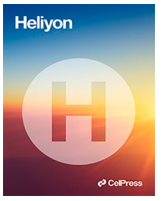
Heliyon 10 (2024) e28838

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Review article

Role of NLRP3 in Parkinson's disease: Specific activation especially in dopaminergic neurons

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ARTICLE INFO

Keywords:
Parkinson's disease
Nucleotide-binding oligomerization domain-like receptor protein 3
Dopaminergic neuron
Neuroinflammation
α-synuclein

ABSTRACT

Parkinson's disease (PD) is a neurodegenerative disorder with motor symptoms like bradykinesia, tremors, and balance issues. The pathology is recognized by progressively degenerative nigrostriatal dopaminergic neurons (DANs) loss. Its exact pathogenesis is unclear. Numerous studies have shown that nucleotide-binding oligomerization domain-like receptor protein 3 (NLRP3) contributes to the pathogenesis of PD. Previous studies have demonstrated that the overactivation of NLRP3 inflammasome in microglia indirectly leads to the loss of DANs, which can worsen PD. In recent years, autopsy analyses of PD patients and studies in PD models have revealed upregulation of NLRP3 expression within DANs and demonstrated that activation of NLRP3 inflammasome in neurons is sufficient to drive neuronal loss, whereas microglial activation occurs after neuronal death, and that inhibition of intraneuronal NLRP3 inflammasome prevents degeneration of DANs. In this review, we provide research evidence related to NLRP3 inflammasome in DANs in PD as well as focus on possible mechanisms of NLRP3 inflammasome activation in neurons, aiming to provide a new way of thinking about the pathogenesis and prevention of PD.

1. Introduction

Parkinson's disease (PD) is a prevalent neurodegenerative disorder globally, ranking second in terms of frequency, and its prevalence steadily increases with age [1,2]. In 2016, about 6.1 million individuals globally were affected by PD, with projections indicating that this number will surpass 12 million by 2040 [1], greatly impacting society. PD's most common clinical manifestations primarily consist of motor symptoms, such as bradykinesia, resting tremor, muscle tonus abnormalities, and postural balance impairments [3]. In addition, non-motor symptoms should not be ignored, including constipation, cognitive impairment, depression, and pain [4]. Most PD patients will gradually lose their ability to care for themselves as the disease progresses, which will seriously affect their quality of life and put heavy pressure on caregivers. Existing treatment options for PD only improve symptoms and do not slow or stop the progression of the disease. This limitation arises from the lack of clarity regarding PD's root causes and mechanisms.

The major neuropathologic changes in PD are degenerative loss of midbrain nigral dopaminergic neurons (DANs) and aggregation

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https://doi.org/10.1016/j.heliyon.2024.e28838
Received 15 November 2023; Received in revised form 22 March 2024; Accepted 26 March 2024
Available online 28 March 2024
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of misfolded α-synuclein (α-Syn) to form Lewy bodies (LBs) [5]. The majority of symptoms in PD are linked to the gradual degeneration of DANs in the substantia nigra pars compacta (SNpc) [6]. However, the exact cause of this neuronal loss in PD remains uncertain. Research on the pathogenesis of PD is still at the doctrinal stage, with existing doctrines such as mitochondrial dysfunction, oxidative stress, autophagy-lysosome pathway imbalance, DAN death, gene mutations, and neuroinflammation [5]. It has been found in numerous studies that neuroinflammation accompanies the onset and progression of PD and plays an important role in PD pathogenesis [7]. Excessive neuroinflammation boosts neuronal death and worsens the progression of PD, whereas suppressing neuroinflammation promotes neuronal survival and improves PD symptoms and prognosis [6].

The nucleotide-binding oligomerization domain-like receptor protein 3 (NLRP3) inflammasome is a significant component of the neuroinflammatory response. It is a multiprotein complex comprising the NLRP3 protein, the connexin apoptosis-associated speck-like protein (ASC) protein, and the effector protein-cysteinyl aspartate specific proteinase 1 precursor (pro-Caspase-1) [8]. Despite extensive research on the interaction of NLRP3 inflammasome with PD, the specific mechanisms, especially those related to DANs and NLRP3, remain poorly understood. Previous studies have shown that microglia activation-mediated overactivation of the NLRP3 inflammasome and release of large amounts of proinflammatory factors lead to the dysfunction of DANs and promote the development of PD [9]. In contrast, several studies have confirmed that microglia activation follows the death of DANs [10,11]. Consistent with this, recent studies reveal that DANs are the cells of origin of aseptic neuroinflammation mediated by the NLRP3 inflammasome [12]. In PD autopsy studies, increased NLRP3 expression was found in nigrostriatal DANs [12,13]. Also, the presence of the NLRP3 inflammasome within DANs and its activation in a cell-autonomous manner to cleave pyroptosis executive protein gasdermin D (GSDMD) was confirmed by cellular and animal models of PD and was enough to lead to DAN death [13]. Thus, activation of NLRP3 inflammasome within DANs may be an important pathogenesis of PD. However, the pathological role of inflammasome activation in neurons in PD has yet to be elucidated, and exploring the role of inflammasomes in neurons and their association with PD will be of great significance in elucidating the pathogenesis of PD and improving the therapeutic efficacy.

In this article, we provide a comprehensive review of the research on NLRP3 within DANs in PD, exploring its role in the pathogenesis of PD. Furthermore, we also focus on the potential therapeutic target of NLRP3 inflammasome and the development progress of NLRP3 inhibitors.

2. NLRP3 inflammasome

2.1. Overview of inflammasome

At the beginning of this century, Martinon et al. [14] first introduced the concept of inflammasome, revealing that inflammasome is a protein complex, which was epoch-making in our understanding of how the immune system triggers inflammation. Inflammasomes have a significant role in the immune response, contributing to pathogen resistance and the detection of abnormal endogenous signals [15]. Chronic stimulation of the Inflammasome has been associated with the development of various diseases. The structure of the inflammasome has three components, including receptor molecules-pattern recognition receptors (PRRs), connexin ASC, and effector molecules-pro-Caspase-1 [16]. Depending on the pattern recognition receptor, different inflammasomes are formed [16].

At present, the most common inflammasome are nucleotide-binding domain (NOD)-like receptor (NLR) family Pyrin domain containing 1 (NLRP1), NLRP3, NLR family CARD domain containing 4 (NLRC4) and absent in melanoma 2 (AIM2) inflammasome [14,17–19]. In addition, NLR family Pyrin domain containing 6 (NLRP6), NLR family Pyrin domain containing 7 (NLRP7) and NLR family Pyrin domain containing 9 (NLRP9) inflammasome have also been found [20–22]. These different classes of inflammasome activate after recognizing different pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), triggering an inflammatory response. NLRP1 is the most significant inflammasome receptor in cutaneous keratinocytes and lung epithelial cells, reflected in acquired function mutations in the NLRP1 gene that lead to severe inflammatory and neoplastic syndromes, primarily affecting the skin and respiratory tract [23,24]. The NLRC4 inflammasome mainly recognizes and activates bacterial invasion, and it must cooperate with another NLR, the NLR family apoptosis inhibitory protein (NAIP), to resist bacterial invasion [25,26]. The AIM2 inflammasome, a member of the pyrin and HIN domain (PYHIN) family that protects itself against pathogens by sensing cytoplasmic double stranded deoxyribonucleic acid (dsDNA) [27,28], is thought to be involved in the self-DNA-induced autoimmune response of systemic lupus erythematosus. NLRP6 inflammasome is clearly involved in protecting the intestinal barrier and regulating biological dysregulation [29]. However, how the intestinal ligand activates the NLRP6 inflammasome remains unclear. NLRP7 is associated with the secretion of interleukin-1β (IL-1β) and tumor necrosis factor [30], but the exact role of NLRP7 in innate immunity is unclear. NLRP9 exists in intestinal epithelial cells and can initiate the formation of inflammasome under the stimulation of dsRNA for a short time, which has a protective effect on intestinal epithelium [31]. The exact molecular mechanism of human NLRP9 inflammasome formation is still unclear.

2.2. Characterization and importance of NLRP3 inflammasome

NLRP3 is an intracellular sensor belonging to the NLRs with nucleotide-binding structural domains (NBD) and leucine-rich repeat sequences (LRR) [32,33]. The NLRP3 inflammasome is recognized as the most significant and deeply studied inflammasome [34]. The NLRP3 inflammasome has some unique features compared to other types of inflammasome. First, it is able to recognize multiple stimuli, including microbial components, endogenous molecules, and various particles, which allows it to sense and initiate inflammatory responses under a variety of physiological and disease conditions [33]. Second, the activation mechanism of the NLRP3 inflammasome is relatively complex [35,36]. Finally, the activity of the NLRP3 inflammasome is tightly regulated to ensure that the

inflammatory response proceeds in moderation. Why is the NLRP3 inflammasome particularly important for inflammation? On the one hand, the NLRP3 inflammasome plays a key role in many inflammatory diseases, including rheumatoid arthritis, neurodegenerative diseases, Crohn's disease, and others [37–39]. On the other hand, the activation mechanism of the NLRP3 inflammasome involves many key inflammatory regulation molecules, which provides potential targets for the development of new anti-inflammatory drugs [40]. In addition, understanding the structure and function of the NLRP3 inflammasome will help to further explore the mechanism of inflammatory response and provide more ideas for future treatment [40].

2.3. Structure and activation pathway of NLRP3 inflammasome

NLRP3 has three structural domains: the N-terminal is the pyrin structural domain (PYD), the central structural domain is the nucleotide binding and oligo aggregation structural domain (NACHT) consisting of the NBD, helical structural domain 1 (HD1), the winged helical structural domain (WHD), and helical structural domain 2 (HD2), and the C-terminal is the LRR structural domain [36]. ASC has PYD and cysteine aspartic protease recruitment domains (CARD). The pro-Caspase-1 consists of an N-terminal CARD structural domain, a central large catalytic structural domain (p20), and a C-terminal small catalytic subunit structural domain (p10). When stimulated, the NLRP3 inflammasome recruits ASC proteins mainly through PYD-PYD junctions and then pro-Caspase-1 through CARD-CARD interactions to promote Caspase-1 dimerization and activation [41].

With few exceptions， activation of NLRP3 requires two steps, the initiation step and the activation step. In the first step, existing studies have identified two ways in which the priming process is involved, one of which is the up-regulation of the expression of NLRP3, a component of the inflammasome, as well as pre-inflammatory factors such as IL-1β. The process of transcriptional upregulation is frequently initiated by PRRs that detect PAMPs or DAMPs, as well as cytokines that play a role in the immune and inflammatory response [33,41,42]. Alternatively, the initiation process of NLRP3 can be modulated by diverse post-translational modifications (PTMs), such as ubiquitination and phosphorylation. When the impairment of PTM occurs, it results in a weakened inhibiting effect on NLRP3 [41,43]. In the second step, NLRP3 is activated by a variety of microorganisms, endogenous sterile stimuli, and environmental toxicants. These triggers include lipopolysaccharide and other bacterial toxins adenosine triphosphate (ATP), reactive oxygen species (ROS), α-Syn, lysosomal disruption, and mitochondrial dysfunction [41]. These initiation signals, as well as activation signaling stimuli, lead to NLRP3 inflammasome assembly, including oligomerization of the pattern recognition receptor NLRP3, formation of ASC speckles, and autoproteolytic activation of the effector protease Caspase-1 precursor into activated Caspase-1 [41]. On the one hand, activated Caspase-1 mediates the inflammatory response by cleaving inflammatory cytokines to convert them to their mature form, and on the other hand, it mediates the pro-inflammatory programmed cell death, known as pyroptosis, by cleaving the pyroptosis execution protein GSDMD to generate the N-terminal end of GSDMD and translocating it to form a membrane pore in the cell membrane [44]. In addition to this, Caspase-1 cuts apart α-Syn at once, promoting its aggregation and subsequently exacerbating neuronal toxicity [45].

3. NLRP3 and PD

The NLRP3 inflammasome is a central pro-inflammatory mediator for neurodegenerative diseases as it gets activated from different aseptic cellular stressors commonly found in these diseases, such as protein damage, oxidative stress, mitochondrial dysfunction, environmental toxins, and neuronal death [38,46–48]. PD is a common neurodegenerative disorder that is pathologically characterized by the loss of DANs in the dense portion of the SNpc and the formation of LBs from α-Syn aggregates. DANs project to the striatum and release dopamine (DA) to regulate motor function. The loss of these neurons results in reduced DA production, which causes significant movement disorders [49]. Numerous studies have shown that NLRP3 inflammasome activation is strongly associated with the development of PD, including elevated expression of NLRP3 and cleaved Caspase-1 in serum from PD patients, postmortem midbrain tissue samples, and midbrain from PD model mice [12,13,45,50,51], and the role of NLRP3 inflammasome activation in DAN loss and α-Syn pathology in PD model mice [45]. On the other hand, α-Syn and DAN death were shown to drive activation of the NLRP3 inflammasome [10]. It follows that activation of NLRP3 inflammasome forms a vicious circle with PD pathology. Components of the NLRP3 inflammasome have been reported to be expressed in microglia [38], astrocytes [52], and neurons [12], and it is unclear whether there is an association of the NLRP3 inflammasome between these cells and the mechanism by which NLRP3 is involved in PD has not been elucidated [53].

3.1. NLRP3 in microglia and PD

Previous studies have amply demonstrated that aseptic inflammatory response mediated by hyperactivation of NLRP3 inflammasome in microglia, leading to apoptosis of DANs, is an important pathological mechanism of PD [9,10,38]. Microglia, the main innate immune cells within the central nervous system (CNS) [54], constantly observe their surroundings through PRRs, including toll-like receptors (TLRs) and NLR, and activate NLRP3 inflammasome, which in turn activate microglia to produce large quantities of inflammatory cytokines, leading to DAN degeneration [38,55]. Gordon et al. [9] found a significant increase in cleaved Caspase-1 (p20) and junctional protein ASC within the SNpc of PD patients, localized in ionized calcium-binding adapter molecule 1 (Iba1) positive microglia. These findings are supported by other researchers [45,51]. Studies *in vitro* and *in vivo* models of PD have shown that the NLRP3 inflammasome in microglia interacts with PD pathomechanisms such as α-Syn, DAN death, and mitochondrial dysfunction. Whether pathological α-Syn is a direct inflammasome activator has been a focus of interest. A mouse model of preformed fibrils (PFFs) was successfully constructed by injecting synthetic α-Syn fibers into the mouse striatum, and it was found that the activation of

microglial NLRP3 inflammasome was triggered by a pathway in which α-Syn fibers and DAN degeneration were jointly triggered [10]. However, the NLRP3 inhibitor MCC950 effectively blocked the release of cleaved Caspase-1, IL-1β, and ASC due to NLRP3 activation in microglia and significantly reduced the number of α-Syn aggregates in the substantia nigra (SN) striata of PFF mice, which protected against dyskinesia and nigral DAN degeneration in PFF mice [10]. It has been reported that α-Syn activates the NLRP3 inflammasome in human-induced pluripotent stem cell-derived microglia through dual stimulation that induces TLR2 and causes mitochondrial damage [56]. It was demonstrated that α-Syn entered microglia in an endocytosis-dependent manner, induced lysosomal swelling, increased histone B release, and induced ROS accumulation, which subsequently triggered the activation of NLRP3 inflammasome, leading to the release of large quantities of inflammatory cytokines such as IL-1β and interleukin-18 (IL-18) [50]. In addition, autophagy is associated with the regulation of neuroinflammation. NLRP3, ASC, and Caspase-1 protein levels are elevated in A53T PD model mice expressing the human α-Syn mutation, while degradation of NLRP3 by molecular chaperone-mediated autophagy (CMA) in microglial cells is inhibited via the p38-TFEB pathway [57]. Damaged microglia autophagy promotes the neurotoxin 1-methyl-4--phenyl-1,2,3,6-tetrahydropyridine (MPTP) induced neuroinflammation and DAN degeneration by regulating NLRP3 inflammasome activation [38,58]. In an MPTP-based mouse model of PD, deletion of NLRP3 leads to reduced microglia activation, reduced DAN loss, and attenuated dyskinesia [38]. Caspase-1 deficiency has also been shown to prevent DAN loss and motor dysfunction [59].

Despite intensive research on chronic neuroinflammation and NLRP3 in PD, the exact source of the CNS inflammatory response is still unknown. α-Syn and its aggregates are mostly within neuronal cells and are only perceived by microglia after neuronal injury [60]. Certain neurotoxins, like MPTP, rely on the presence of neurons to activate microglia and cause damage. They achieve this by directly affecting neurons and indirectly by excessively stimulating microglia [61,62]. Although 1-methyl-4-phenylpyridinium ion (MPP^+) does not directly stimulate microglia, the presence of microglia in neuronal cultures amplifies the toxic effects of MPP^+ on DANs. These studies indicate that the overactive production of microglia contributes to the exacerbation and amplification of neuronal damage caused by pathological stimuli and toxins. This process, known as reactive microgliocytosis, appears to result in broader damage to nearby neurons [58,63]. Microglia hyperactivation, initiated by immune injury or direct neuronal damage, can propagate and potentially amplify throughout the progression of neurodegenerative diseases, leading to sustained and cumulative neuronal loss.

3.2. NLRP3 in dopaminergic neurons and PD

Compelling evidence linking intraneuronal NLRP3 to PD in PD patient samples, mouse models, and *in vitro* cellular models (Table 1). For example, von Herrmann et al. [12] conducted histologic and genomic analyses to investigate the potential role of NLRP3 around the course and development of PD. The histological study confirmed the presence of NLRP3 in DANs in the human brain. Additionally, the study showed increased NLRP3 immunoreactivity in the tissues of individuals with PD. The exon sequence database of the Parkinson's Progression Marker Initiative (PPMI) revealed several genetic variations in NLRP3. Among these, one single nucleotide polymorphism (SNP) was found to be linked to a decreased risk of PD. Further *in vitro* analysis of rs7525979 showed that this synonymous SNP can affect the stability, ubiquitination state, and solubility of the NLRP3 protein and alter the NLRP3 protein life cycle. This study demonstrates that intraneuronal NLRP3 plays an important role in the progression of PD and identifies DA neurons as a potential cellular source of inflammasome activity in PD patients. In addition, Panicker and colleagues assessed key inflammasome components in the SN of the midbrain in postmortem PD patients, confirming significantly elevated levels of NLRP3 and cleaved Caspase-1 in DANs as well as the formation of ASC speckles by immunohistochemistry studies [13]. In that study, Panicker et al. further

Table 1
The involvement of NLRP3 inflammasomes in various PD models and patients.

Species	Cell lines	Model	Mechanisms	References
Mouse	hiPSC-derived microglia	α-Syn	α-Syn activates the NLRP3 inflammasome via TLR2 engagement and mitochondrial damage	[56]
Mouse	SN4741 cells, BV2 cells	A53T-tg mice, α-Syn	p38-TFEB-NLRP3	[57]
Mouse	BV2 cells	Parkin KO, LPS	Parkin regulates microglial NLRP3 degradation and protects neurons	[66]
Mouse	Primary midbrain neuron-glia cells	Rotenone, LPS/ATP	SVHRSP might be a new inhibitor of NLRP3 inflammasome	[67]
Rat	MN9D and BV2 cell line	LPS, 6-OHDA	NF-κB/NLRP3/Caspase-1	[68]
Mouse Human	Microglia	A53T and viral-α-Syn overexpression	Fyn/α-Syn/NLRP3/Caspase-1/IL-1β	[9]
Human Mouse	Primary microglial cell hES differentiated DA neuron, SH-SY5Y cells	α-Syn PFF mice $Parkin^{flx/flx}$ mice $Nlrp3^{A350VneoR}$ mice	NLRP3 is a parkin polyubiquitination substrate Parkin/PARIS/NLRP3	[13]
Human Mouse	Primary microglial	6-OHDA, MPTP Mito Park mice α-Syn PFF mice	α-Syn/NLRP3/Caspase-1/IL-1β	[10,69,70]
Mouse	MES23.5 cells SH-SY5Y cells MN9D cells glial cells	6-OHDA MPTP/ATP LPS/ATP	ROS/NLRP3/Caspase-1/IL-1β	[38,65]
Human	HEK293 cells SH-SY5Y cells LUHMES cells	NLRP3 constructs	SNPs reduce the risk of developing PD NLRP3 rs7525979 alters the efficiency of NLRP3 translation impacting NLRP3 protein stability, ubiquitination state, and solubility.	[12]

observed elevated expression levels of NLRP3 and the effector protein Caspase-1 in a PD animal model as well and confirmed by immunohistochemistry that the activation of NLRP3 inflammasome suggesting that NLRP3 inflammasome within DANs are activated in a cell-autonomous fashion [13]. Consistent with this, multiple *in vitro* models of PD confirm elevated NLRP3 expression in DANs [12,64,65]. For the construction of a PD model by treating DANs MES23.5 cells with 6-hydroxydopamine (6-OHDA), for example, elevated NLRP3, ASC, and Caspase-1 protein expression and decreased pro-Caspase-1 protein expression were detected in the model group, suggesting that there is activation of NLRP3 inflammasome in the MES23.5 cells further leading to apoptosis of DANs [65]. Further, von Herrmann et al. found that DANs specifically express a highly activated NLRP3 allele and demonstrated that this allele causes neuroinflammation and motor deficits in aged mice [64]. Taken together, these studies suggest that the NLRP3 inflammasome has the potential to play a role in DANs within the central nervous system. This offers a new understanding of how neurons may initiate or impact inflammation.

4. Role of NLRP3 in PD within dopaminergic neurons

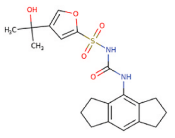
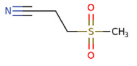
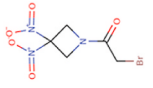
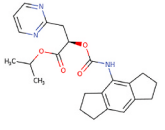
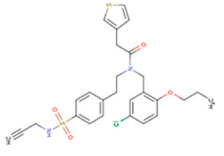
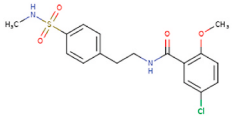
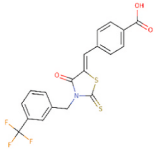
Why are NLRP3 inflammasomes within DANs activated during the course of PD? Typical pathological changes in PD are degeneration and loss of nigrostriatal DANs. Also, nigrostriatal DANs are particularly susceptible to inflammatory injury, which may be related to their reduced antioxidant capacity due to glutathione deficiency, as well as the elevated concentration of redox-active elements such as iron [71–73]. Mitochondrial dysfunction is the most important factor in sporadic and familial PD, caused mainly by mitochondrial electron transport chain complex I abnormalities, genetic mutations, and altered homeostasis [74]. Furthermore, mitochondrial dysfunction is particularly evident in degenerating DANs in PD patients [75]. However, mitochondrial dysfunction, as well as the release of mitochondrial ROS (mt-ROS) and mitochondrial DNA (mt-DNA) into the cytosol, are key upstream events associated with NLRP3 activation [41]. It has been found that NLRP3 within DANs is a Parkin substrate, and Parkin inhibits NLRP3 inflammasome initiation usually by ubiquitinating NLRP3 protein and designating it for proteasomal degradation [13]. Mutations in the Parkin gene can cause autosomal recessive PD, and Parkin dysfunction is also observed in patients with sporadic PD [76–78]. DA has also been reported to induce NLRP3 protein degradation to inhibit NLRP3 inflammasome activation [2]. Another prominent pathological feature of PD is the massive accumulation of α-Syn within DANs [79]. Several studies have shown that α-Syn can effectively activate NLRP3 inflammasome [46,56,80,81]. Thus, in PD, DAN damage reduces DA secretion and thus negative regulation of NLRP3 inflammasome, while overproduction of ROS within DANs, massive aggregation of α-Syn, and Parkin deficiency have an activating effect on NLRP3 inflammasome, leading to DAN degeneration and loss.

At present, three pathways of NLRP3 inflammasome activation have been proposed, including the classical pathway, the non-classical pathway and the alternative pathway. The classical activation pathway refers to the activation of NLRP3 inflammasome through two steps, namely initiation and activation steps, which include the release of NLRP3 self-inhibition or the increase of NLRP3 expression level, the oligomerization of NACHT, the recruitment of ASC and the self-cleavage of Caspase-1, and the cleavage maturation of IL-1β and GSDMD [82–84]. Among the activation mechanisms described below, the activation of NLRP3 inflammasome induced by ROS and α-Syn belongs to the classical activation pathway. The NLRP3 inflammasome complex assembled in Parkin-deficient hDA neurons detected GSDMD-mediated pyroptosis and did not result in detectable IL-1β or IL-18 secretion [13]. These results suggest that the pathway of NLRP3 inflammasome activation induced by Parkin deletion in dopamine neurons may be different from that in myeloid cells [13]. The non-classical activation pathway is that the endotoxin released from bacterial wall degradation stimulates caspase-4 and Caspase-5 in humans and caspase-11 in mice, leading to oligomerization and self-cleavage of Caspase, cleavage of GSDMD, resulting in the plasma membrane pores inducing pyroptosis, and dispersing intracellular K^+ levels [85–87]. Which activates the NLRP3 inflammasome. Finally, the NLRP3 alternative activation pathway, involving the involvement of TLR4 and Caspase-8, does not require K^+ outflow and does not cause pyroptosis, and can cause IL-1β or IL-18 secretion [88]. However, the exact role and molecular target of the initiation and activation of NLRP3 inflammasome in the progression of PD in dopamine neurons remains a challenging task.

4.1. ROS and NLRP3 inflammasome activation

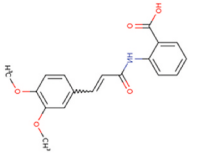
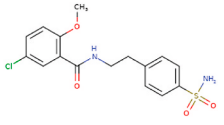
ROS are chemically active compounds characterized by unpaired electrons and high oxygen content. They result in both cellular stress and the cellular immune response [89–92]. ROS in biological systems can arise from cellular oxidative metabolism or be generated by intracellular oxidases like cyclooxygenase and nicotinamide adenine dinucleotide phosphate oxidase [93–95]. ROS is commonly considered to be the primary mediator of NLRP3 inflammasome activation [45,96,97]. The mechanisms of ROS-mediated activation of NLRP3 inflammasome are currently thought to include mt-ROS, oxidized mt-DNA, and thioredoxin interacting protein (TXNIP) [41,98]. A large number of studies using antioxidants (e.g., N-acetylcysteine [NAC]) support the idea that ROS are key mediators of NLRP3 inflammasome activation [99,100]. Han et al. established an *in vitro* model of PD by treating DANs MES23.5 cells with 6-OHDA and found that 6-OHDA could further activate the expression of NLRP3 inflammasome by inducing ROS, which led to apoptosis of MES23.5 cells. In contrast, intervention with NAC, an inhibitor of ROS, significantly reduced NLRP3 activation, thereby protecting neuronal cells. It was demonstrated that Antrodia camphorata polysaccharide (ACP) inhibited 6-OHDA-induced expression of ROS, and NLRP3 and exerted a protective effect in MES23.5 cells. Animal experiments also confirmed that ACP intervention reduced the expression levels of ROS and NLRP3 in the SN striata and improved locomotor activity in PD mice. Despite the large number of studies showing that ROS interacts with NLRP3 inflammasome, the all-important question of how ROS affects NLRP3 inflammasome activation is not fully understood. Although ROS are classically thought to be activators of inflammasomes [3], it has also been suggested that ROS may also play a role in their initiation [41].

Table 2
List of some NLRP3 inhibitors in clinical and preclinical development.

Inhibitor	Structure	Mechanism of action	Disease model	R&D stage	Cause of failure	References
MCC950		Binding to NACHT domain inhibits ATPase activity and closes active conformation	PD, AD, CAPS, ischemic stroke, TBI, T2DM, age-related metabolic, peritonitis, etc.	terminated in Phase II trial	liver toxicity	[56,119,120]
OLT1177		Prevents NLRP3-ASC and NLRP3-Caspase-1 interaction, inhibits ATPase activity of NLRP3	Mouse LPS-induced systemic inflammation, CAPS, PD, AD, colitis, arthritis, etc.	Phase II/III trial	N/A	[69,121]
RRx-001		Binds to Cys409 in NACHT and attenuates NLRP3-NEK7 interaction	EAE, DSS colitis, allergic asthma, glioblastoma, etc.	Phase III trial	N/A	[122,123]
NT-0796		Selective inhibition of NLRP3 and Brain BBB penetrating	PD, Diseases of cardiovascular system, etc.	Phase II trial	N/A	[124]
YQ 128		Selective inhibition of NLRP3 and brain BBB penetrating	LPS induced activation of NLRP3 in peritoneal macrophages in mice	Preclinical trial	N/A	[125]
JC-124		blocking ASC aggregation, activation of caspase-1, and release of IL-1β in macrophages that constitutively express active NLRP3	Mouse model of AD, neuroinflammation in mouse TBI, and mouse AMI, IBD.	Preclinical trial	N/A	[126,127]
CY-09		Binds to Walker A site in NACHT domain, inhibits ATPase activity	Stroke, T2DM, diabetic retinopathy, diabetic liver injury, NAFLD, peritonitis, epilepsy, etc.	Preclinical trial	N/A	[128]

(*continued on next page*)

Table 2 (*continued*)

Inhibitor	Structure	Mechanism of action	Disease model	R&D stage	Cause of failure	References
Tranilast		Binds to NACHT disrupting NLRP3–NLRP3 interactions and blocking oligomerization	gouty arthritis, cryopyrin-associated autoinflammatory syndromes, T2DM, GDM, nanoparticle cerebral toxicity, etc.	Approved	N/A	[129,130]
VTX-2735	Unknown	Selective inhibition of NLRP3	inflammatory diseases and CAPS	Phase II trial	N/A	No
IPS-07004	Unknown	Selective inhibition of NLRP3	Inflammation, Asthma, PD	Phase I trial	N/A	No
VTX-3232	Unknown	Selective inhibition of NLRP3	AD, MS, PD	Phase I trial	N/A	[131]
JC-121		Selective inhibition of NLRP3	Inflammation	Preclinical trial	N/A	[132]
VENT 02	Unknown	NLRP3 inhibitor	Neurodegenerative disease	Preclinical trial	N/A	No
ZYIL-1	Unknown	NLRP3 inhibitor	ALS, CAPS, PD, etc.	Phase II trial	N/A	[133]

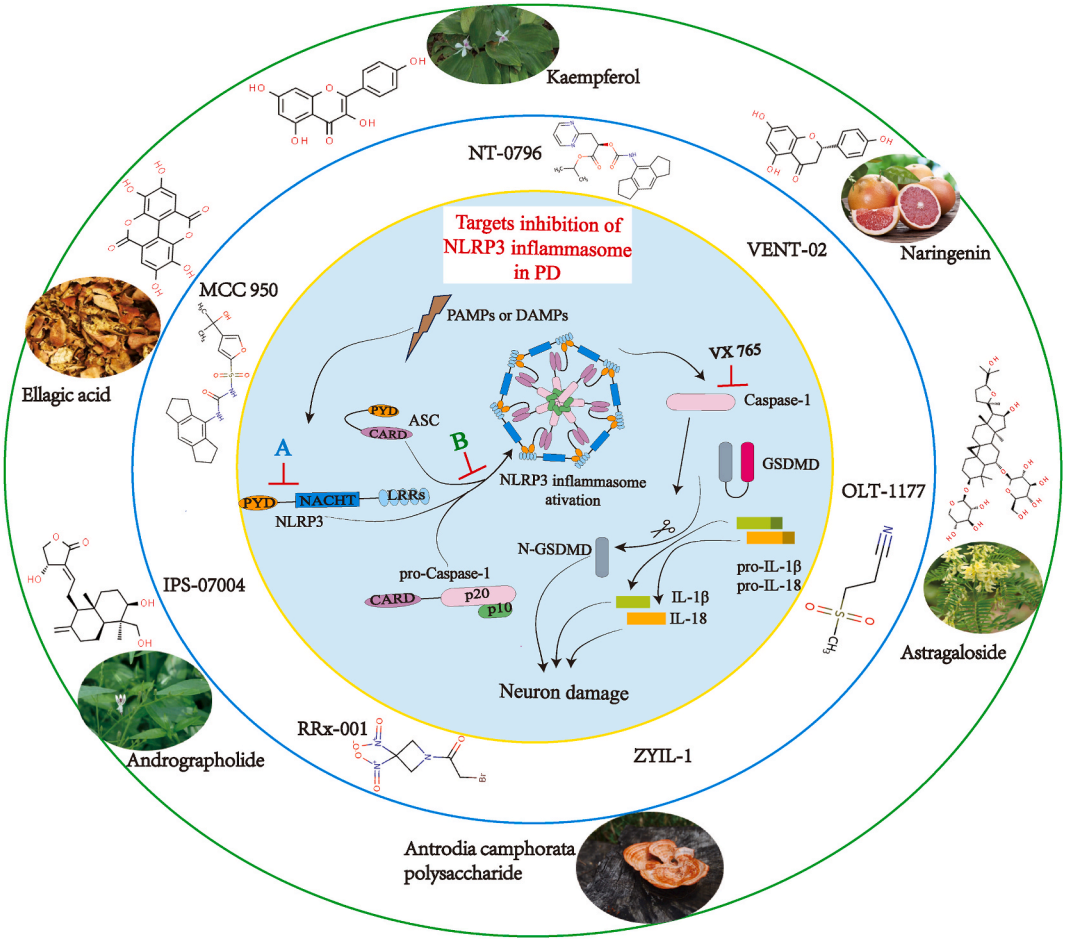


Fig. 1. Targets inhibition of NLRP3 inflammasome activation in PD.

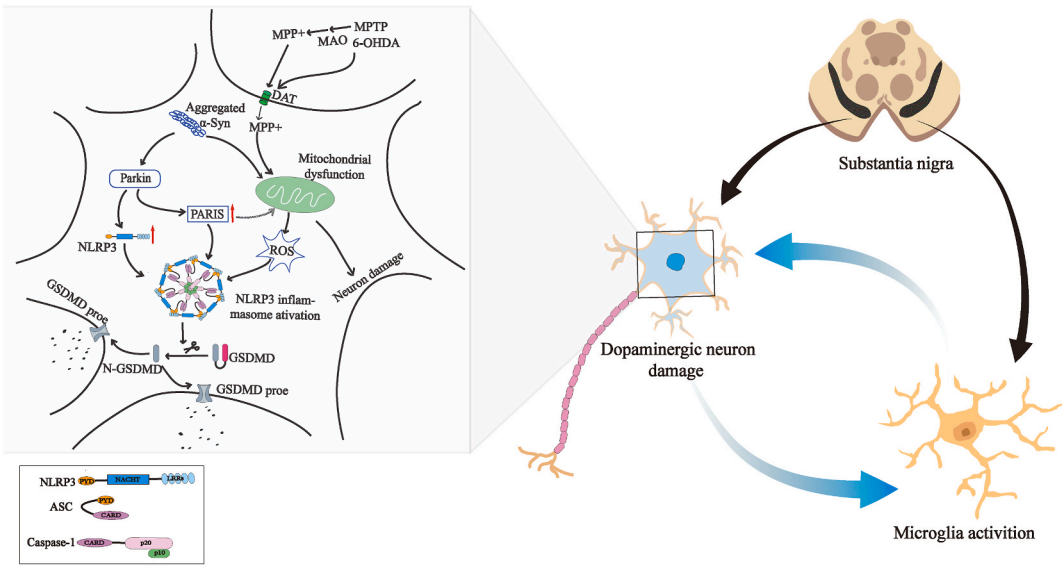


Fig. 2. Simplified mechanistic representation of NLRP3 activation within dopaminergic neurons in PD: Despite the presence of compelling evidence, numerous unresolved questions warrant further discussion.

4.2. Parkin and NLRP3 inflammasome activation

Parkin is an E3 ubiquitin ligase that contains a ubiquitin domain (Ubl) and four loop domains [101]. Mutations in PRKN (encoding Parkin) are frequently responsible for both autosomal recessive and sporadic cases of PD [77,102,103]. The deficiency of Parkin function results in the buildup of impaired mitochondria and increased levels of ROS [104], which are major triggers of the NLRP3 inflammasome [47]. A recent study has shown that NLRP3 within neurons is a parkin substrate and that Parkin inhibits the initiation of inflammasomes usually by ubiquitinating NLRP3 and degrading it through the proteasome [13]. In PD, parkin function is usually disrupted, so NLRP3 levels may be elevated in DANs, potentially increasing the chance of inflammasome activation. Parkin loss of function also leads to NLRP3 inflammasome activation through the accumulation of its interacting substrate (PARIS) ZNF746.In this study, the authors demonstrated through experiments in an animal model of PD induced by DA neuron-specific Parkin deficiency that Parkin depletion resulted in significant upregulation of activated Caspase-1, NLRP3, and ASC speckle formation in SNpc DA neurons, but no significant upregulation was seen in microglia. Cleavage of GSDMD was observed in DA neuron-specific Parkin-deficient mice as well as Parkin-deficient human DANs. In addition, through an immunoprecipitation study of postmortem midbrain lysates from PD patients, the authors found that Parkin and NLRP3 interact. To further verify whether inflammasome activation by itself is sufficient to promote neurodegeneration, the authors chose an NLRP3^{A350VneoR} mouse in which Cre-expressing cells produce a structurally active form of NLRP3. Injection of Cre into the SNpc of adult NLRP3^{A350VneoR} mice via adeno-associated virus (AAV) induced hyperactivation of NLRP3 within DANs and a notable reduction of tyrosine hydroxylase positive (TH^+) neurons in the SNpc. The present experiments provide evidence that Parkin deficiency leads to autonomous activation of NLRP3 inflammasome within neurons and demonstrate that NLRP3 inflammasome activation alone is sufficient to trigger neuronal death. It was further confirmed by behavioral experiments that DAN death is accompanied by dyskinesia. In contrast, the death of Parkin-deficient human DANs and restoration of TH expression was prevented with the NLRP3 inflammasome-specific inhibitor compound MCC950 [13]. However, the current study has not yet elucidated whether Parkin deficiency triggers NLRP3 inflammasome within neurons due to altered mitochondrial quality control, which may result in the release of ROS and other pro-inflammatory factors.

4.3. α-Syn and NLRP3 inflammasome activation

One of the most common and prominent pathological features of PD is the formation of LBs by α-Syn aggregates [105]. Mutations in the SNCA gene cause autosomal dominant PD [106]. Construction of a PD model by intra-striatal injection of α-Syn PFF in mice, which is characterized by the accumulation of LBs in neurons [107]. Panicker et al. conducted a study in which mice were administered α-Syn PFF via intra-striatal injections. The researchers observed indications of inflammasome activation, including elevated levels of NLRP3 and cleavage of Caspase-1 in TH^+ neurons [13]. It was shown that intra-striatal injection of α-Syn PFF resulted in a decrease in Parkin activity in the ventral midbrain, which was accompanied by the initiation and activation of NLRP3 inflammasome [13]. This is consistent with previous studies that inactivation of Parkin after intra-striatal injection of PFF with α-Syn in mice leads to Parkin substrate accumulation and mitochondrial defects [108]. Parkin deficiency has been demonstrated to cause inhibition of mitochondrial biogenesis through the action of PARIS, leading to stress in DANs [109]. Based on this, Panicker et al. conducted a study where they disrupted the ZNF746 gene, which encodes PARIS, in Parkin$^{flx/flx}$ AAV-Cre mice. The purpose was to investigate the potential role of PARIS in the activation of the NLRP3 inflammasome [13]. The findings demonstrate that in the absence of PARIS, the assembly, and activation of inflammasome is almost completely blocked [13]. Intracellular α-Syn aggregation is thought to be the main pathogenic mechanism of DAN death [107,110], but the role of α-Syn-induced inflammasome activation in the pathogenesis of PD has not been elucidated.

5. NLRP3 is a PD therapeutic target

There is increasing evidence indicating that NLRP3 is significantly involved in PD, and that inhibition of the NLRP3 inflammasome attenuates dyskinesia, DAN degeneration, and the formation of α-Syn nucleoprotein aggregates [10,13,56,67]. It can be assumed that inhibition of NLRP3 inflammasome activity has great potential in the prevention and treatment of PD. Current research on NLRP3 disease-modifying therapies is mainly through inhibition of NLRP3-related signaling pathways, including inhibition of NLRP3 itself, inhibition of Caspase-1 [111], IL-1β [112], and GSDMD [113]. However, neither targeting Caspase-1, IL-1β, nor GSDMD is specific, as their cleavage or maturation may be influenced by activation of other types of inflammasome, potentially impacting the host defense response. Inhibition of the NLRP3 inflammasome resulted in more specificity, safety, and better efficacy. With a deeper understanding of the high-resolution structure and activation mechanism of NLRP3, the development of targeted drugs for NLRP3-mediated disease treatment will be more favorable. Several NLRP3 inflammasome inhibitors have recently emerged and been studied in various disease states; Some are already in clinical trials (Table 2). A number of studies have identified the inflammasome as a target for the treatment of PD, utilizing exogenous substances to effectively inhibit NLRP3 inflammasome activity and achieving favorable therapeutic results. Among them, MCC950 is considered to be the NLRP3-specific small molecule inhibitor and the most widely studied, including MitoPark mice, α-Syn PFF mice, A53T-Transgenic mice, and Parkin$^{flx/flx}$ mice [10,13,57,66]. However, development was discontinued due to severe liver toxicity in a Phase II clinical trial in rheumatoid arthritis. Therefore, screening of safe and effective NLRP3 inflammasome inhibitors from herbal medicines is expected to be a candidate treatment for NLRP3-mediated diseases. Many herbs have been used in the treatment of inflammasome diseases and have shown a favorable safety profile (Fig. 1), for example kaempferol, naringenin, astragaloside, antrodia camphorata polysaccharide, andrographolide [114–118]. However, clinical efficacy, safety, and being able to pass through the blood-brain barrier are still big problems for NLRP3 inhibitors that are being developed for the CNS.

6. Conclusion

In PD, most studies on NLRP3 have focused on microglia. However, triggers of the inflammasome assembly may also be present in other cell populations of the PD brain environment, including DANs. This review summarizes the progress of research on NLRP3 and its mechanism of action in PD in recent years. In the current study, evidence for activation of NLRP3 inflammasome in neurons has been reported, including in human PD tissues, in the SN striata of multiple PD model mice, and DANs derived from embryonic stem cells [12,13,64]. DANs are the cells of origin of NLRP3 inflammasome activation, and further studies revealed that NLRP3 inflammasome within DANs is activated in a cell-autonomous manner and leads to loss of neuronal degeneration, which promotes the development of PD [13]. In conclusion, NLRP3 activation-mediated pyroptosis within DANs is an important death pathway for degenerative loss of DANs. NLRP3 in DANs may be activated in a neuronal cell-autonomous manner leading to neuronal death in response to common endogenous or exogenous stimuli in PD such as pathological α-Syn, neurotoxins (MPTP, 6-OHDA), or Parkin deficiency. The increase in neurons and their release of α-Syn or the decrease in DA secretion after injury can promote the activation of NLRP3 inflammasome in microglia and the release of large amounts of pro-inflammatory factors, which further exacerbate the degenerative loss of DANs. Thus, the activation of NLRP3 within DANs and microglia in PD may regulate each other, resulting in a positive feedback type of damage loop (Fig. 2). So, inhibition of NLRP3 activation may become a reliable target for PD disease modification. However, it remains to be determined whether only NLRP3 protein or all inflammasome components of NLRP3 are present in neurons at the same time. Furthermore, the etiology of DAN death in PD is complex, and NLRP3 plays an important role in the development of PD, but the extent to which the inflammatory response causes or promotes DAN loss remains unclear. There are still a lot of questions that need to be answered about how inflammasome activation starts and stays active in PD, as it begins, and how it affects neuronal damage.

The NLRP3 inflammasome is known to be involved in multiple cell death pathways, including apoptosis, pyroptosis [134], and necrosis [135], and understanding how these cell death pathways are interconnected may provide insight into the mechanisms of these cell death pathways and how to inhibit or activate them. In addition, we can explore the role of other inflammasome in PD to see if they interact with the NLRP3 inflammasome or regulate its activity.

Finally, we can develop new therapies by studying how to modulate the activity of the NLRP3 inflammasome. There is currently no effective treatment for the NLRP3 inflammasome in PD, so developing new treatments is the focus of current research. We can inhibit the activity of NLRP3 by screening for small molecule inhibitors or modulators, thereby reducing the inflammatory response and damage to dopamine neurons. In addition, other treatments such as gene therapy and cell therapy can be explored to combat the progression of PD. When developing new treatments, individual differences and the heterogeneity of the disease need to be considered in order to develop personalized treatment plans and improve treatment effectiveness. At the same time, attention should also be paid to the prevention and early diagnosis of the disease to reduce the incidence of PD and prevent the rapid progression of the disease.

Funding statement

This work was supported by the National Natural Science Foundation of China (82260774), Zunyi Science and Technology Bureau (HZ-2022-50, HZ-2021-274, HZ-2020-108, scientific and technological innovation talent team project of the Zunyi [2022]2), and Guizhou Provincial Department of Science and Technology (ZK[2023]-4904).

Data availability statement

No data was used for the research described in the article.

CRediT authorship contribution statement

Juan Yu: Writing – review & editing, Writing – original draft. **Zhanghong Zhao:** Writing – review & editing. **Yuanyuan Li:** Writing – review & editing, Funding acquisition. **Jian Chen:** Writing – review & editing. **Nanqu Huang:** Writing – review & editing, Conceptualization, Investigation, Funding acquisition. **Yong Luo:** Writing – review & editing, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Abbreviations

6-OHDA	6-hydroxydopamine
AAV	Adeno-associated virus
ACP	Antrodia camphorata polysaccharide
ASC	Apoptosis-associated speck-like protein
ATP	Adenosine triphosphate
α-Syn	α-synuclein
Caspase-1	Cysteinyl aspartate specific proteinase 1

CARD	Cysteine aspartic protease recruitment domains
CMA	Chaperone-mediated autophagy
CNS	Central nervous system
DAMPs	Damage-associated molecular patterns
DAN	Dopaminergic neuron
GSDMD	Gasdermin D
HD1	Helical structural domain 1
HD2	Helical structural domain 2
Iba1	Ionized calcium-binding adapter molecule 1
IL-1β	Interleukin-1β
IL-18	Interleukin-18
LBs	Lewy bodies
MPP^+	1-methyl-4-phenyl pyridinium ion
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
mt-DNA	Mitochondrial DNA
mt-ROS	Mitochondrial ROS
NAC	N-acetylcysteine
NACHT	Nucleotide binding and oligo aggregation structural domain
NBD	Nucleotide-binding structural domains
NLRP3	Nucleotide-binding oligomerization domain-like receptor protein 3
NLRs	The NOD-like receptors
NOD	The nucleotide-binding domain
PAMPs	Pathogen-associated molecular patterns
PD	Parkinson's disease
PFFs	Preformed fibrils
PPMI	Parkinson's Progression Marker Initiative
PRRs	Pattern recognition receptors
PTMs	Post-translational modifications
PYD	Pyrin structural domain
ROS	Reactive oxygen species
SN	Substantia nigra
SNP	Single nucleotide polymorphism
SNpc	Substantia nigra pars compacta
TH^+	Tyrosine hydroxylase positive
TLRs	Toll-like receptors
TXNIP	Thioredoxin interacting protein
WHD	Winged helical structural domain

References

[1] E.R. Dorsey, T. Sherer, M.S. Okun, B.R. Bloem, The emerging evidence of the Parkinson pandemic, J. Parkinsons Dis. 8 (2018) S3–S8.

[2] Y. Yan, W. Jiang, L. Liu, X. Wang, C. Ding, Z. Tian, et al., Dopamine controls systemic inflammation through inhibition of NLRP3 inflammasome, Cell 160 (2015) 62–73.

[3] F.M. de Araújo, L. Cuenca-Bermejo, E. Fernández-Villalba, S.L. Costa, V.D.A. Silva, M.T. Herrero, Role of microgliosis and NLRP3 inflammasome in Parkinson's disease pathogenesis and therapy, Cell. Mol. Neurobiol. 42 (2022) 1283–1300.

[4] D. Santos García, T. de Deus Fonticoba, E. Suárez Castro, C. Borrué, M. Mata, B. Solano Vila, et al., Non-motor symptoms burden, mood, and gait problems are the most significant factors contributing to a poor quality of life in non-demented Parkinson's disease patients: results from the COPPADIS Study Cohort, Parkinsonism Relat. Disorders 66 (2019) 151–157.

[5] B. Adams, J.M. Nunes, M.J. Page, T. Roberts, J. Carr, T.A. Nell, et al., Parkinson's disease: a systemic inflammatory disease accompanied by bacterial inflammagens, Front. Aging Neurosci. 11 (2019) 210.

[6] E. Kip, L.C. Parr-Brownlie, Reducing neuroinflammation via therapeutic compounds and lifestyle to prevent or delay progression of Parkinson's disease, Ageing Res. Rev. 78 (2022) 101618.

[7] C. Castillo-Rangel, G. Marin, K.A. Hernández-Contreras, M.M. Vichi-Ramírez, C. Zarate-Calderon, O. Torres-Pineda, et al., Neuroinflammation in Parkinson's disease: from gene to clinic: a systematic review, Int. J. Mol. Sci. 24 (2023) 5792.

[8] Q. Ma, Pharmacological inhibition of the NLRP3 inflammasome: structure, molecular activation, and inhibitor-NLRP3 interaction, Pharmacol. Rev. 75 (2023) 487–520.

[9] N. Panicker, S. Sarkar, D.S. Harischandra, M. Neal, T.I. Kam, H. Jin, et al., Fyn kinase regulates misfolded α-synuclein uptake and NLRP3 inflammasome activation in microglia, J. Exp. Med. 216 (2019) 1411–1430.

[10] R. Gordon, E.A. Albornoz, D.C. Christie, M.R. Langley, V. Kumar, S. Mantovani, et al., Inflammasome inhibition prevents α-synuclein pathology and dopaminergic neurodegeneration in mice, Sci. Transl. Med. 10 (2018) eaah4066.

[11] H.M. Gao, B. Liu, W. Zhang, J.S. Hong, Critical role of microglial NADPH oxidase-derived free radicals in the in vitro MPTP model of Parkinson's disease, Faseb. J. 17 (2003) 1954–1956.

[12] K.M. von Herrmann, L.A. Salas, E.M. Martinez, A.L. Young, J.M. Howard, M.S. Feldman, et al., NLRP3 expression in mesencephalic neurons and characterization of a rare NLRP3 polymorphism associated with decreased risk of Parkinson's disease, NPJ Parkinsons Dis. 4 (2018) 24.

[13] N. Panicker, T.I. Kam, H. Wang, S. Neifert, S.C. Chou, M. Kumar, et al., Neuronal NLRP3 is a parkin substrate that drives neurodegeneration in Parkinson's disease, Neuron 110 (2022) 2422–2437.e9.
[14] F. Martinon, K. Burns, J. Tschopp, The inflammasome: a molecular platform triggering activation of inflammatory caspases and processing of proIL-beta, Mol. Cell. 10 (2002) 417–426.
[15] P. Broz, V.M. Dixit, Inflammasomes: mechanism of assembly, regulation and signalling, Nat. Rev. Immunol. 16 (2016) 407–420.
[16] M. Lamkanfi, V.M. Dixit, Mechanisms and functions of inflammasomes, Cell 157 (2014) 1013–1022.
[17] V. Hornung, A. Ablasser, M. Charrel-Dennis, F. Bauernfeind, G. Horvath, D.R. Caffrey, et al., AIM2 recognizes cytosolic dsDNA and forms a caspase-1-activating inflammasome with ASC, Nature 458 (2009) 514–518.
[18] L. Agostini, F. Martinon, K. Burns, M.F. McDermott, P.N. Hawkins, J. Tschopp, NALP3 forms an IL-1beta-processing inflammasome with increased activity in Muckle-Wells autoinflammatory disorder, Immunity 20 (2004) 319–325.
[19] J.S. Damiano, R.M. Newman, J.C. Reed, Multiple roles of CLAN (caspase-associated recruitment domain, leucine-rich repeat, and NAIP CIIA HET-E, and TP1-containing protein) in the mammalian innate immune response, J. Immunol. 173 (2004) 6338–6345.
[20] S.L. Kempster, G. Belteki, A.J. Forhead, A.L. Fowden, R.D. Catalano, B.Y. Lam, et al., Developmental control of the Nlrp6 inflammasome and a substrate, IL-18, in mammalian intestine, Am. J. Physiol. Gastrointest. Liver Physiol. 300 (2011) G253–G263.
[21] M. Marleaux, K. Anand, E. Latz, M. Geyer, Crystal structure of the human NLRP9 pyrin domain suggests a distinct mode of inflammasome assembly, FEBS Lett. 594 (2020) 2383–2395.
[22] S. Murdoch, U. Djuric, B. Mazhar, M. Seoud, R. Khan, R. Kuick, et al., Mutations in NALP7 cause recurrent hydatidiform moles and reproductive wastage in humans, Nat. Genet. 38 (2006) 300–302.
[23] P. Rozario, M. Pinilla, L. Gorse, A.C. Vind, K.S. Robinson, G.A. Toh, et al., Mechanistic basis for potassium efflux-driven activation of the human NLRP1 inflammasome, Proc. Natl. Acad. Sci. U.S.A. 121 (2024) e2309579121.
[24] C. Guy, M. Baran, P. Ribó-Molina, B.G. van den Hoogen, A.G. Bowie, Viral sensing by epithelial cells involves PKR- and caspase-3-dependent generation of gasdermin E pores, iScience 26 (2023) 107698.
[25] N. Naseer, M.S. Egan, V.M. Reyes Ruiz, W.P. Scott, E.N. Hunter, T. Demissie, et al., Human NAIP/NLRC4 and NLRP3 inflammasomes detect Salmonella type III secretion system activities to restrict intracellular bacterial replication, PLoS Pathog. 18 (2022) e1009718.
[26] V.M. Reyes Ruiz, J. Ramirez, N. Naseer, N.M. Palacio, I.J. Siddarthan, B.M. Yan, et al., Broad detection of bacterial type III secretion system and flagellin proteins by the human NAIP/NLRC4 inflammasome, Proc. Natl. Acad. Sci. U.S.A. 114 (2017) 13242–13247.
[27] S. Lee, R. Karki, Y. Wang, L.N. Nguyen, R.C. Kalathur, T.D. Kanneganti, AIM2 forms a complex with pyrin and ZBP1 to drive PANoptosis and host defence, Nature 597 (2021) 415–419.
[28] V.A. Rathinam, Z. Jiang, S.N. Waggoner, S. Sharma, L.E. Cole, L. Waggoner, et al., The AIM2 inflammasome is essential for host defense against cytosolic bacteria and DNA viruses, Nat. Immunol. 11 (2010) 395–402.
[29] E. Elinav, T. Strowig, A.L. Kau, J. Henao-Mejia, C.A. Thaiss, C.J. Booth, et al., NLRP6 inflammasome regulates colonic microbial ecology and risk for colitis, Cell 145 (2011) 745–757.
[30] C. Messaed, E. Akoury, U. Djuric, J. Zeng, M. Saleh, L. Gilbert, et al., NLRP7, a nucleotide oligomerization domain-like receptor protein, is required for normal cytokine secretion and co-localizes with Golgi and the microtubule-organizing center, J. Biol. Chem. 286 (2011) 43313–43323.
[31] S. Zhu, S. Ding, P. Wang, Z. Wei, W. Pan, N.W. Palm, et al., Nlrp9b inflammasome restricts rotavirus infection in intestinal epithelial cells, Nature 546 (2017) 667–670.
[32] M.E. Haque, M. Akther, M. Jakaria, I.S. Kim, S. Azam, D.K. Choi, Targeting the microglial NLRP3 inflammasome and its role in Parkinson's disease, Mov. Disord. 35 (2020) 20–33.
[33] K. Schroder, J. Tschopp, The inflammasomes, Cell 140 (2010) 821–832.
[34] N. Murphy, T.R. Cowley, J.C. Richardson, D. Virley, N. Upton, D. Walter, et al., The neuroprotective effect of a specific $P2X_7$ receptor antagonist derives from its ability to inhibit assembly of the NLRP3 inflammasome in glial cells, Brain Pathol. 22 (2012) 295–306.
[35] J. Fu, H. Wu, Structural mechanisms of NLRP3 inflammasome assembly and activation, Annu. Rev. Immunol. 41 (2023) 301–316.
[36] H. Sharif, L. Wang, W.L. Wang, V.G. Magupalli, L. Andreeva, Q. Qiao, et al., Structural mechanism for NEK7-licensed activation of NLRP3 inflammasome, Nature 570 (2019) 338–343.
[37] S. Rosengren, H.M. Hoffman, W. Bugbee, D.L. Boyle, Expression and regulation of cryopyrin and related proteins in rheumatoid arthritis synovium, Ann. Rheum. Dis. 64 (2005) 708–714.
[38] E. Lee, I. Hwang, S. Park, S. Hong, B. Hwang, Y. Cho, et al., MPTP-driven NLRP3 inflammasome activation in microglia plays a central role in dopaminergic neurodegeneration, Cell Death Differ. 26 (2019) 213–228.
[39] A.C. Villani, M. Lemire, G. Fortin, E. Louis, M.S. Silverberg, C. Collette, et al., Common variants in the NLRP3 region contribute to Crohn's disease susceptibility, Nat. Genet. 41 (2009) 71–76.
[40] L. Vande Walle, M. Lamkanfi, Drugging the NLRP3 inflammasome: from signalling mechanisms to therapeutic targets, Nat. Rev. Drug Discov. 23 (2024) 43–66.
[41] K.V. Swanson, M. Deng, J.P. Ting, The NLRP3 inflammasome: molecular activation and regulation to therapeutics, Nat. Rev. Immunol. 19 (2019) 477–489.
[42] A. Gritsenko, J.P. Green, D. Brough, G. Lopez-Castejon, Mechanisms of NLRP3 priming in inflammaging and age related diseases, Cytokine Growth Factor Rev. 55 (2020) 15–25.
[43] M. Sharma, E. de Alba, Structure, activation and regulation of NLRP3 and AIM2 inflammasomes, Int. J. Mol. Sci. 22 (2021) 872.
[44] R.C. Coll, K. Schroder, P. Pelegrín, NLRP3 and pyroptosis blockers for treating inflammatory diseases, Trends Pharmacol. Sci. 43 (2022) 653–668.
[45] W. Wang, L.T. Nguyen, C. Burlak, F. Chegini, F. Guo, T. Chataway, et al., Caspase-1 causes truncation and aggregation of the Parkinson's disease-associated protein α-synuclein, Proc. Natl. Acad. Sci. U.S.A. 113 (2016) 9587–9592.
[46] G. Codolo, N. Plotegher, T. Pozzobon, M. Brucale, I. Tessari, L. Bubacco, et al., Triggering of inflammasome by aggregated α-synuclein, an inflammatory response in synucleinopathies, PLoS One 8 (2013) e55375.
[47] R. Zhou, A.S. Yazdi, P. Menu, J. Tschopp, A role for mitochondria in NLRP3 inflammasome activation, Nature 469 (2011) 221–225.
[48] F.L. Anderson, M.M. Coffey, B.L. Berwin, M.C. Havrda, Inflammasomes: an emerging mechanism translating environmental toxicant exposure into neuroinflammation in Parkinson's disease, Toxicol. Sci. 166 (2018) 3–15.
[49] M.J. Armstrong, M.S. Okun, Diagnosis and treatment of Parkinson disease: a review, JAMA 323 (2020) 548–560.
[50] Y. Zhou, M. Lu, R.H. Du, C. Qiao, C.Y. Jiang, K.Z. Zhang, et al., MicroRNA-7 targets Nod-like receptor protein 3 inflammasome to modulate neuroinflammation in the pathogenesis of Parkinson's disease, Mol. Neurodegener. 11 (2016) 28.
[51] F.L. Anderson, K.M. von Herrmann, A.S. Andrew, Y.I. Kuras, A.L. Young, C.R. Scherzer, et al., Plasma-borne indicators of inflammasome activity in Parkinson's disease patients, NPJ Parkinsons Dis. 7 (2021) 2.
[52] S. Alfonso-Loeches, J.R. Ureña-Peralta, M.J. Morillo-Bargues, J. Oliver-De La Cruz, C. Guerri, Role of mitochondria ROS generation in ethanol-induced NLRP3 inflammasome activation and cell death in astroglial cells, Front. Cell. Neurosci. 8 (2014) 216.
[53] N. Panicker, A. Kanthasamy, A.G. Kanthasamy, Fyn amplifies NLRP3 inflammasome signaling in Parkinson's disease, Aging (Albany NY) 11 (2019) 5871–5873.
[54] M. Prinz, J. Priller, S.S. Sisodia, R.M. Ransohoff, Heterogeneity of CNS myeloid cells and their roles in neurodegeneration, Nat. Neurosci. 14 (2011) 1227–1235.
[55] J.G. Walsh, D.A. Muruve, C. Power, Inflammasomes in the CNS, Nat. Rev. Neurosci. 15 (2014) 84–97.
[56] D. Trudler, K.L. Nazor, Y.S. Eisele, T. Grabauskas, N. Dolatabadi, J. Parker, et al., Soluble α-synuclein-antibody complexes activate the NLRP3 inflammasome in hiPSC-derived microglia, Proc. Natl. Acad. Sci. U. S. A. 118 (2021) e2025847118.
[57] J. Chen, K. Mao, H. Yu, Y. Wen, H. She, H. Zhang, et al., p38-TFEB pathways promote microglia activation through inhibiting CMA-mediated NLRP3 degradation in Parkinson's disease, J. Neuroinflammation 18 (2021) 295.

[58] Y. Qin, J. Qiu, P. Wang, J. Liu, Y. Zhao, F. Jiang, et al., Impaired autophagy in microglia aggravates dopaminergic neurodegeneration by regulating NLRP3 inflammasome activation in experimental models of Parkinson's disease, Brain Behav. Immun. 91 (2021) 324–338.
[59] C. Qiao, L.X. Zhang, X.Y. Sun, J.H. Ding, M. Lu, G. Hu, Caspase-1 deficiency alleviates dopaminergic neuronal death via inhibiting caspase-7/AIF pathway in MPTP/p mouse model of Parkinson's disease, Mol. Neurobiol. 54 (2017) 4292–4302.
[60] R. Chakraborty, T. Nonaka, M. Hasegawa, C. Zurzolo, Tunnelling nanotubes between neuronal and microglial cells allow bi-directional transfer of α-Synuclein and mitochondria, Cell Death Dis. 14 (2023) 329.
[61] P.L. McGeer, C. Schwab, A. Parent, D. Doudet, Presence of reactive microglia in monkey substantia nigra years after 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine administration, Ann. Neurol. 54 (2003) 599–604.
[62] Y.C. Chung, J.Y. Baek, S.R. Kim, H.W. Ko, E. Bok, W.H. Shin, et al., Capsaicin prevents degeneration of dopamine neurons by inhibiting glial activation and oxidative stress in the MPTP model of Parkinson's disease, Exp. Mol. Med. 49 (2017) e298.
[63] J.W. Langston, L.S. Forno, J. Tetrud, A.G. Reeves, J.A. Kaplan, D. Karluk, Evidence of active nerve cell degeneration in the substantia nigra of humans years after 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine exposure, Ann. Neurol. 46 (1999) 598–605.
[64] K.M. von Herrmann, F.L. Anderson, E.M. Martinez, A.L. Young, M.C. Havrda, Slc6a3-dependent expression of a CAPS-associated Nlrp3 allele results in progressive behavioral abnormalities and neuroinflammation in aging mice, J. Neuroinflammation 17 (2020) 213.
[65] C. Han, H. Shen, Y. Yang, Y. Sheng, J. Wang, W. Li, et al., Antrodia camphorata polysaccharide resists 6-OHDA-induced dopaminergic neuronal damage by inhibiting ROS-NLRP3 activation, Brain Behav. 10 (2020) e01824.
[66] Y.Q. Yan, R. Zheng, Y. Liu, Y. Ruan, Z.H. Lin, N.J. Xue, et al., Parkin regulates microglial NLRP3 and represses neurodegeneration in Parkinson's disease, Aging Cell 22 (2023) e13834.
[67] Y. Zhang, S. Li, L. Hou, M. Wu, J. Liu, R. Wang, et al., NLRP3 mediates the neuroprotective effects of SVHRSP derived from scorpion venom in rotenone-induced experimental Parkinson's disease model, J. Ethnopharmacol. 312 (2023) 116497.
[68] X.M. He, Y.Z. Zhou, S. Sheng, J.J. Li, G.Q. Wang, F. Zhang, Ellagic acid protects dopamine neurons via inhibition of NLRP3 inflammasome activation in microglia, Oxid. Med. Cell. Longev. 2020 (2020) 2963540.
[69] J. Amo-Aparicio, J. Daly, J.F. Højen, C.A. Dinarello, Pharmacologic inhibition of NLRP3 reduces the levels of α-synuclein and protects dopaminergic neurons in a model of Parkinson's disease, J. Neuroinflammation 20 (2023) 147.
[70] L. Zhou, D. Han, X. Wang, Z. Chen, Probiotic formulation VSL#3 interacts with mesenchymal stromal cells to protect dopaminergic neurons via centrally and peripherally suppressing NOD-like receptor protein 3 inflammasome-mediated inflammation in Parkinson's disease mice, Microbiol. Spectr. 11 (2023) e0320822.
[71] D.A. Loeffler, A.J. DeMaggio, P.L. Juneau, M.K. Havaich, P.A. LeWitt, Effects of enhanced striatal dopamine turnover in vivo on glutathione oxidation, Clin. Neuropharmacol. 17 (1994) 370–379.
[72] R.J. Ward, F.A. Zucca, J.H. Duyn, R.R. Crichton, L. Zecca, The role of iron in brain ageing and neurodegenerative disorders, Lancet Neurol. 13 (2014) 1045–1060.
[73] M.L. Block, L. Zecca, J.S. Hong, Microglia-mediated neurotoxicity: uncovering the molecular mechanisms, Nat. Rev. Neurosci. 8 (2007) 57–69.
[74] M.P. Helley, J. Pinnell, C. Sportelli, K. Tieu, Mitochondria: a common target for genetic mutations and environmental toxicants in Parkinson's disease, Front. Genet. 8 (2017) 177.
[75] D.J. Surmeier, J.A. Obeso, G.M. Halliday, Selective neuronal vulnerability in Parkinson disease, Nat. Rev. Neurosci. 18 (2017) 101–113.
[76] T.M. Dawson, H.S. Ko, V.L. Dawson, Genetic animal models of Parkinson's disease, Neuron 66 (2010) 646–661.
[77] P. Ge, V.L. Dawson, T.M. Dawson, PINK1 and Parkin mitochondrial quality control: a source of regional vulnerability in Parkinson's disease, Mol. Neurodegener. 15 (2020) 20.
[78] K.K. Chung, B. Thomas, X. Li, O. Pletnikova, J.C. Troncoso, L. Marsh, et al., S-nitrosylation of parkin regulates ubiquitination and compromises parkin's protective function, Science 304 (2004) 1328–1331.
[79] W. Poewe, K. Seppi, C.M. Tanner, G.M. Halliday, P. Brundin, J. Volkmann, et al., Parkinson disease, Nat. Rev. Dis. Prim. 3 (2017) 17013.
[80] R. Di Maio, P.J. Barrett, E.K. Hoffman, C.W. Barrett, A. Zharikov, A. Borah, et al., α-Synuclein binds to TOM20 and inhibits mitochondrial protein import in Parkinson's disease, Sci. Transl. Med. 8 (2016) 342ra78.
[81] F. Piancone, M. Saresella, F. La Rosa, I. Marventano, M. Meloni, J. Navarro, et al., Inflammatory responses to monomeric and aggregated α-synuclein in peripheral blood of Parkinson disease patients, Front. Neurosci. 15 (2021) 639646.
[82] F.G. Bauernfeind, G. Horvath, A. Stutz, E.S. Alnemri, K. MacDonald, D. Speert, et al., Cutting edge: NF-kappaB activating pattern recognition and cytokine receptors license NLRP3 inflammasome activation by regulating NLRP3 expression, J. Immunol. 183 (2009) 787–791.
[83] Y. He, M.Y. Zeng, D. Yang, B. Motro, G. Núñez, NEK7 is an essential mediator of NLRP3 activation downstream of potassium efflux, Nature 530 (2016) 354–357.
[84] M.G. Netea, C.A. Nold-Petry, M.F. Nold, L.A. Joosten, B. Opitz, J.H. van der Meer, et al., Differential requirement for the activation of the inflammasome for processing and release of IL-1beta in monocytes and macrophages, Blood 113 (2009) 2324–2335.
[85] J.C. Santos, D. Boucher, L.K. Schneider, B. Demarco, M. Dilucca, K. Shkarina, et al., Human GBP1 binds LPS to initiate assembly of a caspase-4 activating platform on cytosolic bacteria, Nat. Commun. 11 (2020) 3276.
[86] N. Kayagaki, M.T. Wong, I.B. Stowe, S.R. Ramani, L.C. Gonzalez, S. Akashi-Takamura, et al., Noncanonical inflammasome activation by intracellular LPS independent of TLR4, Science 341 (2013) 1246–1249.
[87] L.A. Knodler, S.M. Crowley, H.P. Sham, H. Yang, M. Wrande, C. Ma, et al., Noncanonical inflammasome activation of caspase-4/caspase-11 mediates epithelial defenses against enteric bacterial pathogens, Cell Host Microbe 16 (2014) 249–256.
[88] M.M. Gaidt, T.S. Ebert, D. Chauhan, T. Schmidt, J.L. Schmid-Burgk, F. Rapino, et al., Human monocytes engage an alternative inflammasome pathway, Immunity 44 (2016) 833–846.
[89] C.P. Rosa, T.C.A. Belo, N.C.M. Santos, E.N. Silva, J. Gasparotto, P.P. Corsetti, et al., Reactive oxygen species trigger inflammasome activation after intracellular microbial interaction, Life Sci. 331 (2023) 122076.
[90] Y. Fichman, L. Rowland, M.J. Oliver, R. Mittler, ROS are evolutionary conserved cell-to-cell stress signals, Proc. Natl. Acad. Sci. U.S.A. 120 (2023) e2305496120.
[91] Y. Nosaka, A.Y. Nosaka, Generation and detection of reactive oxygen species in photocatalysis, Chem. Rev. 117 (2017) 11302–11336.
[92] S. Gligorovski, R. Strekowski, S. Barbati, D. Vione, Environmental implications of hydroxyl radicals ((•)OH), Chem. Rev. 115 (2015) 13051–13092.
[93] A. Dominic, P. Banerjee, D.J. Hamilton, N.T. Le, J.I. Abe, Time-dependent replicative senescence vs. disturbed flow-induced pre-mature aging in atherosclerosis, Redox Biol. 37 (2020) 101614.
[94] K. Block, Y. Gorin, Aiding and abetting roles of NOX oxidases in cellular transformation, Nat. Rev. Cancer 12 (2012) 627–637.
[95] S.S. Sabharwal, P.T. Schumacker, Mitochondrial ROS in cancer: initiators, amplifiers or an Achilles' heel? Nat. Rev. Cancer 14 (2014) 709–721.
[96] L.K. Billingham, J.S. Stoolman, K. Vasan, A.E. Rodriguez, T.A. Poor, M. Szibor, et al., Mitochondrial electron transport chain is necessary for NLRP3 inflammasome activation, Nat. Immunol. 23 (2022) 692–704.
[97] A. Dominic, N.T. Le, M. Takahashi, Loop between NLRP3 inflammasome and reactive oxygen species, Antioxidants Redox Signal. 36 (2022) 784–796.
[98] H. Xian, K. Watari, E. Sanchez-Lopez, J. Offenberger, J. Onyuru, H. Sampath, et al., Oxidized DNA fragments exit mitochondria via mPTP- and VDAC-dependent channels to activate NLRP3 inflammasome and interferon signaling, Immunity 55 (2022) 1370–1385.e8.
[99] J.F. Teng, Q.B. Mei, X.G. Zhou, Y. Tang, R. Xiong, W.Q. Qiu, et al., Polyphyllin VI induces caspase-1-mediated pyroptosis via the induction of ROS/NF-κB/NLRP3/GSDMD signal Axis in non-small cell lung cancer, Cancers 12 (2020) 193.
[100] L.Z. Liao, Z.C. Chen, S.S. Wang, W.B. Liu, C.L. Zhao, X.D. Zhuang, NLRP3 inflammasome activation contributes to the pathogenesis of cardiocytes aging, Aging (Albany NY) 13 (2021) 20534–20551.

[101] J.F. Trempe, V. Sauvé, K. Grenier, M. Seirafi, M.Y. Tang, M. Ménade, et al., Structure of parkin reveals mechanisms for ubiquitin ligase activation, Science 340 (2013) 1451–1455.
[102] T. Kitada, S. Asakawa, N. Hattori, H. Matsumine, Y. Yamamura, S. Minoshima, et al., Mutations in the parkin gene cause autosomal recessive juvenile parkinsonism, Nature 392 (1998) 605–608.
[103] J. Park, S.B. Lee, S. Lee, Y. Kim, S. Song, S. Kim, et al., Mitochondrial dysfunction in Drosophila PINK1 mutants is complemented by parkin, Nature 441 (2006) 1157–1161.
[104] K. Wasner, S. Smajic, J. Ghelfi, S. Delcambre, C.A. Prada-Medina, E. Knappe, et al., Parkin deficiency impairs mitochondrial DNA dynamics and propagates inflammation, Mov. Disord. 37 (2022) 1405–1415.
[105] M.X. Henderson, E.J. Cornblath, A. Darwich, B. Zhang, H. Brown, R.J. Gathagan, et al., Spread of α-synuclein pathology through the brain connectome is modulated by selective vulnerability and predicted by network analysis, Nat. Neurosci. 22 (2019) 1248–1257.
[106] H. Liu, C. Koros, T. Strohäker, C. Schulte, M. Bozi, S. Varvaresos, et al., A novel SNCA A30G mutation causes familial Parkinson's disease, Mov. Disord. 36 (2021) 1624–1633.
[107] K.C. Luk, V. Kehm, J. Carroll, B. Zhang, P. O'Brien, J.Q. Trojanowski, et al., Pathological α-synuclein transmission initiates Parkinson-like neurodegeneration in nontransgenic mice, Science 338 (2012) 949–953.
[108] S. Brahmachari, S. Lee, S. Kim, C. Yuan, S.S. Karuppagounder, P. Ge, et al., Parkin interacting substrate zinc finger protein 746 is a pathological mediator in Parkinson's disease, Brain 142 (2019) 2380–2401.
[109] H. Kim, J.Y. Shin, A. Jo, J.H. Kim, S. Park, J.Y. Choi, et al., Parkin interacting substrate phosphorylation by c-Abl drives dopaminergic neurodegeneration, Brain 144 (2021) 3674–3691.
[110] M.G. Spillantini, M.L. Schmidt, V.M. Lee, J.Q. Trojanowski, R. Jakes, M. Goedert, Alpha-synuclein in Lewy bodies, Nature 388 (1997) 839–840.
[111] M. Qian, X. Shen, H. Wang, The distinct role of ADAM17 in APP proteolysis and microglial activation related to alzheimer's disease, Cell. Mol. Neurobiol. 36 (2016) 471–482.
[112] M.S.J. Mangan, E.J. Olhava, W.R. Roush, H.M. Seidel, G.D. Glick, E. Latz, Targeting the NLRP3 inflammasome in inflammatory diseases, Nat. Rev. Drug Discov. 17 (2018) 688.
[113] S.K. Yadav, N. Ito, D. Soin, K. Ito, S. Dhib-Jalbut, Dimethyl fumarate suppresses demyelination and axonal loss through reduction in pro-inflammatory macrophage-induced reactive astrocytes and complement C3 deposition, J. Clin. Med. 10 (2021) 857.
[114] X. Han, S. Sun, Y. Sun, Q. Song, J. Zhu, N. Song, et al., Small molecule-driven NLRP3 inflammation inhibition via interplay between ubiquitination and autophagy: implications for Parkinson disease, Autophagy 15 (2019) 1860–1881.
[115] C. Chen, Y.Z. Wei, X.M. He, D.D. Li, G.Q. Wang, J.J. Li, et al., Naringenin produces neuroprotection against LPS-induced dopamine neurotoxicity via the inhibition of microglial NLRP3 inflammasome activation, Front. Immunol. 10 (2019) 936.
[116] C. Yang, Y. Mo, E. Xu, H. Wen, R. Wei, S. Li, et al., Astragaloside IV ameliorates motor deficits and dopaminergic neuron degeneration via inhibiting neuroinflammation and oxidative stress in a Parkinson's disease mouse model, Int. Immunopharm. 75 (2019) 105651.
[117] S. Ahmed, M. Kwatra, S. Ranjan Panda, U.S.N. Murty, V.G.M. Naidu, Andrographolide suppresses NLRP3 inflammasome activation in microglia through induction of parkin-mediated mitophagy in in-vitro and in-vivo models of Parkinson disease, Brain Behav. Immun. 91 (2021) 142–158.
[118] C.K. Bhusal, D.E. Uti, D. Mukherjee, T. Alqahtani, S. Alqahtani, A. Bhattacharya, et al., Unveiling Nature's potential: promising natural compounds in Parkinson's disease management, Parkinsonism Relat. Disorders 115 (2023) 105799.
[119] R.C. Coll, J.R. Hill, C.J. Day, A. Zamoshnikova, D. Boucher, N.L. Massey, et al., MCC950 directly targets the NLRP3 ATP-hydrolysis motif for inflammasome inhibition, Nat. Chem. Biol. 15 (2019) 556–559.
[120] A. Tapia-Abellán, D. Angosto-Bazarra, H. Martínez-Banaclocha, C. de Torre-Minguela, J.P. Cerón-Carrasco, H. Pérez-Sánchez, et al., MCC950 closes the active conformation of NLRP3 to an inactive state, Nat. Chem. Biol. 15 (2019) 560–564.
[121] C. Marchetti, B. Swartzwelter, F. Gamboni, C.P. Neff, K. Richter, T. Azam, et al., OLT1177, a β-sulfonyl nitrile compound, safe in humans, inhibits the NLRP3 inflammasome and reverses the metabolic cost of inflammation, Proc. Natl. Acad. Sci. U.S.A. 115 (2018) E1530–e1539.
[122] H. Fine, T. Reid, S. Caroen, B. Oronsky, N. Abrouk, N. Butowski, A multicenter, phase 1, dose escalation clinical trial (G-FORCE-1) of XRT, RRx-001 and temozolomide followed by temozolomide +/- RRx-001 in newly diagnosed glioblastoma, Front. Oncol. 13 (2023) 1176448.
[123] J. Fang, J. She, F. Lin, J.C. Wu, R. Han, R. Sheng, et al., RRx-001 exerts neuroprotection against LPS-induced microglia activation and neuroinflammation through disturbing the TLR4 pathway, Front. Pharmacol. 13 (2022) 889383.
[124] D. Harrison, A. Billinton, M.G. Bock, J.R. Doedens, C.A. Gabel, M.K. Holloway, et al., Discovery of clinical candidate NT-0796, a brain-penetrant and highly potent NLRP3 inflammasome inhibitor for neuroinflammatory disorders, J. Med. Chem. 66 (2023) 14897–14911.
[125] Y. Xu, Y. Xu, H. Blevins, C. Guo, S. Biby, X.Y. Wang, et al., Development of sulfonamide-based NLRP3 inhibitors: further modifications and optimization through structure-activity relationship studies, Eur. J. Med. Chem. 238 (2022) 114468.
[126] R. Kuwar, A. Rolfe, L. Di, H. Xu, L. He, Y. Jiang, et al., A novel small molecular NLRP3 inflammasome inhibitor alleviates neuroinflammatory response following traumatic brain injury, J. Neuroinflammation 16 (2019) 81.
[127] J. Zheng, Z. Jiang, Y. Song, S. Huang, Y. Du, X. Yang, et al., 3,4-Methylenedioxy-β-Nitrostyrene alleviates dextran sulfate sodium-induced mouse colitis by inhibiting the NLRP3 inflammasome, Front. Pharmacol. 13 (2022) 866228.
[128] Y. Zhang, Z. Lin, D. Chen, Y. He, CY-09 attenuates the progression of osteoarthritis via inhibiting NLRP3 inflammasome-mediated pyroptosis, Biochem. Biophys. Res. Commun. 553 (2021) 119–125.
[129] Y. Huang, H. Jiang, Y. Chen, X. Wang, Y. Yang, J. Tao, et al., Tranilast directly targets NLRP3 to treat inflammasome-driven diseases, EMBO Mol. Med. 10 (2018) e8689.
[130] J. Cao, Q. Peng, NLRP3 inhibitor tranilast attenuates gestational diabetes mellitus in a genetic mouse model, Drugs R 22 (2022) 105–112.
[131] X. Chen, Y. Chen, Y. Ou, W. Min, S. Liang, L. Hua, et al., Bortezomib inhibits NLRP3 inflammasome activation and NF-κB pathway to reduce psoriatic inflammation, Biochem. Pharmacol. 206 (2022) 115326.
[132] D. Zuo, N. Do, I. Hwang, J. Ann, J.W. Yu, J. Lee, Design and synthesis of an N-benzyl 5-(4-sulfamoylbenzylidene-2-thioxothiazolidin-4-one scaffold as a novel NLRP3 inflammasome inhibitor, Bioorg. Med. Chem. Lett 65 (2022) 128693.
[133] P. Hissaria, K. Kansagra, H. Patel, T. Momin, A. Ghoghari, H. Patel, et al., SafetyTolerability, pharmacokinetics, and pharmacodynamics of ZY-IL1 in three patients with cryopyrin-associated periodic syndromes, Clin. Pharmacol. Drug Dev. 13 (2024) 152–159.
[134] V. Sagulenko, S.J. Thygesen, D.P. Sester, A. Idris, J.A. Cridland, P.R. Vajjhala, et al., AIM2 and NLRP3 inflammasomes activate both apoptotic and pyroptotic death pathways via ASC, Cell Death Differ. 20 (2013) 1149–1160.
[135] S.B. Willingham, D.T. Bergstralh, W. O'Connor, A.C. Morrison, D.J. Taxman, J.A. Duncan, et al., Microbial pathogen-induced necrotic cell death mediated by the inflammasome components CIAS1/cryopyrin/NLRP3 and ASC, Cell Host Microbe 2 (2007) 147–159.