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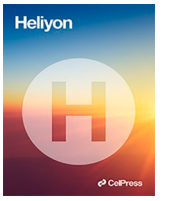

Review article

# Molecular crosstalk between circadian clock and NLRP3 inflammasome signaling in Parkinson's disease

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ABSTRACT

Parkinson's disease (PD) is one of the most common neurodegenerative diseases. Research has recently found that both animal models and patients with PD have circadian dysfunction, accompanied by abnormal expression of circadian genes and proteins, which implies that the circadian clock plays a crucial role in PD etiopathogenesis. In addition, a strong relationship between NLRP3 inflammasome signaling and PD has been observed. Meanwhile, the activation of the NLRP3 inflammasome is highly relevant to dysfunctions of the molecular clock. Therefore, alleviating the neuroinflammation caused by NLRP3 inflammasome signaling by adjusting the abnormal molecular clock may be a potential strategy for preventing and treating PD. In this article, we have reviewed the potential or direct relationship between abnormalities of the circadian clock and NLRP3 inflammasome signaling in PD.

## 1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease globally [1] and mainly exhibits motor symptoms, including bradykinesia, tremor, myotonia, and postural instability, accompanied by nonmotor symptoms, such as depression and insomnia, which seriously affect the patient's quality of life. The current treatment for PD is mainly based on the supplementation of dopamine in the brain, which alleviates some symptoms of patients but cannot slow and prevent the progression of the disease. Previous studies have indicated that there is circadian dysfunction in PD patients, which manifests not only as abnormal expression of clock genes and proteins but also as a series of behavioral and physiological desynchronization [ [2,3]]. There are a variety of abnormal rhythms in the course of PD, such as unusual diurnal fluctuation of levodopa responsiveness [ [4,5]], sleep-wake cycle [6], hormone secretion [7], and blood pressure [8]. Meanwhile, improving the circadian rhythm of PD patients, such as by receiving bright light therapy (BLT) at an appropriate time [9] or taking melatonin (MLT) [10], effectively alleviates the symptoms of patients, which suggests that circadian dysfunction plays a crucial role in PD etiopathogenesis and may be a new target for PD treatment.

In addition, many studies have indicated the relationship between neuroinflammation and PD. The NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome is a crucial regulator of neuroinflammation, which is highly relevant to PD progression [11]. Previous studies have shown that there is enhanced expression of NLRP3, an apoptosis-associated speck-like protein containing a caspase activation and recruitment domain (CARD) (ASC), and caspase-1 in the substantia nigra of PD model mice compared with the

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control group [ [12,13]]. Compared with wild-type mice, NLRP3 knockout mice are significantly resistant to PD symptoms induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and rotenone [ [14,15]]. In addition, using a caspase-1 inhibitor (AC-Y-VAD-CMK), which inhibits the NLRP3/caspase-1/interleukin-1β (IL-β) axis, can significantly protect damaged dopaminergic neurons in the brain and improve motor symptoms in both LPS- and 6-OHDA-induced PD models [16]. There is also enhanced IL-1β, the critical product of NLRP3 inflammasome signaling, in reactive microglia in the autopsied brains of PD patients [17], similar to animal experiments.

Interestingly, two seemingly unrelated mechanisms, the circadian clock and NLRP3 inflammasome signaling, have a strong relationship. Recent studies have shown that the circadian rhythm system crucially controls the organism's inflammation, and it may be relevant to NLRP3 inflammasome signaling [18–20]. Therefore, targeting the abnormal activation of NLRP3 inflammasome signaling mediated by circadian dysfunction to treat or slow PD progression may be a new perspective for clinical and basic research on PD in the future. In this review, we summarized the current regulatory mechanism of the circadian clock system and NLRP3 inflammasome signaling and their position in PD; furthermore, the relationship between them in PD pathophysiology is mentioned.

## 2. The formation and molecular mechanism of the circadian clock

The circadian clock refers to periodic changes in various aspects, from gene expression to behavior [21]. The circadian rhythm system consists of three main components: the rhythm input system, in which multiple zeitgebers, such as light, travel through the retina to the suprachiasmatic nucleus (SCN) [22]; the central rhythm system, which is mainly composed of the SCN, a rhythm pacemaker, where various signals are integrated [23]; and the rhythm output system, where the SCN regulates multiple aspects of our body through the hypothalamic–pituitary–adrenal (HPA) axis and the autonomic nervous system (ANS) to align the body's circadian rhythm with the external environment (such as light conditions) [24]. At the molecular level, the maintenance of the biorhythm system is mainly dependent on transcription/translation negative feedback loops (TTFLs) [25]. The core genes involved in regulating the circadian clock include positive elements, such as brain and muscle ARNT-like 1 (BMAL1) and circadian locomotor output cycles kaput (CLOCK), as well as negative elements, such as three period genes (PER1, PER2, and PER3) and two cryptochrome genes (CRY1 and CRY2) [26]. In the first circadian loop, BMAL1 and CLOCK protein form heterodimers, which bind to the E-Box enhancer in the promoter regions of PER and CRY and then activate their transcription level.

When PER and CRY proteins reach a certain level, they also form heterodimers and translocate back to the nucleus, thus inhibiting the expression of BMAL1 and CLOCK as well as their heterodimer-mediated transcription, which generates negative feedback to regulate the circadian clock. When the level of BMAL1-CLOCK decreases, PER-CRY, a repressor complex, also decreases, thus commencing a new cycle [27]. The secondary feedback loop includes two transcription factors, retinoic acid-related orphan receptors

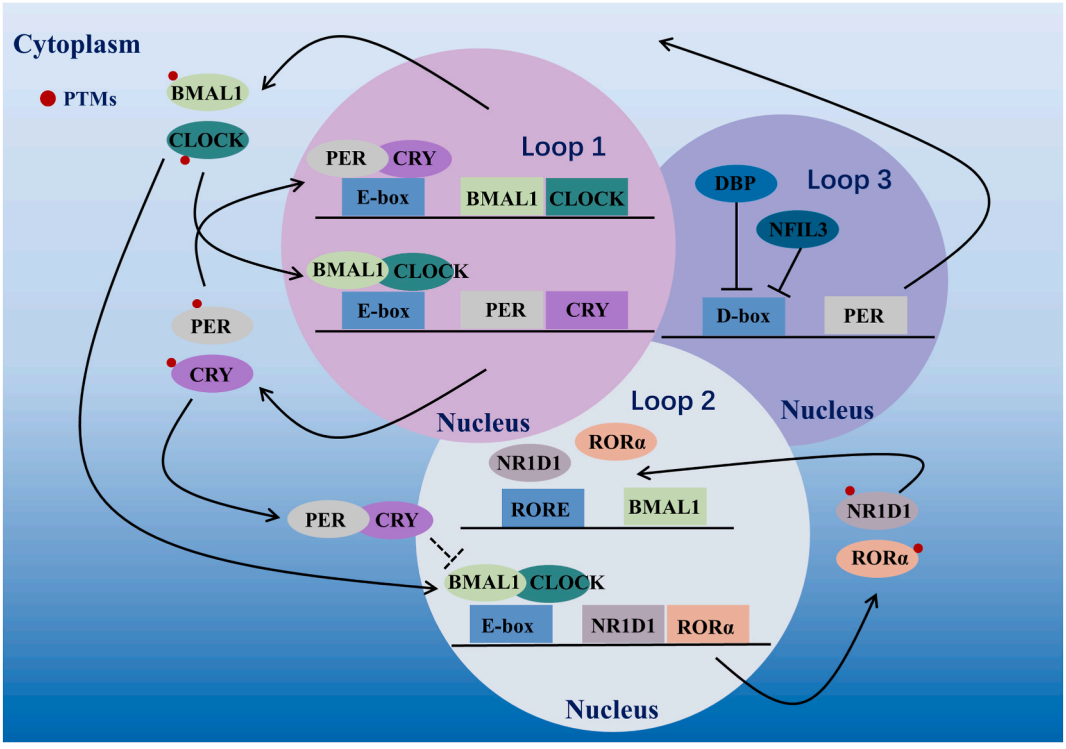


**Fig. 1.** Interrelationship among clock genes. The molecular mechanism of the circadian clock mainly includes (1) positive elements: BMAL1 and CLOCK; (2) negative elements: PERs and CRYs; (3) transcription factors: RORs and REV-ERBs; and (4) others, such as DBP, NFIL3 and PTM.

(RORs) and REV-ERBs (NR1D1/2). They competitively inhibit the expression of BMAL1 by binding to ROREs in the promoter region of BMAL1, thus fine-tuning the circadian clock [ [28,29]].

In addition to the above two loops, the circadian clock is also regulated by D-box binding protein (DBP) and nuclear factor interleukin 3 (NFIL3; also known as E4BP4). They combine with D-box elements on the promoter of some clock genes, such as PER, to activate or inhibit the transcriptional activation of target genes, thus regulating the circadian clock [30]. In addition, to maintain the stability and time specificity of daily circadian rhythm oscillations, the negative feedback loop also needs to be regulated by post-translational protein modifications (PTMs), such as phosphorylation, ubiquitination, sumoylation, and acetylation [31–33], thus affecting the stability and nuclear translocation of clock proteins and balancing the activation and inhibition of gene transcription (Fig. 1).

## 3. The molecular crosstalk between BMAL1/CLOCK and the NLRP3 inflammasome in PD

According to previous studies, disturbance of the expression of clock genes was observed in 6-OHDA- and MPTP-induced PD animal models [ [34,35]], which indicates that the circadian clock plays a vital role in PD pathogenesis. If BMAL1, a core gene of the circadian clock system, is knocked out, the motor ability of mice is seriously impaired [36]. In addition, clinical studies have also indicated that the expression level of BMAL1 mRNA in PD patients is significantly reduced at night, which is associated with their motor symptomatology (such as limb tremor) and the severity of sleep disorders [2]. In MPTP-induced PD mouse models, loss of BMAL1 aggravates neuroinflammatory responses and leads to massive loss of dopamine in the brain, thereby accelerating Parkinson's-like symptoms

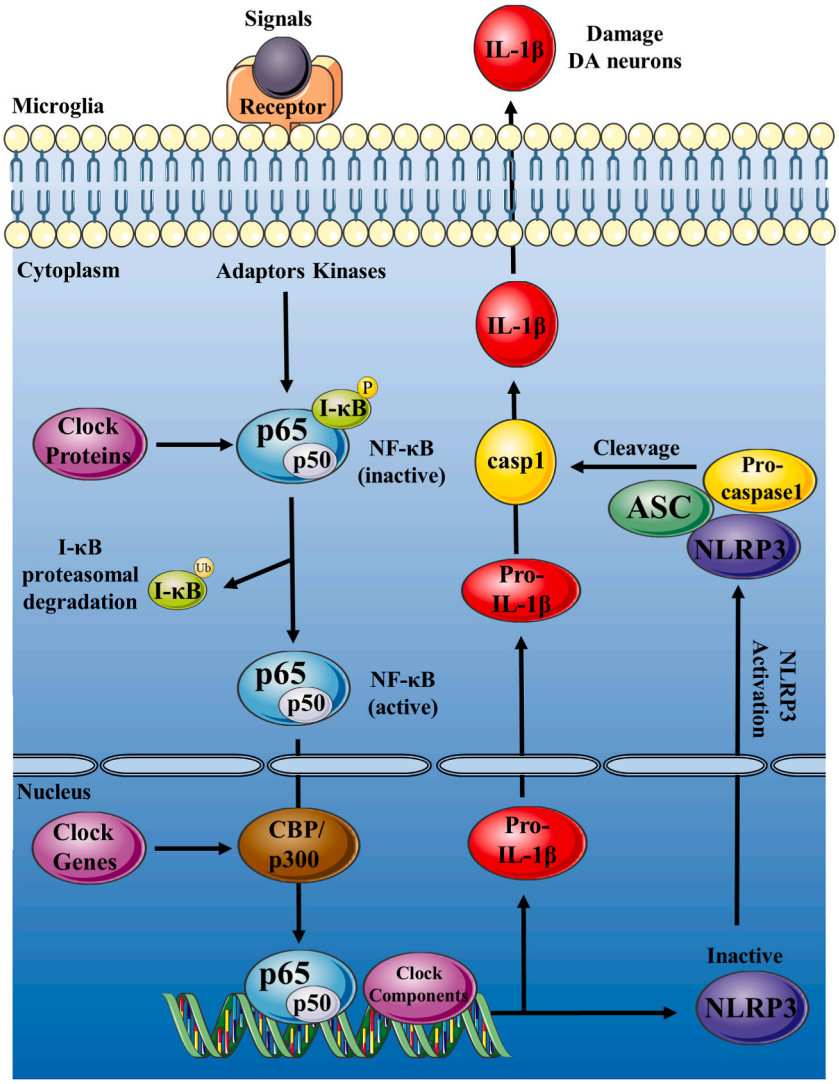


**Fig. 2.** The interaction between the circadian clock and NLRP3 inflammasome signaling. NF-κB signaling plays a crucial role in regulating NLRP3 inflammasome signaling. In addition, various studies have indicated that clock genes and proteins significantly influence this process.

[37]. Most importantly, recent studies have indicated that the influence of BMAL1 in PD may be relevant to NLRP3 inflammasome signaling.

The inflammasome is a multiprotein complex essential to the innate immune system. It mainly exists within the microglial cytoplasm in the central nervous system (CNS) and is divided into various subtypes [38]. The NLRP3 inflammasome is the most well-known and is mainly comprised of NLRP3, the ASC adapter, and pro-caspase-1. When microglia are stimulated by pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs), the NLRP3 inflammasome is activated and promotes the cleavage of pro-IL-1β, pro-interleukin-18 (pro-IL-18), and Gasdermin D (GSDMD), which leads to inflammation in the brain and the pyroptosis of DA neurons. Pyroptosis further induces the release of IL-1β and aggravates the inflammatory response [ [39,40]]. There are two main processes by which the NLRP3 inflammasome plays its role in the CNS, priming and activation. During priming, the function of nuclear factor kappa-B (NF-κB) is vital. NF-κB, a protein complex that controls the transcription of DNA, cytokine production, and cell survival, is necessary for the priming process of NLRP3 inflammasome signaling. Usually, antimicrobial peptides (AMPs) or damage-associated molecular patterns (DAMPs) can activate NF-κB signaling via cytokine receptors or pattern recognition receptors (PRRs), such as TLRs, NLRs, IL-1Rs, and TNFRs, on the membrane of microglial cells and then promote the transcription and translation of NLRP3, pro-IL-1β, and pro-IL-18 [41–43]. The priming stage is essential because the basal level of NLRP3 in the cytoplasm is insufficient to permit inflammasome assembly [41]. Therefore, the level and function of NF-κB are the core factors in the regulation of NLRP3 inflammasome signaling.

According to a previous study, BMAL1 can regulate NF-κB, an essential component of NLRP3 inflammasome signaling, to affect proinflammatory factor expression and then regulate inflammatory responses [44]. In MPTP-induced mice, inactivation of BMAL1 was observed. In addition, there is upregulation of microglia-mediated neuroinflammation in the substantia nigra (SN) and striatum in MPTP-treated Bmal1$-/-$ mice [37]. The direct interaction of BMAL1 and NLRP3 inflammasome signaling has also been explored. BMAL1 participates in NLRP3 inflammasome signaling through NF-κB signaling. It may be related to regulating IκBα, an NF-κB inhibitory factor. BMAL1 deficiency leads to overactivation of the NLRP3 inflammasome and IL-1β signaling in the brain [20]. Additionally, studies have illustrated that CLOCK, another important clock gene in the biorhythm system, is also highly related to PD since it is involved in the regulatory mechanism of dopamine synthesis and transport. CLOCK can regulate the activity of tyrosine hydroxylase, dopamine transporters, and their receptors at the transcriptional level by binding to the E-box element in the promoter region of DA synthesis-related genes [ [45,46]]. In addition, it also affects dopaminergic activity in the ventral tegmental area (VTA) at the posttranscriptional level [47].

However, contrary to BMAL1, CLOCK is directly related to the activation of NF-κB signaling since it can intensify p65 phosphorylation [48]. BMAL1 can counteract this interaction between CLOCK and NF-κB since it can recruit CLOCK to form a heterodimer and thus decrease free CLOCK [49]. CLOCK is also believed to be necessary for the acetylation of p65, a key event in the transcriptional activation of NF-κB [48] essential for NLRP3 inflammasome signaling. CLOCK can also influence the activity of some NF-κB coactivators to promote the activation of NF-κB. For instance, according to a luciferase reporter assay, CLOCK can interact with CREB binding protein (CBP) to activate the NF-κB-responsive promoter [48]. However, the expression of CLOCK in PD remains controversial. In two previous studies, significant downregulation of CLOCK was observed in LPS and rotenone and 6-OHDA models [ [50,51]]. However, Hayashi et al. [35] demonstrated that the CLOCK level in MPTP-reduced mice remains unaltered compared with control mice. In addition, there is the same situation in PD patients [52]. Although the expression of CLOCK may not change in PD, there is a possible epigenetic link between CLOCK and PD that may play a vital role in PD pathogenesis. Lin et al. [53] showed that hypomethylation of the NPAS2 (the paralog of CLOCK) promoter was observed in PD patients compared with healthy controls (Fig. 2).

## 4. The relationship between other clock components and the NLRP3 inflammasome in PD

When NLRP3 inflammasome signaling is activated, the resulting proinflammatory cytokines, IL-1β and IL-18, mediate neuroinflammation and damage dopaminergic neurons in the brains of PD patients. The binding of IL-1β and IL-1R leads to the recruitment of the neuron-specific adapter protein AcPb [54], which phosphorylates NDMR2b and then results in neuronal calcium overload as well as excitatory toxicity [55]. Meanwhile, it can change synaptic activity by disrupting the amount and balance of cell adhesion proteins within the synapse [56]. When IL-18 binds to the IL-18α receptor, it recruits IL-18ApCl and thus activates the STAT3-or NF-κB-mediated transcription of TNF-α, IL-6, and pro-IL-1β, which causes an inflammatory cascade [57]. Furthermore, related studies have indicated that the activation of the NLRP3 inflammasome in the peripheral tissue of mice also increases the level of proinflammatory cytokines in the peripheral circulation and aggravates inflammation in the CNS [58]. Therefore, inhibition of the activation of the peripheral NLRP3 inflammasome and cytokine release effectively prevents the progression of inflammation in the CNS and damage to DA neurons [59]. Related clinical observations also found that the gene and protein expression levels of NLRP3, ASC, caspase-1 and the related inflammatory factor IL-1β in PD patients are higher than those in normal people. It is closely associated with the severity and progression of motor symptoms [60]. Therefore, the activation of the NLRP3 inflammasome in both the central and peripheral systems plays a vital role in PD pathophysiology. Since excessive inflammation can cause severe damage to DA neurons, many studies have explored the regulatory mechanism of NLRP3 inflammasome signaling in terms of alleviating PD inflammation.

Similar to BMAL1 and CLOCK, the role of CRY and PER in PD and their relationship with inflammation have been primarily explored. Animal experiments have indicated that the levels of CRY and PER in the SCN of rotenone-induced PD rats are significantly lower than those in the control group [61]. Meanwhile, abnormal expression of PER has also been confirmed to be closely linked to postural instability and gait difficulties (PIGD) in PD patients [3]. Therefore, CRY and PER also play a vital role in PD pathogenesis. A previous study found that excessive activation of NF-κB signaling was observed in CRY1/2-deficient cells, accompanied by a significant increase in proinflammatory cytokines [62]. In addition, the downregulation of PER also promotes the phosphorylation of p38 and

JNK1, thus leading to the activation of NF-κB signaling [63], a key component of NLRP3 inflammasome signaling. In addition, studies have noted that there are disruptions in PER or CRY expression in inflammatory models, and these disruptions are accompanied by the activation of the NF-κB/NLRP3 axis [ [64,65]]. However, the direct relationship between CRY, PER, and the NLRP3 inflammasome in PD remains unclear.

In addition, various studies have demonstrated that REV-ERBα is a crucial inflammatory regulator that is highly related to NLRP3 inflammasome signaling. The activation of REV-ERBα can significantly inhibit the LPS-induced inflammatory response both in vivo and in vitro because it reduces the production of NLRP3-mediated IL-1β and IL-18, and it may be related to the regulation of BMAL1 [66]. In addition, REV-ERBα can also regulate NLRP3 inflammasome signaling during the priming phase via specific binding to the gene promoter of NLRP3. It can also indirectly inhibit the priming phase of NLRP3 inflammasome signaling by inhibiting NF-κB p65 transcription [ [67,68]]. In Nr1d1 (REV-ERBα)-deficient mice and human macrophages, the expression and activation of NLRP3 are increased, which indicates that NLRP3 inflammasome signaling negatively relies on REV-ERBα levels [69]. The relationship between REV-ERBα, NLRP3 inflammasome signaling, and PD has also been shown. According to previous studies, microglial activation was alleviated, and the microglial phenotype transformed into an anti-inflammatory M2 state by activating REV-ERBα to repress NF-κB-NLRP3 inflammasome signaling in PD models. In addition, the inhibition of REV-ERBα could reverse these effects [ [70,71]]. Additionally, in the SN of MPTP-induced PD mice, the circadian oscillation of REV-ERBα and diurnal changes in microglial morphology disappeared. SR9009, a small molecule which can display activation of REV-ERB, significantly improve motor ability and alleviates the loss of DA neurons by inhibiting NLRP3 inflammation activation [72].

Retinoic acid-related orphan nuclear receptor alpha (RORα), a vital nuclear receptor in the circadian system, is also relevant to immune responses. Studies have indicated that RORα exerts a protective effect during inflammation [ [73,74]]. García et al. [75] demonstrated that MLT inhibits the activation of the NLRP3 inflammasome in an RORα-dependent manner. It is related to regulating the function of the NF-κB signaling pathway. RORα is a positive regulator of IκBα transcription, which can downregulate NF-κB function since it can bind to ROR elements in the IκBα promoter region [76]. It can inhibit the nuclear translocation of p65 and transcription of some inflammation-related genes, such as NLRP3, and thus negatively affect inflammation. RORα function in treating PD has also been reported, which suggests that RORα is a potential target in PD treatment. Li et al. [77] showed that downregulation of RORα levels was observed in PD models both in vitro and in vivo. In addition, MLT treatment significantly protects DA neurons by increasing RORα expression to decrease inflammation (Fig. 2).

In conclusion, BMAL1, CLOCK, CRY, PER, REV-ERB, and ROR participate in the process of NLRP3 inflammasome signaling pathway in several disease models, including PD models, directly or indirectly. These clock genes and proteins regulate IκB transcription or its function (e.g., BMAL1, CLOCK, RORα) [20,48,76], transcription, acetylation, phosphorylation, or nuclear translocation of NF-κB p65 (e.g., BMAL1, CLOCK, CRY1/2, PER1, REV-ERBα, RORα) [48,62,67,68], which influence the priming process of NLRP3 inflammasome signaling. They also affect NF-κB signaling by influencing its upstream regulatory factors, like CBP or phosphorylation of p38 and JNK1 (e.g., CLOCK, PER1) [48,63]. Besides, they exert a crucial regulatory effect on the activation of NLRP3 inflammasome (e.g., BMAL1, REV-ERBα, RORα) [20,66,75]. Additionally, expression of NLRP3 also be directly controlled by circadian expression (e.g., BMAL1, RORα, REV-ERBα) [20,69,76].

According to previous research, BMAL1, CRY, PER, REV-ERB and ROR seem to be negative regulators in the NLRP3 inflammasome-mediated inflammation while CLOCK plays a positive role. They influence each other during inflammatory regulation. For instance, as mentioned above, BMAL1 recruits CLOCK to decrease free CLOCK, which suppresses NF-κB-induced transcriptional activity [49]. Activation of REV-ERBα inhibits the NLRP3 inflammasome signaling pathway, and it is related to BMAL1 [66]. In normal situations, circadian expression maintains a dynamic balance (Fig. 1), which may suppress the overactivation of NLRP3 inflammasome to some degree. However, there is an abnormal expression and function of these clock genes and proteins in PD models and patients [2,34,35,50,51,53,61,72,77]. Therefore, circadian rhythm disorder may be one of the important causes of PD since it is highly relevant to NLRP3 inflammasome-mediated neuroinflammation which plays an essential role in PD pathogenesis.

## 5. α-synuclein, NLRP3 inflammasome, and circadian clock in PD

The most significant pathological features of PD are the loss of dopaminergic neurons in a dense region of the substantia nigra as well as the presence of eosinophilic inclusions termed Lewy bodies, which are formed by the aggregation of misfolded α-synuclein (α-syn) in the cytoplasm of remaining neurons [78]. When researchers discuss PD pathogenesis, mentions of α-syn are always inevitable. According to previous research, α-syn is highly relevant to NLRP3 inflammasome signaling. As one of the DMAPs, aggregated α-syn in damaged neurons is released into the extracellular space [79], which is recognized by Toll-like receptor (TLR) and then activates NF-κB signaling [ [80,81]]. After the activation of NF-κB, NLRP3 inflammasome signaling enters the priming process. The aggregated form of α-syn, which is also a second signal, can lead to the assembly and activation of the NLRP3 inflammasome [82]. The leucine-rich repeat (LRR) of NLRP3 can recognize misfolded α-syn [83], and then, the Lys-63-specific deubiquitination enzyme (BRCC3) deubiquitinates NLRP3 [ [84,85]], which promotes the combination of the N-terminal pyrin domain (PYD) of ASC with that in NLRP3 [86]. After the NLRP3-ASC complex is formulated, the C-terminal CARD of ASC combines with the CARD of pro-caspase-1, which results in the self-cleavage of pro-caspase-1 into caspase-1 [87]. Activated caspase-1 promotes the maturation and release of proinflammatory cytokines, most notably IL-1β and IL-18 [88], which mediate a severe inflammatory response. In addition, the activation of caspase-1, the result of the activation of NLRP3 inflammasome signaling, can fracture α-syn, exaggerate the aggregation of α-syn, and finally damage residual neurons [11], which creates a vicious cycle of neuroinflammation. It is important to note that although both the monomer and the fibrous form of α-syn can trigger NLRP3 inflammasome signaling into the priming process, only the fibrous form promotes the signal into the activation process [89], which may be related to the specific cross-β structure of the

fibrous form [90].

According to previous studies, there is a potential relationship between α-syn and the circadian clock. Autophagy plays an essential role in the degradation of α-syn aggregates. Autophagy is a mechanism of degrading and recycling proteins to maintain cell homeostasis. It has been established that clearances of α-syn aggregation are highly dependent on autophagy since the effect of proteasomal degradation is limited [91]. According to a previous study, proteins related to autophagy in the brain are displayed in a diurnal manner, and they are disrupted by sleep fragmentation [92]. PD patients always suffer from some premonitory symptoms, such as restless leg syndrome, which causes sleep fragmentation, before their disease is diagnosed [93]. Therefore, circadian clock disturbance may affect α-syn clearance by influencing proteins related to autophagy.

Oxidant stress is also related to PD pathogenesis since it affects conformational changes and aggregation of α-syn. In addition, oxidant stress is also regarded as playing a mechanistic role in hyperactivity-induced α-syn spreading, which promotes PD in a recent study [94]. The circadian clock also regulates the level of oxidant stress. For instance, BMAL1, a core clock gene described above, can reduce cell oxidant stress since it controls the transcription factors of some elements related to the antioxidant response [95]. In addition, higher oxidative damage was observed in BMAL1 or PER knockout mice [ [96,97]]. These results indicated that circadian disruption may contribute to PD through increased oxidant stress. In addition, a previous study has shown that mitochondrial dysfunctions are relevant to the chronic production of ROS, a primary cause of oxidative damage, in PD [98]. Many studies have also demonstrated that mitochondria participate in the toxicity induced by α-syn aggregation in PD since lacking α-syn can resist mitochondrial toxins [98–100]. Mitochondrial respiration shows a specific rhythm during the day and is regulated by the circadian clock [101], which indicates that dysfunction of the circadian clock participates in PD pathogenesis and is related to mitochondria and α-syn. A series of prospective studies have demonstrated that circadian abnormalities, such as excessive daytime sleepiness (EDS) [102] or sleep behavior disorders [ [103,104]], are independent predictors of PD. In addition, melatonin, a regulator of circadian rhythm, seems to block α-syn formation and aggregation [105]. Therefore, according to several studies as described above, circadian dysfunction not only aggravates neuroinflammation, which may be relevant to NLRP3 inflammasome signaling but also may influence α-syn via many potential pathways to contribute to the pathology of PD. Interestingly, α-syn is also an activator of NLRP3 inflammasome signaling, which indicates that circadian dysfunction may influence inflammation induced by the NLRP3 inflammasome again by affecting α-syn aggregation.

## 6. Conclusion and future direction

As mentioned above, the loss of circadian rhythm was observed in PD patients and animal models. It is highly related to disruptions in the levels and functions of clock genes and proteins such as BMAL1, CLOCK, PER, CRY, and two transcription factors: RORs and REV-ERBs. In addition, NLRP3 inflammasome signaling plays an essential role in PD pathogenesis, and it is also regulated by some clock genes and proteins, especially BMAL1 and REV-ERBα. In addition, α-syn aggregation, a primary pathological marker in PD, is also relevant to neuroinflammation through NLRP3 inflammasome signaling and associated with circadian dysfunction. All the evidence paints a complete picture that PD may result from circadian dysfunction since circadian cycle disturbances can exaggerate PD pathology. However, this opinion is still controversial since some researchers regard circadian dysfunction as a consequence of PD progression. For instance, α-syn aggregation was found in the SCN, which may damage key cells there.

To deepen our understanding of PD, we can pay more attention to the circadian clock in the future. Researchers can use genetic modification techniques, such as knockout animals, to explore the role of clock genes in PD as well as their relationship with NLRP3 inflammasome signaling and thus identify some effective drugs that target these clock genes to inhibit neuroinflammation, such as the REV-ERB agonist. Studies can also focus on whether there is a circadian rhythm or loss of the circadian rhythm of genes or proteins related to NLRP3 inflammasome signaling or its upstream signaling pathways, such as AMPK and p38 MAPK signaling, in PD and its relationship with clock genes or proteins. In addition, researchers can currently also use genomics and proteomics techniques to explore PD pathogenesis. For example, we can use mass spectroscope-based proteomics and sophisticated analytical tools to identify the expression of NLRP3-related proteins throughout the whole day, analyze their changes over time in PD, and, most importantly, detect whether these changes are related to disruptions of the circadian clock. The epigenetic link between clock genes and the NLRP3 inflammasome in PD, such as methylation or demethylation, is also a promising direction. In addition, although many studies have examined the relationship among circadian dysfunction, neuroinflammation, and PD, the causal relationship among the three remains unclear and should be explored further.

In conclusion, there is strong support that the circadian clock is relevant to PD pathogenesis via NLRP3 inflammasome signaling. However, we still need more high-quality studies to provide further reliable evidence. We hope that circadian targets will be used in treating PD clinically in the future.

## Data availability statement

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

## CRediT authorship contribution statement

**Jiahua Huang:** Writing - review & editing, Writing - original draft, Investigation, Conceptualization. **Wenwei Li:** Writing - review & editing, Supervision, Resources, Funding acquisition, Conceptualization.

## 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.

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