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Review

The mechanisms of NLRP3 inflammasome/pyroptosis activation and their role in Parkinson's disease

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ABSTRACT

Parkinson's disease (PD) is a typical neurodegenerative disease and the pathological feature of which is the death of dopamine neurons in the substantia nigra region. At present, neuronal death caused by inflammatory cytokine-mediated neuroinflammation is being extensively studied. The nucleotide-binding oligomerization domain-, leucine-rich repeat and pyrin domain-containing 3 (NLRP3) inflammasome is an inflammatory complex existing in microglia. Its activation promotes the secretion of the inflammatory cytokine interleukin-1β/18 (IL-1β/18) and induces pyroptosis, a type of cell death that possesses the potential for inflammation, to rupture microglia to further release IL-1β. In this review we focus on the mechanisms of activation of the NLRP3 inflammasome and pyroptosis and their inflammatory effects on the development of PD. In addition, we focus on some inhibitors of NLRP3 inflammatory pathways to alleviate the progression of PD by inhibiting central inflammation and provide new therapeutic strategies for the treatment of PD.

1. Introduction

The main pathological feature of Parkinson's disease (PD) is the irreversible damage of dopamine neurons in the substantia nigra, and the clinical symptoms of PD are mainly dyskinesia, tremor and balance disturbances [1]. The pathogenesis of PD is very complex, and the development of PD is the result of a combination of many factors. Recently, the mechanism of neuronal death mediated by neuroinflammation is drawing much attention [2–4]. Neuroinflammation, as an innate immune response in the central nervous system (CNS) of normal body, helps the brain and spinal cord to resist the invasion of pathogens and promote the repair of nerve tissue by removing the damaged tissues and pathogens. However, under certain pathological conditions, overactivated inflammatory response in the CNS may lead to neuronal injury and further aggravate the development of diseases.

During the inflammatory response, microglial cells are the major cellular mediators of brain inflammation [5]. And inflammatory responses mediated by inflammatory cytokines such as IL-1β from microglial cells play an important role in the development of PD [6,7]. The major events that regulate IL-1β secretion of microglia are the inflammasome activation and the process of inflammatory cell death termed pyroptosis [8]. The inflammasome is a multiprotein complex in the microglial plasma and it can be divided into subtypes based on the different combinations of molecules [9]. The most well-known inflammasome is the NLRP3 inflammasome, which is mainly composed of NLRP3, apoptosis-associated speck-like protein containing a caspase activating recruitment domain (ASC) and caspase-1. These three components are assembled to react to microbial infections or endogenous danger signals. The activation of NLRP3 can promote secretion of IL-1β and induce pyroptosis [10–12]. Pyroptosis is a type of programmed cell death that plays an important role in maintaining homeostasis and removing unnecessary cells. The activation of pyroptosis can further induce the release of IL-1β to promote the inflammatory response [13,14].

In this review, we describe the mechanisms of NLRP3 inflammasome/pyroptosis activation and their inflammatory effects in PD. We also describe some NLRP3 inhibitors that may be potential PD therapeutic agents. Moreover, it is necessary to further confirm whether NLRP3 inflammasome, pyroptosis and related molecules in their signaling pathways could be therapeutic targets for inflammatory mechanisms in PD.

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2. The activation mechanism of NLRP3 inflammasome

2.1. The formation of inflammasome

The innate immune system is body's first line of defense against the invasion of pathogens, and it is important for maintaining body's homeostasis. Inflammasome in CNS is involved with host immune responses to microbial infections and endogenous disease related signals [15]. Inflammasome consists of the following three components: (1) a pattern recognition receptor (PRR) as the sensor molecule, (2) an adaptor protein ASC, (3) a pro-caspase-1 as the effector molecule [16]. The nucleotide-binding oligomerization domain-like receptor (NLR) or the AIM2-like receptor (ALR) generally acts as sensor molecules in inflammatory activation, especially the NLR. NLR is one type of PRRs that can be activated by many endogenous or exogenous activators [17,18]. Up to now, at least five NLRS (NLRP1, NLRP3, NLRP6, NLRP7, and NLRC4) participate in forming inflammasomes [9,19]. Through the leucine-rich repeat (LRR) domains, NLR can identify different stimuli and then terminate its autoinhibitory state. Downstream adaptor ASC binds with the altered NLR via the pyrin domain and assembles into multimers. Subsequently, ASC induces monomeric pro-caspase-1 aggregation to initiate pro-caspase-1 self-cleavage to become the active caspase-1 [20], which results in the maturation and secretion of proinflammatory cytokines interleukin (IL)-1β and IL-18 [18]. These secreted proinflammatory cytokines further amplify inflammatory response by binding with the corresponding cellular receptors. In addition, inflammasome activation causes a pro-inflammatory form cell death called as pyroptosis [21,22].

Compared with other inflammasomes, NLRP3 inflammasome is well known for its involvement with human diseases. It has a large variety of stimuli such as bacterial toxins, adenosine triphosphate and endogenous protein released from damaged cells [23–26]. In addition to the effects of stimuli on NLRP3 inflammasome activation, the expression of NLRP3 receptor proteins also affects the inflammasome activation. At the beginning of NLRP3 inflammasome activation, the low expression of NLRP3 protein is insufficient to stimulate the activation process, but activation of NF-κB pathway induced by Toll-like receptor (TLR) agonists or certain cytokines can promote the expression of NLRP3 and pro-IL-1β, then leading to the activation of inflammasome. This process is described as priming process [27–29]. In other words, the priming process puts the inflammasome into the pre-activation state of preparation, and inflammasome is completely activated when it interacts with the corresponding stimulants such as ATP, pore-forming toxins or viral RNA. These stimulants have different biological activities and structures but all of them are capable of activating NLRP3 inflammasome. Therefore, we believe that these stimulants may mediate NLRP3 activation by causing some common cellular events rather than physically interacting with the NLRP3 inflammasome [30]. Moreover, the activation of NLRP3 is not the result of a single cellular events but a combination of multiple cellular events [30].

2.2. Signals to activate the inflammasomes

A few of cellular danger signals are regarded as activator of inflammasome, including efflux of potassium, increased intracellular calcium, reactive oxygen species (ROS), Ca^{2+} signaling, mitochondrial dysfunction and cathepsin B released from destabilized lysosome. We mainly describe the activation of NLRP3 inflammasome mediated by K^+ efflux and ROS (Fig. 1).

2.2.1. K^+ efflux

Many studies have suggested that K^+ efflux is one of the important cellular events that trigger NLRP3 activation [31–33]. Numerous activators of the NLRP3 inflammasome almost all contribute to potassium efflux, thereby reducing the concentration of K^+ in the cytoplasm, but the pathways of K^+ efflux caused by the various activators are different. Extracellular ATP binds with the ligand-gated ion channel P2X7R, then the opened ion channel allows K^+ to pass through to form K^+ efflux [32,34]. While bacterial toxins, such as Gramicidin, nigericin and valinomycin, form membrane pores in the cell membrane to promote K^+ efflux [34].

But the exact link between reduced content of intracellular K^+ and activation of the NLRP3 inflammasome remains unclear. Some studies have shown that K^+ efflux plays a role mainly in the upstream of ASC during NLRP3 activation. NLRP3 activation can be prevented by directly inhibiting K^+ efflux or maintaining the extracellular high K^+ state (maximum inhibitory effect when the [K^+] is 45 mM) [31]. Based on the above facts, we think K^+ efflux is very necessary for the activation of NLRP3. However, there is a different view on whether K^+ efflux can independently activate NLRP3. Some researchers think that K^+ is not enough to activate NLRP3 inflammasome alone. The activation of NLRP3 is also related to changes of the intracellular ionic environment [10,35,36]. While others believe that K^+ efflux is the minimal cellular event that is sufficient to activate the NLRP3 inflammasome. The influx of Na^+ is related to NLRP3 activation but is not an absolute requirement [31].

In addition to understanding the role of K^+ efflux in NLRP3 activation, we need to know a downstream protein of K^+ efflux called NEK7. NEK7 is a type of mammalian NIMA-related kinase that acts downstream of K^+ efflux to mediate NLRP3 activation [37–39]. Activation stimulators of NLRP3 promote the interaction of NEK7 with NLRP3 through catalytic domain of NEK7 and the LRR domain of NLRP3. The above process depends on K^+ efflux. NEK7 mediates activation of NLRP3 inflammasome specifically through regulating oligomerization of NLRP3, ASC speck formation, and caspase-1 activation. In the absence of NEK7, both caspase-1 activation and IL-1β release are attenuated [38]. Thus, NEK7 is an important regulator of NLRP3 activation.

2.2.2. Mitochondrial dysfunction and ROS

Mitochondria are important cellular organelles that generate energy and produce ROS. ROS is mainly produced in the intima of mitochondria, which is closely related to enzyme complexes in mitochondrial respiratory chain [40]. Approximately 2% of the oxygen consumed in the normal mitochondria is converted into ROS. But when mitochondria are damaged or insufficient oxygen supply occurs, a large amount of ROS can be produced, which further exacerbates mitochondrial structural and functional damage [41]. Therefore, mitochondrial dysfunction and ROS-induced oxidative stress are closely linked. These ROS and mtDNA released from damaged mitochondria can be considered as damage associated molecular patterns (DAMPs) and thus activate the immune response. Specifically, ROS is likely to participate in the activation of NLRP3, thereby enhancing the inflammatory response [42–44]. At present, the exact mechanism by which ROS activates NLRP3 inflammasome is unclear. However, some studies have demonstrated that ROS may induce NLRP3 activation by influencing the priming process [45]. As we have known, NLRP3 inflammasome can enhance the inflammatory response by releasing proinflammatory cytokines such as IL-1β. We could detect a decrease in caspase-1-mediated IL-1β secretion when given some ROS inhibitors or cleaners [42]. So these also suggest that ROS might promote the activation of inflammation.

In addition to ROS, mtDNA from damaged mitochondria regulates inflammasome activation through promoting the activation of caspase-1 and the release of proinflammatory cytokines [46]. Hence, maintaining mitochondrial homeostasis and integrity may play an important role in repressing the inflammatory response. Some studies have also shown that autophagy can regulate the activation of NLRP3 inflammasome by maintaining the integrity of mitochondria. Antagonism of autophagic protein is shown in the activation of NLRP3 inflammasome. Inhibition of autophagy or depletion of autophagic protein can trigger mitochondrial damage and lead to increased production of ROS,

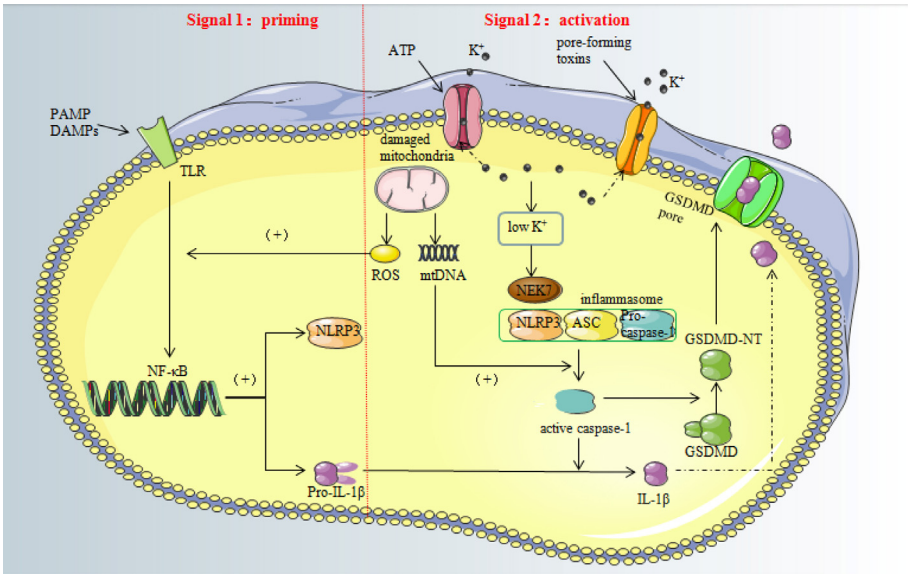

Fig. 1. The mechanisms of NLRP3 inflammasome/pyroptosis activation.
The left side of the figure depicts priming process. Exogenous pathogenic microorganisms or endogenous cytokines can be recognized by TLRs, activating the downstream transcription factor NF-κB to upregulate the expression of NLRP3 and IL-1β.
The activation process on the right shows that ATP and some bacterial toxins can form channels on the membrane for K^+ to pass through and cause K^+ efflux. Intracellular low K^+ status allows downstream NEK7 molecules to bind NLRP3 to mediate the activation of caspase-1. Damaged mitochondria can release ROS and mtDNA, the former can promote the activation of NLRP3 inflammasome by acting on priming process, and the latter can promote the activation of caspase-1. Activated caspase-1 can promote the maturation of IL-1β and cleave the GSDMD to generate GSDMD-NT. GSDMD-NT translocates to the inside of the plasma membrane and forms membrane pores to mediate pyroptosis. Mature IL-1β can be further released through the membrane pore to expand the inflammatory effect.

contributing to the NLRP3 inflammasome activation [46,47].

3. Features and activation mechanisms of pyroptosis

In addition to the secretion and maturation of IL-1β/18, the inflammasome activation triggers a form of inflammatory cell death named pyroptosis. Pyroptosis-induced cell rupture also promotes the release of inflammatory cytokines such as IL-1β without affecting their maturation [48]. Both IL-1β/18 and pyroptosis can cause inflammatory or anti-infective effects. What's more, pyroptosis has an anti-infective effect independent of the release of IL-1β [49]. When considering the effects of inflammasome in inflammatory diseases, pyroptosis should be considered a potential inflammatory mechanism along with IL-1β and IL-18 secretion. By establishing pyroptosis as a removal mechanism to kill the infected macrophages and dendritic cells, the pathogenic bacteria can be effectively cleared. For example, activated caspase-1 clears *Salmonella typhimurium* and *Legionella pneumophila* by inducing pyroptosis instead of secreting IL-1β/18. While some pathogen infections are likely to be controlled through the co-management of cytokine secretion and pyroptosis [49]. The above studies show that pyroptosis has its unique biological effect and promotes inflammation in vivo along with inflammasome.

3.1. GSDMD-NT as an executive protein mediates pyroptosis

Pyroptosis, usually accompanies the activation of inflammasomes, is an inflammatory programmed cell death pathway and mediated by inflammatory caspases [48,50,51]. It is characterized by the formation of pores in the plasma membrane, cell swelling, membrane rupture and the release of pro-inflammatory cytosolic contents into the extracellular space [52,53]. Previous studies have suggested that pyroptosis plays an important role in immunity and some diseases, but the exact mechanism by which inflammatory caspases lead to the formation of a membrane pore remains unclear until the advent of gasdermin D (GSDMD) as an executive protein for pyroptosis [54,55].

GSDMD is a 53-kDa protein located downstream of inflammatory caspase [51]. Activated caspase can generate the N-terminal fragment of GSDMD (GSDMD-NT) and the C-terminal fragment of GSDMD (GSDMD-CT) through cleaving GSDMD at specific protein sites. Some studies have suggested that GSDMD-NT is necessary and sufficient to trigger pyroptosis [48,56]. While the intrinsic pyroptosis-inducing activity of GSDMD-NT is inhibited when GSDMD-NT and GSDMD-CT are tightly linked together. The cleavage of GSDMD remove the GSDMD-CT to make the GSDMD-NT change from inhibitory state to active state, which is essential to trigger pyroptosis [48]. On account of its lipotropism, GSDMD-NT targets the intracellular membrane and transfers to the membrane, then induces the formation of membrane pores [54,57]. In vitro experiments also demonstrate that the GSDMD-NT can combine with liposomes to form membrane pores [54]. GSDMD-deficient cells demonstrate the unobvious pyroptosis after LPS or other canonical inflammasome activators induction. The release of mature IL-1β/18 is also decreased in Gsdmd$^{-/-}$ cells, despite the inflammasome is completely activated [48]. These studies complement the gap in the pyroptosis pathway and provide evidence for GSDMD-NT is the ultimate executive protein for pyroptosis (Fig. 1).

Depending on the inflammatory caspases involved in the activation pathway, pyroptosis can be classified into caspase-1-dependent pyroptosis and caspase-1-independent pyroptosis [51]. Although caspase-1-dependent or caspase-1-independent pyroptosis are morphologically similar, there are significant differences in their activation pathways. In canonical inflammasome activation pathways, including the activation of NLRP1b, NLRP3, NLRC4, AIM2 and Pyrin, the inflammasome sensor molecule recognizes pathogen-associated molecular patterns or danger-associated molecular patterns and thus to activate downstream effector molecule caspase-1. As an outcome of canonical inflammasome activation, caspase-1 can maturate IL-1β/18 and also trigger pyroptosis [49,58]. Human caspase-4, human caspase-5, or mouse caspase-11, by contrast, can direct recognize LPS to execute pyroptosis through cleaving GSDMD, which is also called ascaspase-1-independent pyroptosis [56,59,60]. Although different pathways involve in corresponding caspases, they both act on the common substrate GSDMD to mediate pyroptosis. It remains unclear whether other regulators exist during the process of triggering pyroptosis.

3.2. Difference between pyroptosis and apoptosis, necroptosis

Similar to apoptosis and necroptosis, pyroptosis belongs to programmed cell death. Necroptosis and pyroptosis can be collectively referred to as programmed necrosis, an inflammatory form of programmed cell death, that is characterized by swelling and rupture of cells and release of inflammatory cytokines [61]. In contrast, apoptosis caused by apoptotic caspase activation does not cause an inflammatory response in the body [62]. All of them are regulated by respective regulatory proteins and possess their own morphological characteristics. To better understand these pathways of programmed cell death, we compare the differences in morphology and mechanism between

pyroptosis and apoptosis as well as necrosis.

Caspase activation is crucial for programmed cell death. Caspases can be divided into apoptotic caspases (caspase-2, 3, 6, 7, 8, 9) and inflammatory caspases (caspase-1, 4, 5, 11), which respectively mediate apoptosis and pyroptosis [55,63]. In addition to the different caspases involved, the target proteins of caspases during apoptosis and pyroptosis are different. Inflammatory caspases induce cell death through cleaved GSDMD-NT, while the apoptotic specific target protein such as PARP1 remains intact in this time [12,64]. The morphological feature of pyroptosis is the formation of pores in the plasma membrane and membrane rupture, leading to leakage of the cytosolic inflammatory cytokines IL-1β/18, which also indicates the inflammatory potential of pyroptosis compared with apoptosis that does not rupture the plasma membrane [14,51]. Thus, in terms of activation mechanisms and morphological characteristics, pyroptosis and apoptosis are different.

Although apoptosis and pyroptosis are activated by different kinds of caspase, the two processes are not completely separated. Another member of the gasdermin family, GSDMDE, is an important mediator that links apoptosis and pyroptosis [65]. At the end of the apoptosis process, if apoptotic cells are not cleared by cleared cells such as macrophages, they will progress to another cell process called secondary necrosis, which causes a pathological phenotype similar to programmed necrosis such as cell swelling and plasma membrane rupture [65–67]. Studies have shown that the process of secondary necrosis is mediated by GSDMDE. GSDMDE is specifically cleaved by upstream activated caspase-3 at Asp270 to generate GSDMDE-NT that transfers to the cell membrane and forms a membrane pore, thereby inducing secondary necrosis [66,67]. The secondary necrosis has a pathological phenotype of programmed necrosis and is mediated by activation of caspase, so it can be attributed to pyroptosis. Specifically, it can be called as caspase-3-mediated pyroptosis or GSDME-associated pyroptosis.

In the process of necroptosis, mixed lineage kinase domain-like (MLKL) oligomers, similar to the role of GSDMD in pyroptosis, act as executive protein to mediate cell death [68]. Compared with pyroptosis, necrosis is characterized by the fact that caspase is not required for its execution, suggesting that MLKL does not need to be cleaved by caspase. However, both MLKL and GSDMD-NT are lipophilic and can translocate to the plasma membrane respectively to form membrane pores, which resulted in rupture of the plasma membrane and eventual cell death [69]. The difference is that selective channels formed by MLKL on the plasma membrane can induce ion influx to form intracellular high-permeability state to cause cell explosion, whereas GSDMD forms non-selective channels on the plasma membrane [70,71]. The morphological differences between necroptosis and pyroptosis depend on their mechanism differences. It was observed that necroptosis causes an explosive burst of cells, whereas cell rupture caused by pyroptosis is flat [69].

4. The inflammasome and pyroptosis in PD

Parkinson's disease is a popular neurodegenerative disease and demonstrates a common feature of neuroinflammation [2,4,72,73]. Emerged in the early stages of PD, neuroinflammation progressively promote the disease progresses. As for the neurodegenerative diseases mediated by inflammation, studies have shown that the inflammatory cytokines such as IL-1β released by the activated microglia play an important inflammatory role in the central nervous system [74]. As mentioned above, inflammasome and pyroptosis can promote the secretion of mature IL-1β. The following mainly reviews the roles of inflammasome and pyroptosis in PD.

The most prominent pathological features of PD are the loss of the dopaminergic neurons in the substantia nigra compact and the presence of aggregated inclusions containing aggregated and misfolded α-synuclein (αSyn), termed as Lewy bodies (LBs) [75–77]. Despite intensive research, there is no unified theory to explain the cause of death of dopaminergic neurons. Some studies suggest that neuroinflammation may be involved in the process of neuronal degeneration by producing deleterious proinflammatory cytokines such as IL-1β [78]. IL-1β is first synthesized as an inactive precursor and then secreted as a mature form by the activation of the inflammasome complex [79]. Pyroptosis can increase the inflammatory effect by promoting the secretion of IL-1β in conjunction with the activation of inflammasome [80].

Aggregated αSyn, as a pathologically relevant protein of PD, can be released into the extracellular space from damaged neurons and then activate microglial cells [81]. It is first recognized by Toll-like receptors in the membrane to activate NF-κB pathway and promote the production of IL-1β precursor protein [29,82]. After that, aggregated αSyn can act as an endogenous dangerous signal to activate NLRP3 inflammasome and induce pyroptosis when it is taken up by microglial cells [83]. Activation of NLRP3 inflammasome recruits and activates caspase-1 to promote the maturation of IL-1β and the induction of pyroptosis which further promotes IL-1β secretion. Mature IL-1β is secreted extracellularly to exert an inflammatory effect to further damage dopamine neurons [84,85]. It has also been demonstrated in rat models of PD that the introduction of exogenous IL-1β into the substantia nigra site promotes the death of dopaminergic neurons. However, many studies have also found that αSyn, morphologically similar to amyloid fibrils in AD, can form fibrils with cross-β-sheet structure in LBs [86]. Both monomeric and fibrillar αSyn can induce gene expression of pro-IL-1β through the TLR2 signaling pathway to promote its synthesis, but only fibrillar αSyn can activate the inflammasome to promote the secretion of mature IL-1β [78]. In addition to activation of microglial, neuroinflammation is also related with astrocytes and peripheral immune cells that enter the CNS. Together, these cells cause a vicious circle of neuroinflammation to amplify the inflammatory response [87]. Studies have shown that in addition to the activation of NLRP3 in the brain, peripheral inflammation caused by activation of NLRP3 in the lungs can infiltrate inflammatory cells into the brain, thereby expanding the central inflammatory response and exacerbating the degeneration of dopaminergic neurons [88].

In addition to promoting secretion of IL-1β to mediate neuroinflammation in PD, NLRP3 inflammasome may induce other effects that kill dopamine neurons, but the exact mechanism is not clear. Some studies have also shown that dopamine neurons can inhibit NLRP3 activation in microglia through the DRD1-cAMP pathway. In the absence of DRD1, upregulation of NLRP3 activation in microglial cells, increased secretion of IL-1β, and increased dopamine neuronal damage were observed in the brains of mice of PD model [15,89]. These results suggest that dopamine neurons and NLRP3 inflammasome can regulate each other. Not only NLRP3 can promote inflammatory reaction to damage dopamine neurons, but dopamine neurons can also inhibit NLRP3 activation.

5. NLRP3 inflammasome as a therapeutic target for PD

At present, clinical treatment of PD mainly increases the content of dopamine transmitter in the brain, including direct supplementation of the exogenous dopamine precursor levodopa; monoamine oxidase B inhibitor (MAOBI) such as selegiline reduces the oxidative degradation of dopamine. Dopamine receptor agonists such as pramipexole can also be used to exert a dopaminergic effect. Nevertheless, Neuroinflammation as an important pathogenesis of PD can also be a potential therapeutic target to alleviate the damage of dopamine neurons caused by inflammatory factors such as IL-1β. Studies have shown that NLRP3 inflammasome mediates the maturation and secretion of IL-1β and that the NLRP3 inflammasome and its downstream molecular ASC are activated during the pathogenesis of PD. In the PD mouse model treated with neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), NLRP3$^{-/-}$ mice can inhibit the progression of PD compared to wild-type mice, which also illustrates the link between the NLRP3 inflammasome and PD [89]. Studies have shown that mice

lacking Nlrp3 can resist the development of PD symptoms caused by the exposure to the rotenone [90]. In the MPTP-induced PD model, nigral dopaminergic neurons in mice lacking the key inflammatory body effector caspase-1 can resist the invasion of MPTP to a certain extent [91]. In LPS-induced and 6-OHDA-induced PD models, dopaminergic neurons can be protected by inhibiting the activity of NLRP3/caspase-1/IL-1β axis by administration of a caspase-1 inhibitor (Ac-YVAD-CMK) [92]. In addition to studies in animals, elevated expression of NLRP3 in DA neurons was also found in PD patients. The genetic variation of NLRP3 is associated with a significant reduction in the risk of PD [93]. Moreover, there is direct clinical evidence that the levels of IL-1β and IL-18 in the cerebrospinal fluid of PD patients are higher than those in the cerebrospinal fluid of the control patients [94]. Similarly, this result was also verified in the detection of serum samples. The serum samples of PD patients showed a remarkable elevation of IL-1β levels accompanied by an activation of NLRP3 inflammasome compared to healthy controls [95]. Besides, a recent study showed an obvious activation of NLRP3 inflammasome at the sites of dopaminergic cell loss in PD patients. The components of NLRP3 inflammasome, including NLRP3, adaptor ASC and the effector molecule caspase-1, are up-regulated in microglia located in substantia nigra of PD patients [96]. The above evidences indicate that NLRP3 inflammasome is closely related to PD. The treatment of PD with NLRP3 inflammasome pathways as a therapeutic target to relieve neuroinflammation is becoming well understood and widely concerned. There are also compounds that have been shown to exert anti-inflammatory effects by affecting different levels of molecules in the NLRP3 inflammasome pathway. The use of these compounds may improve the symptoms of PD and show neuroprotection to some extent.

IL-1β plays an inflammatory role as the final effector of the NLRP3 inflammasome pathway. IL-1 receptor antagonists (IL-1Ra), such as anakinra, have good CNS permeability and can block the mutual binding of IL-1β and its receptor to inhibit the activity of IL-1β [97]. The blockade of the inflammatory effects of IL-1β may play a role in curbing the progression of PD. However, although the anti-inflammatory effect of anakinra has been demonstrated in the treatment of cryopyrin-associated periodic syndrome (CAPS) -associated neurologic disease, it still cannot completely block all inflammatory reactions [98]. The reason is that besides releasing IL-1β, inflammasome-dependent pyroptosis can also promote the release of other inflammatory factors. Therefore, inhibition of inflammasome activation may be more beneficial than single anti-IL treatment in suppressing the inflammatory response to alleviate the progression of PD.

Up to date, some progress has been made in the study of inhibitors targeting the NLRP3 inflammasome. Some exogenous compounds have been shown to inhibit inflammatory activity through different mechanisms.

Recent studies have shown that fenamate non-steroidal anti-inflammatory drugs (NSAIDs) such as Flufenamic acid and mefenamic acid can inhibit the activation of NLRP3 [99]. We all know that NSAIDs can also inhibit cyclooxygenase to exert anti-inflammatory effects. This double inhibition of inflammation may be more powerful than a single inhibition of the NLRP3 inflammasome pathway. Moreover, these clinically-qualified fenamate have been shown to play a role in neuroprotection in an animal model of Alzheimer's disease (AD) [99]. This also suggests that we can use fenamate as a potential therapeutic agent for PD.

Glyburide is the second generation of sulfonylurea hypoglycemic agents that treat type 2 diabetes mainly by inhibiting the ATP-sensitive K^+ channels of pancreatic β-cells [100]. Glyburide has been shown to inhibit the secretion of NLRP3-dependent IL-1β, but has no effect on the secretion of IL-1β induced by other types of inflammasomes [101]. ASC serves as an adaptor protein of the inflammasome linking the cryopyrin domain of NLRP3 and pro-caspase-1. Cryopyrin has also been shown to be inappropriate activated in some neurodegenerative diseases and may be the target of glyburide. If Cryopyrin activity is blocked, it can inhibit the activation of downstream caspase-1, thereby reducing the secretion of IL-1β [101].

MCC950 is a small molecule compound with similar structure to sulfonylurea. It has been reported that MCC950 can specifically inhibit the activation of NLRP3 inflammasome at a concentration of nanomolar to reduce the secretion of IL-1β [97]. However, MCC950 has no effect on NLRP1, NLRC4 or AIM2 inflammasomes. Therefore, specific inhibition of NLRP3 activation does not result in the complete blockade of IL-1β secretion in vivo and can maintain the body's immune response to some extent. MCC950 therefore has less immunosuppressive effects than anti-IL treatment. MCC950 functions mainly by blocking NLRP3-induced oligomerization of the ASC, whereas the formation of ASC oligomers is a key event in NLRP3 inflammasome activation. The pharmacological effects of MCC950 are also confirmed in the course of alleviating the severity of experimental autoimmune encephalomyelitis (EAE, a multiple sclerosis disease model). Therefore, MCC950 is a promising therapeutic for NLRP3-related inflammatory diseases such as PD [97].

The ketone metabolite b-hydroxybutyrate (BHB) can replace ATP as a source of energy in the absence of energy to maintain the body's survival. In fasting, high-intensity exercise or ketogenic diet conditions, we can detect increased BHB expression in vivo. Some studies indicate that endoplasmic reticulum stress regulated by BHB can induce the activation of NLRP3 [102]. Fasting resulted in increased BHB production, decreased endoplasmic reticulum stress and reduced formation of inflammasome in rats compared with normal diet rats. In addition, some researchers showed that BHB may suppress NLRP3 inflammasome by reducing potassium efflux or decreasing the ASC speck formation [15,102].

Recent studies have shown that peroxisome proliferator-activated receptor β/δ (PPARβ/δ) agonist GW501516 can attenuate NLRP3-mediated neuroinflammation in MPTP model mice and inhibit astrocyte responses to some extent. However, the specific mechanism of its function is still unclear and it can be related to the inhibition of oxidative stress in the midbrain This compound does not readily cross the blood-brain barrier, which is also a problem to be solved in the later drug development [103].

Bile acid is a cholesterol derivative that activates cell membrane receptor transmembrane G protein-coupled receptor-5 (TGR5) to cause activation of downstream PKA kinase. Activation of PKA kinase induced by bile acid-activated TGR5 can lead to ubiquitination and phosphorylation of NLRP3 inflammasome, thereby inhibiting the activation of NLRP3 inflammasome. In vivo studies have also shown that bile acids can block NLRP3 inflammasome-dependent inflammation [104].

In addition, there are some phytochemicals that inhibit the activation of NLRP3 inflammasomes. Isoliquiritigenin, a chalcone derived from licorice, inhibits ASC oligomerization caused by MLRP3 activation, thereby inhibiting caspase-1 activation and IL-1β release [105]. Bachelin is a major polyphenolic compound extract from Scutellariae Radix, showing anti-inflammatory effects in the central nervous system. An antidepressant study showed that baicalin can inhibit NLRP3 inflammasomes to reduce IL-1β levels in the prefrontal cortex [106]. Another study showed that the use of baicalin to reduce inflammation during *Haemophilus parasuis* infection was also achieved by inhibiting NLRP3 inflammasome [107].

There are also compounds that exert anti-inflammatory effects by inhibiting the activation of pyroptosis. Piperine is a chemical found in black pepper. One study showed that piperine can protect macrophages from pyroptosis and reduce IL-1β release by inhibiting ATP-induced AMP-activated protein kinase (AMPK) activation. In vivo and vitro experiments have demonstrated that piperine administration can reduce IL-1β levels in inflammatory models [108].

The above compounds targeting NLRP3 if applied to PD individuals will produce what kind of effect needs further study. However, the therapeutic effects of these drugs on some inflammatory-related diseases suggest that the therapeutic strategy of inhibiting the NLRP3

inflammatory pathway is promising. To develop more effective NLRP3 inhibitors to treat PD is the focus we should pay attention to.

6. Conclusion

Previous studies have found that inflammatory reactions and immune abnormalities are always accompanied by the occurrence and development of PD. Microglia, as innate immune cells in the CNS, can be activated by the PD-associated pathological protein such as aggregated αSyn. aSyn entering the cell is recognized by the NLRP3 inflammasome as an endogenous danger signal, which initiates the downstream signaling pathway by recruiting and cleaving caspase-1which converts the inflammatory cytokine pro-IL-1β to an active form and causes pyroptosis that further promotes the secretion of IL-1β. The secretion of IL-1β further damages dopamine neurons, which in turn releases αSyn again. Thereby creating a vicious circle that amplifies the inflammatory response. aSyn spreads like a plague in the CNS, causing irreversible damage to dopaminergic neurons. Therefore, we should focus on immunomodulatory therapeutic strategies to reduce the impact of neuroinflammation on PD.

In this review we have seen the activation of NLRP3 Inflammasome and pyroptosis and their inflammatory effects in PD. These facts prove that the NLRP3 inflammasome and related molecules in the pyroptosis pathways may be the therapeutic target of neuroinflammation to inhibit the development of PD. Future research should explore the activation pathways of NLRP3 inflammasome and pyroptosis and identify the role of each factor in this process. We should, as far as possible, translate the study of the mechanistic network of neuroinflammation into a therapeutic strategy for PD [103].

Conflict of interest

The authors have no conflicts of interest to declare in relation to this article.

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