infectious nerve injury, acute CNS damage, and neurodegenerative diseases (Kumar et al., 2016; Xian et al., 2016; Song et al., 2017). Microglial cells are macrophage-like cells that reside in the CNS, which are the main cellular mediator of innate immune response (David et al., 2015) and pyroptosis (Vande Walle and Lamkanfi, 2016) after injury. They will continuously monitor the designated brain/spinal cord area, and participate in the regulation of the development of the CNS and later neuroprotective processes (Nayak et al., 2014). Microglial cells express a large amount of PRRs, which is responsible for the early identification of PAMPs and DAMPs, such as TLR, NLR, and triggering receptor expression on myeloid cells 2 (TREM2) (Fu et al., 2014). Over-activation of microglial cells promote the over-production of cytotoxic factors, such as TNF-α, IL-1β, IL-18, IL-6, ROS, and nitric oxide (NO), etc., then, it will be converted to M1 type and lead to neuroinflammation, oxidative stress and neuronal dysfunction (Nayak et al., 2014). Our previous studies have found that microglial cells were activated after SCI, and their secreted proinflammatory factors (TNF-α and IL-6) and M1 phenotypic marker protein (CD86) were significantly increased in the spinal cord from SCI group (Wu et al., 2021). Inhibition of microglial activation has a positive effect in the ameliorating pyroptosis and protecting neurons. MCC950, a selective inhibitor of NLRP3 inflammasome, significantly reduces neuroinflammation, brain edema, pyroptosis, and neurological dysfunction by inhibiting microglial activation in animals with brain trauma (Ismael et al., 2018; Xu K. Y. et al., 2018). In addition, CD73 [also known as ecto-5′-nucleotidase (NT5E)], an AMP hydrolase, is also found to inhibit the activation of NLRP3 inflammasome and GSDMD, reduce the pyroptosis of microglial cells, and play an important anti-neuroinflammatory effect in SCI recovery (Xu et al., 2021; Xu et al., 2021). The excessive activation of microglial cells is also a principal element of DN. Overaggregation of microglial cells is observed in both non-diseased and diseased regions of patients with diabetes mellitus complicated with acute cerebral infarction (Li et al., 2011). Moreover, hyperglycemia can activate NF-kB to increase the inflammatory response of microglial cells around the injury area of spinal cord, and aggravate secondary injury after SCI in diabetic mice (Kobayakawa et al., 2014). It is also found the significantly increase of activated microglial cells in the brain of APP/PS1xdb/db mouse (Ramos-Rodriguez et al., 2015). Moreover, high glucose stimulation can also activate NLRP3 inflammasome, trigger the pyroptosis of retinal microglial cell and lead to diabetic retinopathy (DR) (Huang et al., 2021). In a word, the over-activation of microglial cells is an important regulatory mechanism for pyroptosis in DN. Therefore, inhibition of microglial overactivation may be an important way to inhibit excessive pyroptosis in the process of DN.

Astrocyte Activation
In addition to macrophages/microglia, astrocytes are also the important effector of inflammation in the nervous system (Karve et al., 2016; Shrivastava et al., 2017). Astrocytes have a series of functions, including glutamate uptake, synapse formation, structural support, and immune defense (Barreto et al., 2011). After injury, astrocytes show the features of hypertrophy, proliferation, and form the long protuberance, which will extend to the severely injured site and participate in the formation of dense astrocyte scar (Cregg et al., 2014). Maintaining the normal function of astrocytes plays an important role in the nerve function and repair after injury, especially in the diabetic environment. In a mouse model of type 2 diabetes, it is found that excessive activation of astrocytes in spinal cord can lead to mechanical allodynia (Liao et al., 2011). Reactive astrocytes can produce a large amounts of pro-inflammatory mediators to exacerbate the inflammatory response. The inflammasomes, such as NLRP1, NLRP3, NLRP6, and NLRC4, have been found in astrocytes (Walsh et al., 2014; Gustin et al., 2015; Freeman et al., 2017; Zhang et al., 2020). Recent studies further found that the difficulty in SCI recovery and thromboembolic stroke is closely related to the excessive activation of the NLRP1 inflammasome in astrocytes (Abulafia et al., 2009; de Rivero Vaccari et al., 2012). Moreover, Zhang et al. (2020) also found that the expression of NLRP6 in astrocytes is significantly increased under oxygen glucose deprivation/reoxygenation (OGD/R) condition, and leads to the excessive inflammation and pyroptosis of nerve cells. Chronic hyperglycemia is shown to activate astrocytes, interfere with the normal nerve growth, and induce the activation of inflammasomes (Rahman et al., 2020). This result suggests that active astrocytes may be likely to be an important target during diabetes leading to the cell pyroptosis in nervous system. Thus, it is worth further exploring whether inhibition of astrocyte activation is a potential therapeutic strategy for DN treatment.

Ion Channel
The imbalance of intracellular ion homeostasis is a common caused event of cell death, which has been found to have a certain relationship with pyroptosis. It has been reported that K⁺ efflux is involved in the activation of inflammasomes (Gong et al., 2018). Purinergic ligand-gated ion channel seven receptor (P2X7-R) is a ligand-gated ion channel that mediated by potassium ion carriers and ATP (Alves et al., 2014). The P2R-X ion channel can activate the assembly of inflammasomes and subsequent caspase-1 through triggering K⁺ efflux and Ca²⁺ influx, and amplify the pro-inflammatory signals (Savio et al., 2018). Previous studies
have shown that deletion of P2X7R reduces the incidence of diabetes, indicating that P2X7R may be an important target to reduce the occurrence and development of diabetes-related complications (Zhang et al., 2018). Overexpression of P2X7R can result in K+ efflux and increase membrane permeability in db/db mouse periodontitis model and LPS stimulated macrophages model, thereby increasing the possibility of pyroptosis (Karmakar et al., 2016; Zhou et al., 2020). In addition, P2X7R/NLRP1/caspase-1 is also one of the important pathway of inflammatory cascade in damaged neurons from diabetic patients. In the study of diabetic hippocampal neuron damage, it is proposed that the inhibition of P2X7R/NLRP1/caspase-1 pathway can alleviate nerve damage (Jing et al., 2021). Moreover, there is also evidence that the initiation of P2X7R ion channel is also a key regulatory factor in the microglial activation. Overexpression of P2X7R is found and involved in the microglial activation in primary cultured hippocampal microglial cells (Monif et al., 2010), which may be a another pathway to trigger pyroptosis. In summary, the P2X7R ion channel may also be an important target for regulating pyroptosis in DN.

The transient receptor potential melastatin-related 2 (TRPM2) channel is also involved in the abnormal activity of Ca2+ ion channel. TRPM channel, a non-selective cation channel, plays a vital role in the process of development, proliferation, and death of cell. It has been reported that high glucose can induce oxidative stress through TRPM2 channel to promote Ca2+ influx (Wuensch et al., 2010). Under high glucose condition, the TRPM2 channel mediated promotion of Ca2+ influx is closely related to the overproduction of ROS and TXNIP-mediated activation of NLRP3 inflammasome (Tseng et al., 2016). TRPM2 can also inhibit LPS-induced pyroptosis in macrophages by inhibiting the production of ROS (Wang H. et al., 2017). Recently, DN has been paid more and more attention. TRPM channel may also be a potential target for reducing the oxidative stress and subsequently the activation of NLRP3 inflammasome during diabetes associated nerve injury.

**Autophagy**

Autophagy is also involved in the regulation of pyroptosis. Autophagy activation is found to inhibit the activation of NLRP3 inflammasome in both brain injury (He et al., 2017) and liver injury (Han et al., 2016). In a normal organism, autophagy can reduce the occurrence and development of pyroptosis through removing damaged mitochondria and inhibiting the maturation and secretion of IL-1β and IL-18 (Nakahira et al., 2011; Yang F. et al., 2019). There is a study showed that autophagy activation by adrenomedullin (ADM) can promote the ROS–AMPK–mTOR axis and consequently alleviate pyroptosis in interstitial cells (Li et al., 2019). In addition, the relationship between autophagy and pyroptosis has also been payed more and more attention in diabetes-associated complications. It has been reported that metformin can activate AMPK/autophagy to inhibit the activation of NLRP3 inflammasome and pyroptosis, thereby exerting cardioprotective and anti-inflammatory effects in diabetic cardiomyopathy (Yang F. et al., 2019). At the same time, the study also indicates that mild hypothermia may inhibit the pyroptosis through enhancing autophagy after diabetic cerebral ischemia, thus alleviating brain injury (Tu et al., 2019). However, the molecular mechanism underlying diabetes-induced autophagy to reduce pyroptosis needs to be further investigated. Overall, autophagy may also be key regulatory factor between DN and pyroptosis.

Base on the above studies, it suggests that diabetes regulate pyroptosis through nerve cells, mitochondria, ion channels, and autophagy, and thus participate in the regulation of nerve injury repair. These regulatory mechanisms are a systemically regulated process from the cellular level to the molecular level. They have mutual cross-talking among them rather than exist independently. For example, both ion channel destruction and mitochondrial function damage can promote oxidative stress. Moreover, the destruction of ion channel can directly activate pyroptosis by promoting mitochondrial function damage, which is not conducive to nerve injury repair in diabetic condition. Additionally, the action of diabetes on microglial cells and astrocytes also has a common characteristic, and excessive inflammatory response is the ultimate caused factor for the development of pyroptosis. Therefore, the treatment of DN requires comprehensive consideration of various factors, and comprehensively inhibits the occurrence and development of pyroptosis from the cellular level to the molecular level.

**PYROPTOSIS IN DIABETIC NEUROPATHY**

Despite the continuous improvement of global medical standards, diabetes still affects the life quality of people of the world. According to the International Diabetes Foundation, more than 700 million people will be diagnosed with diabetes by 2045 (Che et al., 2020). Diabetes is a chronic metabolic abnormal disease, and long-term hyperglycemia can lead to a series of complications through a combination of mechanisms, such as excessive inflammation, increased AGE, elevated cellular stress, and mitochondrial damage. Diabetes leads to a variety of neurological diseases, such as diabetic encephalopathy (DE), diabetic neurodegeneration, and DPN. Chronic hyperglycemia has been shown to affect cognition, signal transduction, neurotransmission, and synaptic plasticity, leading to nerve damage or neuropathy (Chen et al., 2018; Fang et al., 2018). Pyroptosis is involved in the pathogenesis of DN (Figure 2). Next, we will review the relationship between pyroptosis and series of DN.

**Diabetic Encephalopathy**

In recent years, there are more and more attention has been paid to diabetes-induced brain injury. Diabetes aggravates the inflammatory response after brain injury with manifested as neurodegeneration, cerebral infarction, and progressive cognitive decline (Erukainure et al., 2019; Liu et al., 2020). Compared with patients with normal brain injury, patients with DE have more severer disease, slower recovery, and higher mortality (Sun et al., 2016). Some studies have shown that microglial cells play a specific role in neuronal injury after ischemic injury. Excessive
activation of microglial cells produces a large amount of proinflammatory cytokines, lead to neuron necrosis and apoptosis, thereby exacerbating diabetic cerebral ischemia/reperfusion (I/R) injury (Huang et al., 2015). Furthermore, it is found that IncRNA-Fendrr is highly expressed in diabetic brain I/R model and microglial cells treated with high glucose or hypoxia/reoxygenation (H/R), which protects the ubiquitination and degradation of NLRC4 protein through E3 ubiquitin ligase HERC2, increases the pyroptosis of microglial cells, and thus aggravates diabetic brain I/R damage (Wang L. Q. et al., 2021). These studies indicate that pyroptosis plays a important role in the occurrence and development of DE, especially the NLRP3 inflammasome pathway. There are some studies showed that STZ-induced diabetic mice cause hippocampal neuronal apoptosis and pyroptosis in an NLRP3-dependent manner, and lead to depression-like behavior (Li et al., 2020). In the research on the therapeutic effect of melatonin, it was found that melatonin can regulate the miR-214-3p/caspase-1 and miR-214-3p/ATG12 pathways, and inhibit the neuronal pyroptosis and excessive autophagy with the evidence of decreased levels of NLRP3, caspase-1, GSDMD-N, IL-1β, LC3, Beclin 1, and ATG12 (Che et al., 2020). Hong et al. (2018) also found that MCC950, a specific inhibitor of NLRP3, can improve cerebral I/R injury in diabetic mice and increase the survival rate of diabetic ischemic stroke mice. Moreover, it was found that hyperglycemia promotes the assembly and activation of NLRP1 inflammasome, and initiates neuroinflammation and neuronal damage (Meng et al., 2014), suggesting NLRP1 may also be a potential treatment to prevent hyperglycemia-related brain damage, which is further confirmed by Jing et al. (2021) study. They found that Naofucong can significantly inhibit the P2 × 7R/NLRP1/caspase-1 pathway and improve the HT22 hippocampal neuron damage induced by high glucose (Jing et al., 2021). Furthermore, in the studying of the gestational diabetes, it was showed that the aggregation of chemotactic proteins in the offspring’s brain tissue induces the neuronal loss, increases the aggregation of macrophages, and activates the pyroptosis of macropages in a ChemR23-dependent manner, which leads to neurological damage and cognitive impairment in the offspring (Liang et al., 2019). In a word, DE is an extremely complicated process, and the specific role of pyroptosis in various of encephalopathy needs to be further explored (Table 1). However, it is certain that NLRP3 and NLRP1 are important caused factors in the development of DE. Therefore, targeting the inflammasomes, especially NLRP3, may be an important strategy for DE treatment, and NLRP3 inhibitors, such as OLT1177 or CY-09, can be selected to further explore their function in DE.

### Diabetic Peripheral Neuropathy

Diabetic peripheral neuropathy is one of the most common complications of type 2 diabetes. DPN usually affects the sensory and motor neuron of peripheral nerve, and lead to symptoms such as lower extremity pain and foot ulcers, which seriously affects the life quality of patients (Yang H. et al., 2019). This is mainly due to hyperglycemia causing inflammation and damage of peripheral nerve, slowing the speed of nerve conduction, and leading to excessive release of ROS. Previous studies reported that paclitaxel can induce mitochondrial damage and ROS overproduction in peripheral nerves accompanied by the activation of NLRP3 inflammasome and the infiltration of macrophages, leading to nerve pain (Jia et al., 2017). In DPN, hyperglycemia-induced the over-production of ROS is a recognized pathogenesis for DPN (Mraček-Sposta et al., 2018). Thus, it is most likely that over-production of ROS activates NLRP3 inflammasome and triggers the pyroptosis during the development of DPN. Cheng et al. found Loganin can reduce the pyroptosis of Schwann cells (SCs) by reducing intracellular ROS and inhibiting the activation of NF-κB and NLRP3 inflammasome during DPN development (Cheng et al., 2020). These studies indicate that pyroptosis is involved in the occurrence and development of DPN. Inhibition of ROS and NLRP3 inflammasome activity are the important theoretical therapy for DPN. However, it is still need to further explore the potential target of pyroptosis in DPN treatment. Our study found that fibroblast growth factor 1 (FGF1) expression is significantly inhibited after DPN, and exogenous FGF1 could alleviate DPN by alleviating oxidative stress in SCs (Li et al., 2021). Moreover, FGF21 and FGF10 also show significant therapeutic potential in peripheral nerve injury, both of which can reduce oxidative stress and promote neurological recovery. FGFs have also been found to exert anti-pyroptosis property, especially FGF21 (Zeng et al., 2020). Therefore, we speculate that FGFs may be an choice for inhibiting pyroptosis and alleviating DPN.

| Diseases                                | The mechanism that triggering pyroptosis                                                                 | Inflammasomes | References               |
|-----------------------------------------|---------------------------------------------------------------------------------------------------------|---------------|--------------------------|
| Diabetic cerebral I/R model             | Activated and induced microglial pyroptosis                                                            | NLRP3         | Liang et al., 2019       |
| Cognitive disorder in offspring of diabetes | Aggregation of macrophages caused by the aggregation of chemotactic proteins                           | NLRP3         | Liang et al., 2019       |
| Diabetic cognitive impairment           | P2 × 7R/NLRP1/caspase-1                                                                                 | NLRP1         | Jing et al., 2021        |
| Diabetic depression                     | ROS overproduction                                                                                     | NLRP3         | Li et al., 2020          |
| Diabetic brain damage                   | miR-214-3p/caspase-1-ATG12 axis                                                                         | NLRP3         | Che et al., 2020         |
| Diabetic cerebral ischemia              | Activation of autophagy                                                                                | NLRP3         | Tu et al., 2019          |
| Diabetic ischemic stroke                | Activation of NLRP3 inflammasome                                                                       | NLRP3         | Hong et al., 2018        |
| Diabetic brain injury                   | Pannexin 1 mediated the activation of NLRP1 inflammasome                                                | NLRP1         | Meng et al., 2014        |
Diabetic Retinopathy (Optical Nerve)
As the prevalence of type 2 diabetes continuously increase, DR has affected nearly 93 million people worldwide (Abcouwer and Gardner, 2014). Neurodegeneration is an important caused event for DR, and neurosensory retina is considered to play an important regulatory role in DR development. Although DR has always been considered as a diabetic microvascular disease, recent studies showed that the retinal neurodegeneration precedes the microvascular dysfunction during DR development, and leads to microvascular abnormalities (Abcouwer and Gardner, 2014). DR is generally divided into two stages: early non-proliferative DR and later proliferative DR (Lutty, 2013). In the early non-proliferative DR, it will occur neuroinflammation, capillary loss, glial cells activation, and increased vascular permeability, thereby impairing visual function and partly contributing to vascular abnormalities in the later proliferative DR (Lutty, 2013; Abcouwer and Gardner, 2014). A large number of basic and clinical researches indicate that retinal neurons and glial cells profoundly affect the retinal microvascular system (Moran et al., 2016). At present, neurovascular units is used to describe the mutual application of neurons, glial cells, and vascular-related cells that regulate retinal blood flow, structure, and function in the retina (Metea and Newman, 2007). Diabetes affects the entire neurovascular unit of the retina. High glucose-mediated the continuous activation of glial cells leads to the loss of retinal ganglion, microvascular dysfunction, and neurodegeneration (Cuenca et al., 2014). Huang et al. (2021) found that high glucose induces the pyroptosis of retinal microglial cells by activating NLRP3 inflammasome. Another study also showed that Nlrp3 gene knockout down-regulates the expression of caspase-1 and pro-inflammatory cytokines, and reduces the death of retinal ganglion cells after crush injury of optic nerve (Puyang et al., 2016). Moreover, high glucose significantly induces elevated levels of caspase-1 and IL-1β in Müller cells and microglial cells during DR (Feenstra et al., 2013). A large number of studies report the phenomenon of pyroptosis in endothelial cells (Gu et al., 2019) and pericytes (Gan et al., 2020; Yu et al., 2021) during DR development. The pyroptosis of microglial cells or neuron in early stage will create an inflammatory microenvironment of the neurovascular unit, which may be the main inducer for the pyroptosis in endothelial cells and pericytes. These studies suggest that pyroptosis plays an important role in the development of DR, and early prevention of pyroptosis during neuropathy in the early stage of DR may be an important approach to treat late-stage microvascular abnormalities.

Diabetes With Spinal Cord Injury
Spinal cord injury affects millions of people worldwide, which causes severe motor deficits in the area below the injured segment (Singh et al., 2014). After mechanical trauma, the spinal cord suffers local blood edema and neuroinflammation, followed by a series of secondary injuries, which enlarges the inflammatory response around the original injury center (Beattie, 2004). Increasing evidences suggest that the NF-κB pathway is triggered after SCI, and activates NLRP3 inflammasome (Zhou et al., 2016). It was observed that SCI enhances the expressions of pyroptosis-related protein markers (GSDMD, cleaved caspase-1 and cleaved caspase-11) and inflammatory mediators (IL-1β and IL-18) after SCI (Zendele et al., 2016; Al Mamun et al., 2021). This indicates that pyroptosis plays a key role in SCI (Zheng et al., 2019). Due to the high incidence of diabetes, more and more studies have focused on the impact of diabetes on SCI repair (Lien et al., 2016). Diabetes with SCI is characterized by poor recovery ability and high mortality. The study in experimental animals and clinical data found that hyperglycemia can promote the progressive damage of neuronal function after SCI (Lavela et al., 2006). Although there are few reports on the pyroptosis in diabetes complicated with SCI, hyperglycemia is reported to increase the inflammatory response of microglial cells by activating NF-κB, aggravate the secondary injury, and thus suppress the recovery of SCI (Kobayakawa et al., 2014). NF-κB is reported to initiate the activation of NLRP3 inflammasome by inducing the expression of pro-IL-1β and NLRP3 (Zhong et al., 2016). In conclusion, it is well worth further studying the regulatory role of pyroptosis in diabetes mellitus with SCI.

Enteric Neuropathy
Gastrointestinal motility is regulated by the internal and external nerves of the intestine (Al-Shboul, 2013). It has found that HFD and obesity are related to gastrointestinal motility disorders (Al-Shboul, 2013). Previous study also showed that diabetes or HFD can increase the dysfunction of intermuscular neurons mediated by elevated oxidative stress, leading to dyskinesia (Voukali et al., 2011). Moreover, the level of cleaved caspase-1 in the myenteric ganglion of obese subjects is higher than that in normal-weight subjects (Ye et al., 2020). In a study with western diet (WD) (a high-fat diet) mice as a model, caspase-11-dependent pyroptosis results in the loss of intestinal nerve cells, leading to the delayed colonic transport and reduced colonic diastolic response (Ye et al., 2020). These studies suggest that pyroptosis may be an important therapeutic target for diabetes-induced enteric neuropathy.

CONCLUSION
Pyroptosis is a new mode of programmed cell death, its role in the regulation of DN has been pay more and more attention. The current studies have found that hyperglycemia-mediated chronic inflammation, oxidative stress, mitochondrial damage, ROS overproduction, and ion channel dysfunction may be the molecular mechanism that initiates the pyroptosis, nerve injury, and lastly neurological dysfunction. Undoubtedly, blood glucose control is the most critical and fundamental step in the treatment of DN. In addition to blood glucose control, some agents with anti-inflammatory and antioxidant properties, such as cytokine inhibitor, ROS inhibitor, and NLRP3 inflammasome inhibitor, can also be selected to treat DN. However, it is still unclear the specific molecular target that triggers pyroptosis and the regulatory mechanism of various cell pyroptosis in nerve system during diabetes neuropathy, which is the key problem that hinders the targeted therapy of DN. Thus, it needs to be further
explore the interrelationship between pyroptosis, diabetes, and its related neuropathy, and provide a theoretical basis for the treatment of DN.

AUTHOR CONTRIBUTIONS

JYX wrote the manuscript. SC and JZ participated in literature collection and producing the figures. KX and HJ participated in literature collection and edited the manuscript. CW edited the manuscript. JX and YW conceived the study and wrote the manuscript. All authors reviewed and approved the final manuscript.

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