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Review

Roles of clock genes in the pathogenesis of Parkinson's disease

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ABSTRACT

Parkinson's disease (PD) is a common motor disorder that has become increasingly prevalent in the ageing population. Recent works have suggested that circadian rhythms disruption is a common event in PD patients. Clock genes regulate the circadian rhythm of biological processes in eukaryotic organisms, but their roles in PD remain unclear. Despite this, several lines of evidence point to the possibility that clock genes may have a significant impact on the development and progression of the disease. This review aims to consolidate recent understanding of the roles of clock genes in PD. We first summarized the findings of clock gene expression and epigenetic analyses in PD patients and animal models. We also discussed the potential contributory role of clock gene variants in the development of PD and/or its symptoms. We further reviewed the mechanisms by which clock genes affect mitochondrial dynamics as well as the rhythmic synthesis and secretion of endocrine hormones, the impairment of which may contribute to the development of PD. Finally, we discussed the limitations of the currently available studies, and suggested future potential studies to deepen our understanding of the roles of clock genes in PD pathogenesis.

1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease characterized by a range of motor features such as rigidity, bradykinesia, tremors, postural instability, speech deficits, impaired handwriting, and grip force (Khan et al., 2018). The most significant pathological change found in PD is the progressive loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc) (Surmeier, 2018). Normally, dopaminergic neurons are responsible for transmitting dopamine to the striatum and other basal ganglia nucleus. However, when at least 50–60% of these neurons are degenerated, the dopamine in the basal ganglia becomes depleted and this can lead to the classical motor symptoms of PD (Maiti et al., 2017; Wegrzynowicz et al., 2019). Besides motor symptoms, some patients also experience various non-motor features such as olfactory deficits, visual abnormalities, sleep disturbances, excessive secretion of saliva, and some neuropsychiatric symptoms such as anxiety and depression also observed (Pfeiffer, 2016; Zis et al., 2015). Another hallmark of PD is the presence of Lewy body inclusions composed of a protein known as α-synuclein. If not folded properly, α-synuclein becomes insoluble and forms aggregates as an intracellular inclusions within the neuronal cell body (Lewy bodies) and processes (Lewy neuritis), which contribute to the pathogenesis of the disorder (Ma et al., 2019).

In recent years, the role of circadian rhythms in PD has become increasingly apparent (Li et al., 2017b). Aberrations in the circadian rhythms have been frequently reported in PD patients as well as experimental models of the disorder, which suggest that they may play an important role in PD. Circadian rhythms are managed by a molecular clock within the suprachiasmatic nucleus (SCN), residing in the anterior part of hypothalamus, which is entrained by the dark-light cycle. The

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molecular clockwork consists of different core clock genes such as *circadian locomotor output cycles kaput protein (CLOCK)*, *brain and muscle ARNT-like 1 (BMAL1)*, *period circadian regulators 1* and *2* (*PER1* and *PER2*), and *cryptochrome circadian regulators 1* and *2* (*CRY1* and *CRY2*), These genes are organized in a transcription-translation feedback loop that oscillates every 24 h (Caba et al., 2018; Takahashi, 2017). While initial studies suggest the association between PD and clock genes, their mechanistic link is not fully understood yet. In the current review, we summarize the recent understanding of the role of clock genes in PD, emphasizing on the relationship between the altered clock genes expression as well as their genetic polymorphisms and the disorders; and how clock genes are linked to the regulation of mitochondrial dynamics and hormonal destabilization in PD.

2. Parkinson's disease

PD is a complex progressive neurodegenerative disease characterized by a generalized slowing of movements and resting tremor or rigidity (Balestrino and Schapira, 2020). The exact causative agent is still unknown. It is frequently thought to be an age-related disorder. However, it has been firmly established by now that the influence of genetic susceptibility and environmental factors cannot be neglected. For example, a meta-analysis showed that having a family history of PD increases the risk of developing the disorder by 3–4 times, which reflects the contribution of genetic factors in the PD development (Noyce et al., 2012). In fact, genetic variations represent almost 25% of the total PD risk factors, and can be classified into low penetrance (e.g. *MAPT, GCH1, GAK, BST1, HLA, DRB5, SYT11* and some *SNCA* variants), moderate penetrance (e.g. *GBA and LRRK2* variants) or high penetrance (e.g. *ATP13A2, FBX07, PINK1, PARK7, PRKN, VSP35,* and some *SNCA* variants) types, which have a high, moderate and low frequency respectively. Based on the type of the causative genetic variants, PD can be divided into either monogenic or idiopathic forms, whereby the monogenic form is caused by the rare high-penetrance variants whereas the idiopathic form is caused by the common or moderate variants (Day and Mullin, 2021). Interestingly, the monogenic form may result in a distinct disease progression pattern compared to the idiopathic form. Notably, most laboratory PD models have emphasized on the monogenic pathways of PD pathogenesis (Day and Mullin, 2021). Monogenic PD can be further classified into either autosomal dominant or recessive forms, depending on the genes mutated. For example, *SNCA* mutations are found to be in close association with the autosomal PD (Dashtipour et al., 2017; van Heesbeen and Smidt, 2019a, 2019b). Other types of mutations or multiplications, such as single nucleotide polymorphisms (SNPs), can also alter the disease risk by manipulating the gene expression (Langmyhr et al., 2021; Maszlag-Török et al., 2021; Tan et al., 2021; Usenko et al., 2021). In Caucasian or Asian populations, for instance, the rs35621, rs356165, rs11931074 and rs7684318 polymorphisms, among others, had been found to be linked to a higher risk of PD (Shu et al., 2018). Recent studies have also shown that shortening of telomeres, as a result of their inability to replicate the ends of linear chromosomes, also leads to PD pathology (Wu et al., 2020).

Genetic factors interact with various environmental risk factors to result in the final phenotype (Álvarez-Castro, 2020). Therefore, both factors should be considered in terms of disease diagnosis, treatment, and laboratory study. For instance, caffeine consumption is known to decrease PD risk by working as an adenosine A2A receptor antagonist to enhance dopamine neurotransmission, although the risk can be mitigated by polymorphisms in the adenosine A2A receptor gene (Chuang et al., 2016; Palacios et al., 2012; Popat et al., 2011), On the contrary, exposure to heavy metals such as iron, copper, manganese and lead increases PD risk by causing genetic alterations to the genes involved in PD pathogenesis, such as *LRRK2, PARK1,* and *PINK1*. Some heavy metals are also considered to be brain neurotoxins, which cause oxidative stress, neuronal damage particularly mitochondrial damage, and neurotransmission impairment with dramatic effects in basal ganglia (Ball et al., 2019).

A positive correlation between exposure to pesticide and PD has also been documented, although the specific molecules responsible for this observation as well as the molecular mechanisms involved have not been fully elucidated. It is, however, known that pesticides are able to destroy neurons that are responsible for producing dopamine, which may explain their correlation with PD pathogenesis (Goldman et al., 2017). For example, dieldrin, which is a neurotoxin pesticide, has been found to contribute to a higher risk of PD in a dose-dependent manner via impairment of the dopaminergic neurons and consequently alteration in the entire CNS. Similarly, rotenone also elevates the risk of PD by facilitating the accumulation of alpha-synuclein protein (Ball et al., 2019). Another pesticide, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), is converted by astrocytes to 1-methyl-4-phenylpyridium (MPP+) in the brain, where it targets the substantia nigra and consequently enhances the PD risk (Ball et al., 2019). Thus, many individuals who have been exposed to MPTP exhibit advanced PD stage, and it is for this reason that several animal models of PD are generated by treating the animals with this pesticide (Ball et al., 2019). Evidence for the role of pesticides in PD pathogenesis is further strengthened in the Geoparkinson study conducted by Dick et al. on the Malta, Romania, Sweden, Italy and Scotland populations (Dick et al., 2007), where it was noted that individuals working in sectors in which exposure to pesticides and trace elements were frequent had an increased risk for the development of PD. This suggests that the exposure to pesticides may be a causative or potentially modifiable risk factor for PD. Many other lifestyle factors, such as consumption of the well water, poor living standard and employment in the agricultural sector, have also been hypothesized to contribute to PD pathogenesis. For example, a cohort study based on the French population showed that there was an increase in PD-related hospital administration among people employed in the agricultural sector (Pouchieu et al., 2018). A similar study based on the Hawaii population also found that plantation workers were more prone to the development of PD (Petrovitch et al., 2002). These observations suggest that pesticide and occupational exposures could be linked to PD development, although further studies are necessary to validate the causal relationship between the above-mentioned risk factors and the disorder (Gunnarsson and Bodin, 2019).

Besides pesticide and occupational exposures, a study conducted by Fang et al. showed that there exists an inverse relationship between high physical activity and the development of PD (Fang et al., 2018). Similarly, and perhaps surprisingly, inverse correlations between PD and smoking (Domínguez-Baleón et al., 2021), calcium ion blockers (Chen et al., 2021a) and statins (Chen et al., 2021a) have been consistently reported. In addition, the administration of β2-antagonists has been found to lead to an increase in the incidence of PD, while β2-agonists tend to decrease the risk of PD (Mittal et al., 2017).

Today, while there is no holistic technique for early diagnosis and prognostication of PD, clinicians often apply a combination of tests and biomarkers to identify the potential PD development and its outcomes (Li and Le, 2019) (Fig. 1). Nonetheless, PD patients are commonly presented with motor symptoms, such as tremor, rigidity, bradykinesia and postural instability, although it is now known that PD has a prodromal phase prior to the onset of the motor symptoms (Khan et al., 2018; Rees et al., 2019). The motor symptoms of PD are typically attributed to the loss of dopaminergic neurons in the SNpc and the Lewy body deposition in the midbrain that may occur due to toxins, drugs, pesticides, brain microtrauma, genomic defects, etc (Naughton et al., 2017; Ritz et al., 2016; Shrestha et al., 2020). The loss of dopaminergic neurons causes variations to the dopamine content, whose rhythmic release can be regulated by the circadian clock (Mendoza and Challet, 2014). In addition, changes in rate of synthesis of tyrosine hydroxylase, which is one of the major rate limiting enzymes in the dopamine synthesis, as well as dopamine transporters may also be observed, and these processes are known to be regulated by clock genes (Lauretti and Praticò, 2020).

Besides motor symptoms, PD patients are also commonly present

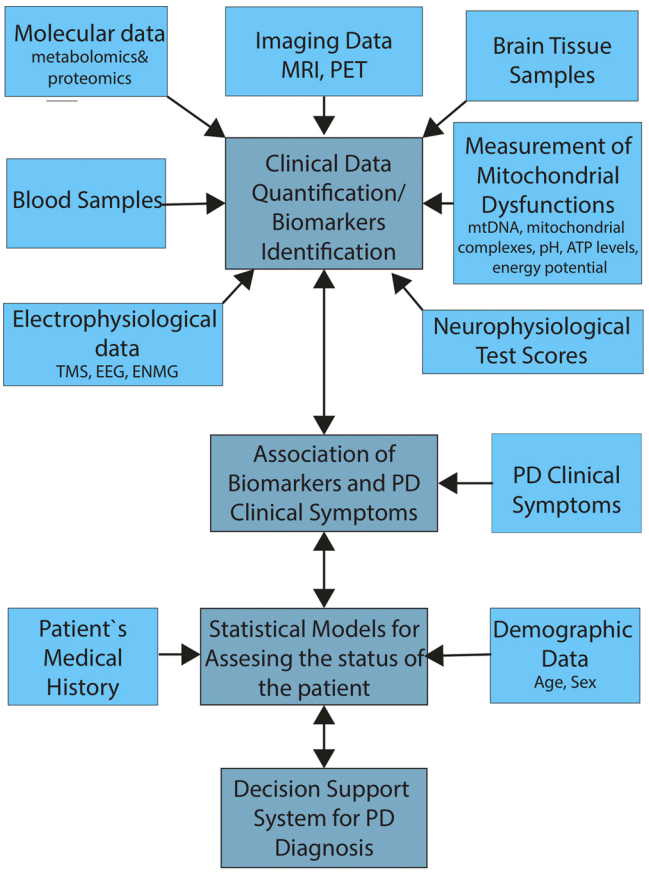

Fig. 1. A proposed PD Decision Support System for the early diagnosis and efficient assessment of the disease.

with non-motor symptoms, such as mood disorders, dizziness, sexual problems, cognitive changes, sleep disorders and visual disorders. Sleep and visual disorders are, in fact, among the earliest non-motor symptoms found in PD patients. Sleep disorders could be observed in patients even before the diagnosis of PD, but become more frequent and severe as the disease progresses (Bohnen and Hu, 2019; Melka et al., 2019; Zesiewicz and Hauser, 2007). Sleep is directed by the complex interplay between sleep-wake homeostasis and circadian rhythms in the body, which are regulated by clock genes (Dijk and Landolt, 2019).

Normally, humans have a robust 24-hour circadian rhythm in sleep desire that is controlled by the SCN in response to light signals from the retinal cells throughout the day and melatonin release from the pineal gland during the night (Gentry et al., 2021). In PD patients, however, the SCN activity is reduced, which results in elimination of the rhythmic secretion of melatonin or other hormones related to clock gene that lead to sleep-wake disruptions (French and Muthusamy, 2016). These disruptions include increased sleep latency, reduced sleep efficiency, and reduced rapid eye movement sleep (Keir and Breen, 2019). Visual disorders, on the other hand, occur when PD patients suffer from retinal damage as a result of aging, synucleinopathy and melanopsin system dysfunction. These cause a decrease in the number of melanopsin-containing retinal ganglion cells (RGCs) in PD patients, which is accompanied by a decrease in the complexity of their network and morphological changes. Dysfunction in the photosensitive RGSs in the inner retinal is also linked to poor sleep quality in PD patients (Feigl et al., 2020). Besides, dopaminergic neurons of the retina form synapses with melanopsin-containing RGCs, which mediate circadian photoentrainment in response to environmental light. Thus, circadian dysfunction in PD is commonly linked to an altered dopaminergic modulation of melanopsin cells. In the modern society, clock disruption is often associated with photoentrainment (Xie et al., 2019). In fact, several studies have established a link between photoentrainment and altered clock genes expression (Bluhm et al., 2012; Farhat et al., 2009; Lax et al., 2019; Ruan et al., 2012). Disrupted photoentrainment (and therefore clock gene regulation) can be clinically examined by using methods such as pupillometry, which can differentiate retinal affection in the inner and outer retina as seen in PD patients. In addition, pupillometry is useful for indicating circadian synchronization in the elderly, autonomic dysfunction and disease stage in PD (Giza et al., 2011; Novotny and Plischke, 2017; You et al., 2021). Apart from that, many of the non-motor symptoms mentioned above, such as mood disorder and cognitive changes, are also linked to clock genes (Bolsius et al., 2021; Schuch et al., 2018). These observations highlight the important roles of clock genes in the pathogenesis of PD.

The gold standard treatment for PD is levodopa (L-Dopa) (Lee, 2019). L-Dopa has the ability to cross the blood brain barrier, making it a strong candidate for PD treatment. Moreover, L-Dopa is the precursor of dopamine, thus it can directly increase the concentration of dopamine inside the brain (Haddad et al., 2018). In the initial stages, L-Dopa administration had shown profound effects on improving motor-related symptoms. It is now known that L-Dopa may also increase the lifespan of PD patients (Morgan et al., 2014). However, L-Dopa has been reported to speed up the process of neuronal degeneration through oxidative metabolism, which can result in dyskinesia (Jankovic et al., 2015; Pandey and Srivanitchapoom, 2017). Thus, although the administration of L-Dopa may halt the disease progression, its long term use may result in negative effects.

Apart from L-Dopa, dopaminergic agonists (DAs), anticholinergic drugs, monoamine oxidase inhibitors (MAOIs) and catechol-O-methyltransferase inhibitors (COMTIs) are also used in the treatment of PD. DAs such as pergolide and ropinirole can directly stimulate the postsynaptic DA receptors and, along with L-Dopa, they can help in delaying the onset of motor fluctuations (BROOKS, 2000). However, they are more expensive in comparison to L-Dopa and can cause side effects such as sleeping disorders, hallucinations and cognitive problems. On the other hand, anticholinergic drugs such as benztropine and trihexyphenidyl function by blocking the muscarinic receptors near to the striatal interneurons (Lester et al., 2010). They have been shown to reduce tremors but are also known to cause many side effects such as cognitive impairment, confusion, and hallucinations. Besides, MAOIs such as selegiline and rasagiline also showed anti-PD effect (Cereda et al., 2017; Finberg, 2020; Szökő et al., 2018; Tábi et al., 2020). They are generally more effective in patients with moderately advanced PD suffering from levodopa related motor complications. Catechol-O-methyltransferase inhibitors (COMTIs) act by blocking the degradation of peripheral levodopa and increasing the central L-Dopa and dopamine levels (Khan et al., 2021). However, hepatotoxicity has been reported with their use. Their primary role is to prolong the effect of L-Dopa and therefore can be used as an adjunctive therapy in patients with reported motor fluctuations. Apart from that, non-conventional therapies, such as administration of Berberine, may ameliorate PD symptoms by facilitating the conversion of L-Dopa produced by intestinal bacteria into dopamine (Wang et al., 2021). Similarly, the use of L-Dopa nanocarriers, such as the self-assembled nano-L-Dopa (Nano-^{DOPA}), also increased the dopamine levels and at the same time, decreased the incidence of dyskinesia symptoms that are commonly observed when L-Dopa is given through other routes or modes (Vong et al., 2020). Other treatments, such as the administration of intravenous dopamine and PT-320, are also promising options for PD treatment (Moreau et al., 2020; Yu et al., 2020).

3. Epigenetic regulation in Parkinson's disease

Apart from genetic alterations mentioned above, epigenetic modifications are also commonly observed in PD. Epigenetics refers to alteration in the expression or function of specific DNA loci without any change in the sequence itself. When epigenetic modifications occur in

PD-related genes, a change in expression levels of the genes, and consequently their protein products, happens, and can lead to PD pathogenesis.

Different types of epigenetic modifications have been known (Pavlou and Outeiro, 2017; van Heesbeen and Smidt, 2019a, 2019b). The main epigenetic modification is DNA methylation which involves the addition of a methyl group to a particular amino acid (cytosine) in the CpG islands (Pavlou and Outeiro, 2017). DNA methylation is responsible for switching (on and off) of genes leading to the control and regulation of their expression levels. In PD, methylation of the *synuclein alpha* (*SNCA*) gene has been frequently investigated as it is among the most important genes involved in the disorder (Guhathakurta et al., 2017). Despite this, the findings have been inconclusive (Pavlou et al., 2017). On one hand, it has been shown that the hypomethylation or demethylation of intron 1 CpG island was correlated to a high level of *SNCA* expression, which was in turn associated with the incidence of PD (Jowaed et al., 2010; Matsumoto et al., 2010). This observation could be attributed to the low level of the Dnmt1 protein, which is responsible for DNA methylation maintenance (Desplats et al., 2011). When the expression of *SNCA* is high, sequestration of Dnmt1 occurs in the cytoplasm, which subsequently decreases the expression level of the former via hypomethylation (Desplats et al., 2011). In addition to *SNCA*, Dnmt1 retention has also been linked to hypomethylation of the *selenoprotein W* (*SEPW1*) and *cAMP-dependent protein kinase type II regulatory subunit alpha* (*PRKAR2A*) genes (Desplats et al., 2011). Nevertheless, on the other hand, next-generation sequencing data showed that hypermethylation of *SNCA* intron 1 and promoter region was observed in PD patients in comparison to controls (De Boni et al., 2011). Apart from that, a study indicated no change in the methylation level of *SNCA* gene in PD patients compared to control in the leukocyte samples via examination of the methylation level of 13 CpG islands located in *SNCA* intron (Song et al., 2014). More studies are therefore needed to elucidate the role of *SCNA* methylation in the pathogenesis of PD.

In addition of *SCNA*, methylation in many other genes has been investigated with regard to their association with PD. For example, the glycoprotein *NMB* (*GPNMB*), *Parkinson's disease 16* (*PARK16*) and syntaxin-*1B* (*STX1B*) genes have been shown to exhibit irregular methylation in the PD brain samples after postmortem examination (International Parkinson's Disease Genomics Consortium (IPDGC) and Wellcome Trust Case Control Consortium 2 (WTCCC2), 2011). Likewise, *Fanconi anemia group C* (*FANCC*) and *tankyrase 2* (*TNKS2*) displayed irregular methylation levels (Weis et al., 2019), while similarly, hypermethylation was demonstrated in *peroxisome proliferator-activated receptor gamma coactivator 1-alpha* (*PGC1A*) (Piccinin et al., 2021). A study done by Malish et al. showed hypermethylation of the following genes in PD: *HLA-DQA1, TMEM9, MOG, TRIM10, GFPT 2, KCTD5, HLA-DRB5, VAV2, MRI1, MAPT, HLA-DRB6, LASS3, GSTTP2, ARHGEF10* and *GSTTP1* (Masliah et al., 2013). Apart from that, hypomethylation was observed in the following genes: *MAGI2, FOXK1, DNAJA3, JAKMIP 3, DMBX1, SLC25A24, GSTT1, LRRC27, LGALS7, MYOM2, TUBA3E, APBA1, TMCO3, FRK* and *MIR886* (Masliah et al., 2013). In addition, epigenome-wide association studies have also identified irregular DNA methylation in 20 genes in PD patients compared to healthy individuals (Masliah et al., 2013; Moore et al., 2014). All these observations illustrate the importance of DNA methylation in PD.

Another epigenetic modulator that controls the gene expression is the microRNAs (miRNAs), which are short (18–22 nucleotides) noncoding RNAs that inhibit gene expression by binding complementarily to the target mRNAs to achieve transcription suppression and/or degradation of the mRNA transcripts (Arshad et al., 2017; Fyfe, 2019). A number of miRNAs have been shown to contribute to PD through the alteration of gene expressions. For instance, miR7 and miR-153 together control and regulate α-synuclein expression (Singh and Sen, 2017; Titze-de-Almeida et al., 2020), while miR-106a increases its expression (Zhao et al., 2019). In addition, miR-205 has been reported to be a regulator of *leucine-rich repeat kinase 2* (*LRRK2*) which is one of the key genes involved in PD pathogenesis (Singh and Sen, 2017), while miR-34b and miR-34c have been found to be associated with a decrease in the expression of PD-associated genes, *PARK2* and *PARK7* (Miñones-Moyano et al., 2011; Villar-Menéndez et al., 2014). Apart from that, profiling of the levels of miRNAs in human subjects also revealed a downregulation of miR-124 (Kanagaraj et al., 2014), miR-34b, miR-34c (Miñones-Moyano et al., 2011), miR-133b (Kim et al., 2007), miR-22, miR-1, and miR-29 (Margis et al., 2011) in PD patients; as well as an upregulation of hsa-miR-4639–5p (Chen et al., 2017), miR-373, miR-224, and miR-21 (Alvarez-Erviti et al., 2013), miR-1826, miR-450b-3p, and miR-505 (Khoo et al., 2012). An alteration in the levels of miR-10b, miR-10a, miR-212, miR-132, and miR-495 has also been found in PD patients (Gillardon et al., 2008), indicating the potential role of miRNAs in the development of PD.

Gene expression is also epigenetically regulated by a complex process known as chromatin remodeling, which includes various types of histone modifications such as phosphorylation, ubiquitination, acetylation, SUMOylation, hydroxylation, and other posttranslational modifications (Bandres-Ciga et al., 2020; Rathore et al., 2021). These modifications are known to play a substantial role in the dopaminergic neuron differentiation and development, although their role in PD pathogenesis is still unclear since little information is available (van Heesbeen et al., 2013). Nevertheless, it has been observed that changes in histone acetylation, usually at the H2A, H3, and H4 subunits, are common in the dopaminergic neurons of the midbrain of PD patients (Park et al., 2016). In fact, α-synuclein, which often accumulates in Lewy bodies and neurites, is known to suppress H3 histone acetylation by interacting with sirtuin-2 deacetylase (Liu et al., 2020b). In addition, H3 histone modification has been shown to regulate the level of the *microtubule-associated protein tau* (*MAPT*) (Renani et al., 2019).

4. Clock genes

Almost all organisms possess a cell-autonomous circadian clock which generates and maintains a 24-hour oscillation in physiological processes (Cox and Takahashi, 2019). Central to the circadian clock is a set of genes, collectively known as the 'clock genes', which encode various transcription factors that rhythmically regulate the expression of downstream genes (Cox and Takahashi, 2019). Some of the key clock genes include the *CLOCK* at chromosome 4q12 in humans, *BMAL1* at chromosome 11p15.3, *PER1* and *PER2* at chromosomes 17p13.1 and 2q37.3 respectively, and *CRY1* and *CRY2* at chromosomes 12q23.3 and 11p11.2 respectively. In addition to regulating the downstream targets, the protein products of these genes are known to interact, and form an autoregulatory loop, with one another (Takahashi, 2017).

The *CLOCK* gene, whose protein product possesses histone acetyltransferase (HAT) activity, is known to be constitutively expressed at both transcriptional and translational levels. Several alternatively spliced variants of *CLOCK* have been identified, although the function of these splice variants remains poorly understood (Crosby and Partch, 2020). The Clock protein contains two Per-Arnt-Sim (PAS) domains, through which it heterodimerizes with Bmal1 in the cytoplasm (Fig. 2). This heterodimerization not only further enhances the HAT activity of the Clock protein, but also allows the nuclear transport of the Clock-Bmal1 complex. In the nucleus, the heterodimer binds to the enhancer boxes (E-boxes; the 5'-CACGTG-3' and 5'-CACGTT-3' sequences) of the downstream genes and decondenses their chromatin to allow the access of the gene transcription machinery (Cao et al., 2021; Freeman et al., 2019). Apart from catalyzing the acetylation of histones, the Clock-Bmal1 heterodimer also recruits the transcriptional coactivators such as mixed lineage leukemia protein-1 (MLL1) and histone deacetylase inhibitors such as Jumonji, AT-rich interactive domain 1 (JARID1A) to facilitate the promotion of downstream gene expression (Rosensweig and Green, 2020).

Among the downstream genes activated by the Clock-Bmal1 heterodimer are the *PER* and *CRY* genes mentioned above. When *PER* and

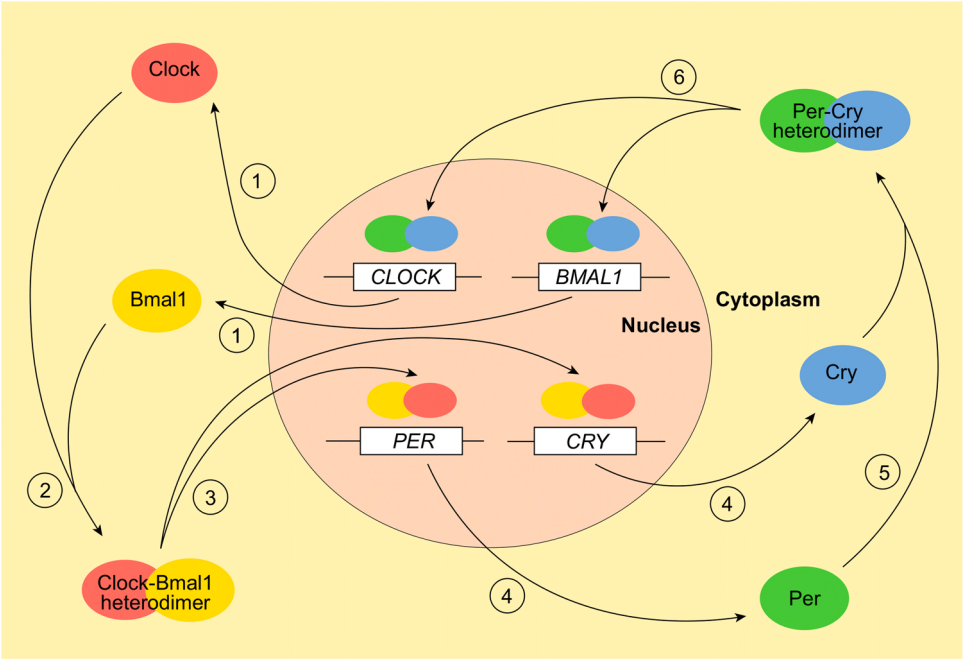

Fig. 2. Interrelationship among the clock genes. (1) *CLOCK* and *BMAL1* encode Clock and Bmal1 respectively. (2) Clock and Bmal1 form heterodimer with each other. (3) The Clock-Bmal1 heterodimer reenters the nucleus to facilitate the transcription of *PER* and *CRY*. (4) *PER* and *CRY* encode Per and Cry respectively. (5) Per and Cry form heterodimer with each other. (6) The Per-Cry heterodimer reenters the nucleus to inhibit the transcription of *CLOCK* and *BMAL1*.

CRY are expressed abundantly, their protein products, too, form heterodimers, which subsequently re-enter the nucleus to inhibit the Clock-Bmal1 complex, thus forming an autoregulatory feedback circuit (Takahashi, 2016) (Fig. 2). Inhibition of the Clock-Bmal1 complex by Per-Cry heterodimers can occur via multiple mechanisms, including causing conformational changes to the former as well as promoting phosphorylation (Saini et al., 2019). In addition, Per is also known to regulate the recruitment of Sin3-histone deacetylase complex to Clock-Bmal1-bound DNA to revert the acetylation status of the bound gene (Duong et al., 2011). Various combinations of Per paralogs (Per1 and Per2) and Cry paralogs (Cry1 and Cry2) are known to form heterodimers with one another (Silva and Domínguez, 2019). Nevertheless, the functional role of the two paralogs appears to be unequal, as mutations that lead to the loss of Per1 activity were found to alter the circadian period length of the circadian clock in vivo, whereas null mutations of *PER2* caused arrhythmicity (Bae et al., 2001; Cermakian et al., 2001). Interestingly, a decreased expression of *PER1* and *CRY1* was shown to respectively lead to an enhanced expression of *PER2* and *CRY2*, a phenomenon termed paralog compensation, but this compensatory expression was not observed when the expression of *PER2* and *CRY2* was reduced (Baggs et al., 2009).

The expression of *PER1* and *PER2* in the SCN was also affected by light, as the human circadian system uses a network of photosensitive RGCs that express the photopigment melanopsin. Thus, light signals through the retino-hypothalamic pathway converge on cAMP-response elements in the promoters of several clock genes. It has been shown that light at dawn advanced the clock, specifically by advancing the onset of the *PER1* mRNA rhythm and acutely increasing its mRNA transcription; whereas light at dusk delayed the clock, specifically by delaying the offset of the *PER2* mRNA rhythm and increasing mRNA stability. There are also suggestions that the underlying molecular mechanisms of circadian entrainment differ between morning and evening light exposure. Recently research in animal model showed that blue light was capable of slightly modulating *PER1* gene and increasing *PER2* expression (Dannerfjord et al., 2021; Foster et al., 2020; Ramos et al., 2014; Schwartz et al., 2011).

Apart from *PER* and *CRY*, the Clock-Bmal1 heterodimer also regulates the expression of genes encoding nuclear receptors (*REV-ERBα* and *REV-ERBβ*), and retinoic acid-related orphan receptors (*RORα* and *RORβ*) (Angelousi et al., 2018). These receptors compete for the ROR binding site on *BMAL1* promoter, and therefore influence the expression of the latter. Specifically, Ror activates the expression of *BMAL1*, whereas Rev-Erb represses it, which in turn inhibits the function of the Clock protein. Thus, these genes together form a secondary regulatory feedback loop. In addition, several other genes regulated by the Clock-Bmal1 heterodimer include, but not limited to, *arginine vasopressin* (*AVP*), which encodes a hormone that regulates osmotic balance in the bloodstream; *D-site binding protein* (*DBP*), which modulates the expression of numerous circadian rhythm genes; *cardiotrophin-like cytokine factor 1* (*CLCF1*), which suppresses the locomotor activity at appropriate circadian phases; and *prokineticin 2* (*PK2*), which transmits signals from the suprachiasmatic nucleus to control the circadian rhythm (Finger and Kramer, 2021; Kraves and Weitz, 2006; Li et al., 2009; Trott and Menet, 2018).

Mutations and alterations to the clock genes and proteins have been shown to result in functional impacts. For example, an A-to-T mutation in exon 19 of *CLOCK*, which leads to a 51-amino acid truncation of the Clock protein, was found to be correlated with abnormal and eventually loss of circadian periodicity in vivo (Gao et al., 2020). Similarly, knockdown of *BMAL1* in mice was found to result in a total loss of circadian rhythmicity. Besides, depending on the site of mutations, alterations to *PER* and *CRY* sequences can affect their intracellular localization, mRNA degradation, and translation (Crosby and Partch, 2020; Lee et al., 2014). In addition, phosphorylation of Clock, Bmal1, Per and Cry proteins through the action of casein kinase and/or other kinases also marks them for ubiquitination and subsequent proteasomal degradation (Hirano et al., 2016; Srikanta and Cermakian, 2020; Yoshitane and Fukada, 2021). There is also emerging evidence of post-transcriptional modifications in clock genes, as exemplified by the N^6-methyladenosine (m^6A) methylation of *PER2* and *BMAL1*, which have been demonstrated to affect their nuclear transport (Preußner and Heyd, 2016). Finally, the 3'-untranslated region (3'-UTR) of the clock genes has been shown to be a common binding site of numerous microRNAs, which suggests that the level of the clock genes may be

regulated at the post-transcriptional level (Jiang et al., 2018; Park et al., 2020; Tan et al., 2012; Tang et al., 2020; Yoo et al., 2017).

Clock genes are also known to play important roles in regulating cell cycle and division. For example, Per1 is known to promote cell cycle arrest in response to DNA damage by regulating the expression of checkpoint kinase 2. Similarly, in injured mice with dysfunctional *CRY1* and *CRY2*, *Clock/Bmal1* was found to activate the transcription of *WEE1* whose protein product delayed the G2/M transition in mitosis. For these reasons, the loss of circadian control can result in abnormal cell growth as well as telomere length, which implicates clock genes in diseases like cancers (Farshadi et al., 2020; Kagawa, 2012). In fact, in cancers, clock genes were found to play additional regulatory roles, such as by controlling the transcription of p53 pathway genes (mediated by Bmal1), or by targeting Myc oncoprotein for degradation (mediated by Cry2) (Huber et al., 2016; Shostak, 2017). Besides, circadian clock also plays an important role in the control of autophagy in liver cells, due in part to its transcriptional target genes which are involved in mitochondrial division and fusion. In fact, recent evidence shows that autophagy is under strong circadian regulation at the proteomic and post-translational levels (Wang et al., 2018b).

Apart from that, clock genes also regulate several physiological processes. For example, by controlling the expression of ion channel genes in the autonomic nervous system, clock genes can affect an individual's blood pressure and heart rate (Rabinovich-Nikitin et al., 2021; Tong et al., 2013). In addition, by regulating the formation of the brown adipose tissue which plays key functions in maintaining body temperature, clock genes have been associated with the control of the core body temperature (Coiffard et al., 2021). Besides, clock genes can regulate metabolic and immune responses, such as the secretion of proinflammatory interleukins. For this reason, lifestyle changes, such as disturbances in the light regime, a decrease in the amplitude ambient temperature, a shift in the time of eating, the distribution of the energy value of food during the day, lead to metabolic disorders and the development of low-intensity systemic inflammation (Kaidashev, 2020). Moreover, clock-controlled transcription factors are known to have a prominent role in muscle differentiation and maintenance (Li et al., 2021). The circadian clock also regulates basic body functions such as pulmonary capacity, sleep, and processes in the nervous tissue that cause neurological and psychiatric diseases such as auto-aggressive behavior, neuropathic pain, etc. Some studies also found an association between the development of certain symptoms and specific chronotypes determined by the circadian rhythm, which may help to develop chronotherapy and improve treatment by prescribing drugs in accordance with the patient's circadian rhythm (Boiko et al., 2017; Burish et al., 2019).

5. Clock gene expression in Parkinson's disease

In 2006, Yujnovsky et al. documented in the NG108–15 cell line that MAPK signaling pathway mediates the signal transduction from dopamine receptor 2 to the Clock:Bmal1 heterodimer, potentiates its function as a transcription factor (Yujnovsky et al., 2006). The group also noted that alterations to the Clock activity terminate the dopamine-mediated signaling (Yujnovsky et al., 2006). Since then, the expression of clock genes has been commonly investigated in PD animal models whose dopaminergic nigrostriatal neurons are intentionally damaged with neurotoxins like MPTP and 6-hydroxydopamine (6-OHDA) to mimic the PD pathology (Chia et al., 2020). For example, Hayashi et al. experimented in mice treated with MPTP that exhibit both the motor and non-motor symptoms of PD, and found that the expression of *CLOCK* gene remained unaltered in the course of time, in contrast with *BMAL1, PER1, PER2, CRY1, DEC1* and *REV-ERBA* which showed a decreased amplitude (Hayashi et al., 2013). Taking a few steps further, Li et al. investigated the potential effect of treatment with levodopa in the circadian rhythm deregulation (Li et al., 2017c). In the 6-OHDA mouse model, the researchers documented the downregulation of *BMAL1* expression in the L-Dopa-treated mice in the SCN at 4:00 ZT and 16:00 ZT, at 10:00 ZT in the striatum. The expression acme of *PER2* came later at 16:00 ZT. This clock genes deregulation was noticed in spite of the improvement in motor function, as noted in treadmill performance (Li et al., 2017c).

In addition to MPTP and 6-OHDA-treated mice, several gene expression studies were conducted on mice which had been induced to develop PD using lipopolysaccharides, rotenone or manganese (Deng et al., 2020; Lawana and Cannon, 2020; Pingale and Gupta, 2020). An example of this is a study which applied rotenone on previously sensitized mice with a single injection of LPS. This did not aggravate only the animals' motor function and the histologic features (Huang et al., 2017), but further affected the expression of circadian machinery. When LPS and rotenone were applied, significant downregulation of *CLOCK* and *BMAL1* gene expression was observed, which unequivocally points out the significance of clock genes in the pathogenesis of PD (Li et al., 2019). Similar results were reported in a study by Li et al., which reported significant downregulation of *CLOCK* and *BMAL1* genes in male Sprague-Dawley rats treated with manganese injections in the peritoneal cavity (Li et al., 2017a).

Despite the common belief that clock genes regulate only sleep, our knowledge broadened with the studies on *BMAL1 -/-* mice. These mice did not only have altered sleep-wake patterns, but also showed a progeria phenotype due to the accumulation of reactive oxygen species in tissues (Chen et al., 2021b). *BMAL1* is also known to control quotidian trafficking to inflammatory lesions (Pick et al., 2019; Waggoner, 2020). A landmark study on the expression of clock genes in rotenone-induced PD in male mice reported the loss of diurnal rhythm in *BMAL1*, *CRY1* and *CRY2* expression in SCN, while the expression of *PER2* gene remained unaltered (Mattam and Jagota, 2015). In addition, exogenous administration of melatonin restored only the phase of *PER1* expression and did not affect the phase of *PER2* and *CRY2* expression in SCN (Mattam and Jagota, 2015). Finally, Wang et al. reported that the generation of reactive oxygen species is mediated by the SIRT1- BMAL1 pathway (Wang et al., 2018a). Specifically, injection of 6-OHDA in vivo and in vitro significantly downregulated the expression of *CLOCK*, *BMAL1* and *PER2* clock genes, as well as *CAT* and *GPX*, which constitute parts of the cell's antioxidant machinery. Resveratrol, a potent SIRT1 agonist, decreased the levels of acetylated BMAL1 and antagonized partially the binding of Bmal1 and Cry. These effects were induced by 6-OHDA (Wang et al., 2018a). Oxidative stress is proven to be a precipitating factor of PD.

Apart from animal studies, a number of studies have examined the expression of clock genes on human subjects. For example, Cai et al. observed, in samples of peripheral blood, a decrease in the expression of *BMAL1*, while *PER1* expression remained unchanged (Cai et al., 2010). This observation was particularly evident during low lighting conditions at night. The decreased expression could not be attributed to L-Dopa, since the results were confirmed in treatment naïve patients. Interestingly, this effect correlates with the patients' Unified PD Rating Scale score, making *BMAL1* expression a possible predictive and prognostic biomarker (Cai et al., 2010). Ding et al. subsequently took a step further to study *BMAL2, CLOCK* and *DEC1* genes in the patient population, and found that *BMAL2* was downregulated in a similar pattern as *BMAL1*, but no alteration was observed for the other two genes (Ding et al., 2011).

Apart from that, while investigating the sleep phenotype during a 24-hour time period, Breen et al. documented a linear expression of *BMAL1* in PD patients in contrast with the oscillatory pattern of controls and a spike in the expression of *PER2* at 04:00 (David P. Breen et al., 2014). This study reveals important clinical and pathophysiologic clues about the disease (Leroy et al., 1998). In addition, Delgado-Lara et al. investigated the effect of melatonin supplementation on *BMAL1* and *PER1* expression (Delgado-Lara et al., 2020). They reported an upregulation of *BMAL1*, in contrast to the *PER1* expression which was unaffected. It is interesting that these results can be ascribed to placebo effect, a common

phenomenon at least to the motor phenotypes of the disease, which enhances the dopamine secretion in the mesolimbic system (Delgado--Lara et al., 2020). Besides, Pacelli et al. documented an interconnection of metabolic cellular processes with circadian rhythm machinery, using fibroblasts from PD patients with the mutated *PARK2* gene (Pacelli et al., 2019). More specifically, they reported the loss of oscillatory pattern of expression in *CLOCK* and *PER1* genes, while *BMAL1* remained unaffected (Pacelli et al., 2019).

A few studies also investigated the possible epigenetic link between clock genes and PD. This is exemplified by Lin et al., who investigated a possible contribution of clock genes promoter methylation in PD's pathogenesis (Lin et al., 2012). This study, which was conducted on 206 PD patients and 181 healthy controls, showed that only *CRY1* and *NPAS2* (the paralog of *CLOCK*) promoters exhibited methylation, and only the latter was significantly hypomethylated in PD patients (Lin et al., 2012). Nonetheless, other genes, including *CLOCK*, *BMAL1*, *PER1*, *PER2* and *CRY2*, were found to be not regulated epigenetically by DNA methylation in both cases and controls. However, another study found the presence of DNA methylation in 7 out of 80 dementia patients in the CpG island of the following nine clock-related genes: *CK1ε, BMAL1, CRY2, CLOCK, PER1, PER2, PER3*, *TIM,* and *CRY1,* while there was no methylation in any of the control individuals (Liu et al., 2008). Moreover, patients having Dementia with Lewy bodies (DLB) exhibited the highest frequency (35.7%) of the methylation in the CpG island in the circadian genes (Chouliaras et al., 2020; Liu et al., 2008). These observations suggest that DNA methylation could play some contributory role in the development of PD.

6. Clock gene polymorphisms and Parkinson's disease

Genetic polymorphisms are the most abundant source of DNA sequence variation in humans. Depending on the location of the polymorphisms, they may influence the transcriptional efficacy of the gene or the structure (and therefore, the function) of the protein product. Since dysregulated gene expression and altered protein functions are among the major hallmarks of many disorders, genetic polymorphisms have been implicated as a risk factor in many diseases, including PD (Pang et al., 2019; Pihlstrøm et al., 2016), Alzheimer's disease (Carmona et al., 2018; Naj and Schellenberg, 2017), cerebrovascular disease (Della-Morte et al., 2016), infectious diseases (Mozzi et al., 2018), cancers (Tan, 2018; Tan et al., 2020; Tan and Ankathil, 2015), periodontal and cardiovascular diseases (Aarabi et al., 2017), psoriasis (Capon, 2017), and virtually all genetic diseases (Timpson et al., 2018).

Perturbations to the clock gene network can lead to irregularities in circadian rhythm and have been associated with metabolic dysfunction, oxidative stress and inflammatory abnormalities, which may contribute to pathogenesis of PD (Maury, 2019). Thus, over the past decade, several studies have investigated the association between polymorphisms in the clock genes and the risk of PD and its symptoms (Table 1). The earliest study in this area of research was conducted by Hua et al. (Hua et al., 2012) who investigated the association of *CRY1* rs2287161 and *CRY2* rs10838524 polymorphisms with depression symptoms in PD. The rs2287161 polymorphism is located 3' downstream of the polyadenylation site of *CRY1* and has been predicted to affect the binding and regulatory function of the RFX5 transcription factor (Gabriel and Zierath, 2019). Similarly, the intronic rs10838524 polymorphism of *CRY2* may hinder the binding of the CTCF transcription factor and may therefore influence its transcription (Kovanen et al., 2017). In fact, mathematical modeling suggest that the rs10838524 polymorphism can cause an increased transcription rate of *CRY2* (Liberman et al., 2018), although a study on breast tissues did not find a significant difference in the expression levels of the gene among the different genotypes of the polymorphism (Lesicka et al., 2019). In the genetic association study conducted by Hua et al. (2012) on 408 individuals with PD, it was found that the homozygous CC genotype of the *CRY1* rs2287161 polymorphism was significantly associated with a higher score of Hamilton Rating Scale for Depression, whereas no association was observed for the *CRY2* rs10838524 polymorphism. Despite this, the statistical significance of *CRY1* rs2287161 was lost when the data was adjusted for other potential confounders, suggesting that the polymorphism could play a limited role in the development of depression in PD.

Table 1
Association of polymorphisms in clock genes with PD risk and symptoms.

Gene	Polymorphism	Main findings	Reference
CLOCK	rs1801260	Associated with an increased risk of PD, as well as motor fluctuation and sleep disorder	(Lou et al., 2018, 2017)
BMAL1	rs900147	Associated with a decreased risk of PD; subgroup analysis found that the association was significant among PD patients with TD	(Gu et al., 2015)
PER1	rs2253820	Associated with an increased risk of PD; subgroup analysis found that the association was significant among PD patients with PIGD	(Gu et al., 2015)
PER2	rs2304672	No significant association	(Lou et al., 2017)
CRY1	rs2287161	Associated with a higher score of Hamilton Rating Scale for Depression	(Hua et al., 2012)
CRY2	rs10838524	No significant association	(Hua et al., 2012)

Besides, Gu et al. (2015) used a mid-throughput method to genotype 132 tag polymorphisms in eight genes involved in the clock pathway, including *CLOCK*, *BMAL1*, *PER1*, *CRY1*, and *CRY2*, on 1394 individuals with PD and 1342 healthy controls. Among the 132 tag polymorphisms, only the rs900147 of *BMAL1* and rs2253820 of *PER1* were significantly associated with a decreased and an increased risk of PD, respectively. Interestingly, when the PD cases were categorized into different subtypes, statistically significant association was only observed in tremor dominant (TD) cases for *BMAL1* rs900147, and in postural instability and gait difficulty (PIGD) cases for *PER1* rs2253820 polymorphism. The functional impacts of these two polymorphisms are not well-understood. However, both polymorphisms are located in the exon and/or promoter regions of their respective genes, and may therefore influence the transcription or the amino acid structure of the protein products (Gu et al., 2015).

More recently, Lou et al. (2017) investigated the association of *CLOCK* rs1801260 and *PER2* rs2304672 polymorphisms with susceptibility to PD on a series of 646 PD cases and 352 healthy controls. The *CLOCK* rs1801260 polymorphism was previously found to lead to a higher expression level of the gene (Ozburn et al., 2016), although this finding needs to be viewed with caution as the gene expression data was normalized to a single, non-empirically validated reference gene, a practice which may cause misleading interpretation (Bustin et al., 2009; Tan, 2019; Tan et al., 2017). On the other hand, the functional impact of the *PER2* rs2304672 polymorphism is less well-understood, although it has been commonly found to be associated with a number of phenotypes (Froy and Garaulet, 2018; Yegin et al., 2021). In the aforementioned study by Lou et al. (2017), it was observed that the variant allele carriers of the *CLOCK* rs1801260 polymorphism showed almost a 2-fold risk of developing PD compared to individuals who did not carry the allele, whereas significant association was not observed for the *PER2* polymorphism. Further to this observation, the same group of researchers examined the association between the *CLOCK* rs1801260 polymorphism and various symptoms in PD in the same cases (Lou et al., 2018). They did not find any significant association between the polymorphism and dyskinesia, depression, or orthostatic hypotension. However, the variant allele carriers of the polymorphism were observed to be more susceptible to motor fluctuation and sleep disorder compared to non-variant allele carriers.

7. Mitochondria dynamics and other pathways affecting circadian rhythmicity

Although PD cases are often characterized as sporadic with unclear etiology, approximately 10% of the patients have well-defined genetic causes (as described above) and/or exhibit mitochondrial abnormalities (Alexiou et al., 2019, 2018b; Chen et al., 2019; Park et al., 2018). Mitochondria are a dynamic population of non-autonomous organelles that interact with each other. Neurons are reliant on mitochondrial dynamics. Mitochondria are also actively recruited to subcellular sites such as the axonal and dendritic neuron processes, where they are involved in critical cellular functions (Alexiou et al., 2018a; Rangaraju et al., 2019; Seager et al., 2020). Thus, disruptions in mitochondrial dynamics are highly correlated to neurodegeneration (Johnson et al., 2021; Tapias, 2019).

High mitochondrial fusion and fission rates are independent events in a wild-type cell, which constantly change individual mitochondria's identity (Fig. 3). Mitochondria mix their contents through fusion, enabling protein complementation, mtDNA repair, equal distribution of metabolites, and autophagy of isolated damaged mitochondrial segments (Twig et al., 2008). On the other hand, fission facilitates equal segregation of mitochondria into daughter cells during cell division and enhances mitochondrial distribution along cytoskeletal tracks. Mitochondrial fission is regulated by dynamin-related protein (Drp-1), while fusion is regulated by optic atrophy 1 (Opa1) and mitofusins (Mfn) 1 and 2 (Frezza et al., 2007). Disruptions in both fusion and fission have been shown to affect mitochondrial movement, thus affecting their functions. Therefore, abnormalities in fission and fusion have been thought to contribute to PD pathogenesis (Mani et al., 2021). In addition, failure in fission and fusion can impede the mitophagy process, which is mediated mainly through the Pink1/Parkin pathway (de Goede et al., 2018). Parkin targets mitochondria with low membrane potential, which are then destroyed through the autophagosome. Recent studies revealed that Pink1 and Parkin also play a role in promoting mitochondrial fission or inhibiting fusion (Gao et al., 2021; Ma et al., 2018; Peng et al., 2018). For this reason, aberrations in *PINK* and *PARKIN* genes which encode the two proteins have been seen in a number of neurodegenerative diseases like the Alzheimer's disease (AD), Huntington's disease (HD), as well as PD (Quinn et al., 2020).

Interestingly, PD has also been shown to be linked to human bioenergetics. An example of this is the paradoxical kinesia (PK), where an idiopathic PD patient may suddenly present excellent motor responses in emotional or physical stress, due probably to noradrenergic augmentation, compensatory activation of cerebellar circuitry, or activation of the basal ganglia reserves (Bonanni et al., 2010; de la Fuente-Fernández et al., 2002; Goerendt, 2004; Schlesinger et al., 2007). Latest studies have also revealed the correlation of mitochondrial bioenergetics in cell metabolism to circadian rhythmicity (Aguilar-López et al., 2020; Puig et al., 2018), thus implicating clock genes in the regulation of glucose, lipid homeostasis, and mitochondrial oxidative metabolism (de Goede et al., 2018). Indeed, in vitro models have presented the relationship between clock gene expression and the mitochondrial oxidative phosphorylation (Silva Ramos et al., 2016). Using synchronized cells, researchers have achieved an autonomous ultradian mitochondrial respiratory activity abrogated by silencing the *BMAL1*. In contrast, pharmacological inhibition of the mitochondrial oxidative phosphorylation system resulted in dramatic deregulation of the rhythmic clock-gene expression (Scrima et al., 2016). New pieces of evidence have also identified the connection between circadian timekeeping disruption and abnormalities in mitochondrial dynamics in several neurodegenerative diseases like AD, PD, and HD (Aguilar-López et al., 2020; Oliva-Ramírez et al., 2014; Videnovic et al., 2014a). For example, Bmal1 has been shown to affect mitochondrial fusion in the heart via mechanisms unrelated to Drp-1, Opa1 and Mfn1/2 (Jacobi et al., 2015; Kohsaka et al., 2014). In addition, the peroxisome proliferator-activated receptor gamma coactivator 1 alpha (PGC-1α), a key inducer of mitochondrial biogenesis, is known to be expressed in a rhythmic manner and stimulates the transcription of *BMAL1* and *CLOCK* via interactions with RORa and RORb proteins (de Goede et al., 2018; Liu et al., 2007). Several other studies also found that *PARKIN* mutations are strongly correlated with the circadian machinery of the mitochondrial dynamics (Breen et al., 2014b; Jacobi et al., 2017; Pacelli et al., 2019). These findings provide a clear indication of the involvement of clock genes in mitochondrial dynamics in neurodegenerative diseases like PD.

The role of clock genes in PD pathogenesis is not only limited to mitochondria dynamics. The molecular circadian clock also regulates antioxidative defense, which plays a major role in initiating a cascade of biochemical processes that cause dopaminergic cell death. For this

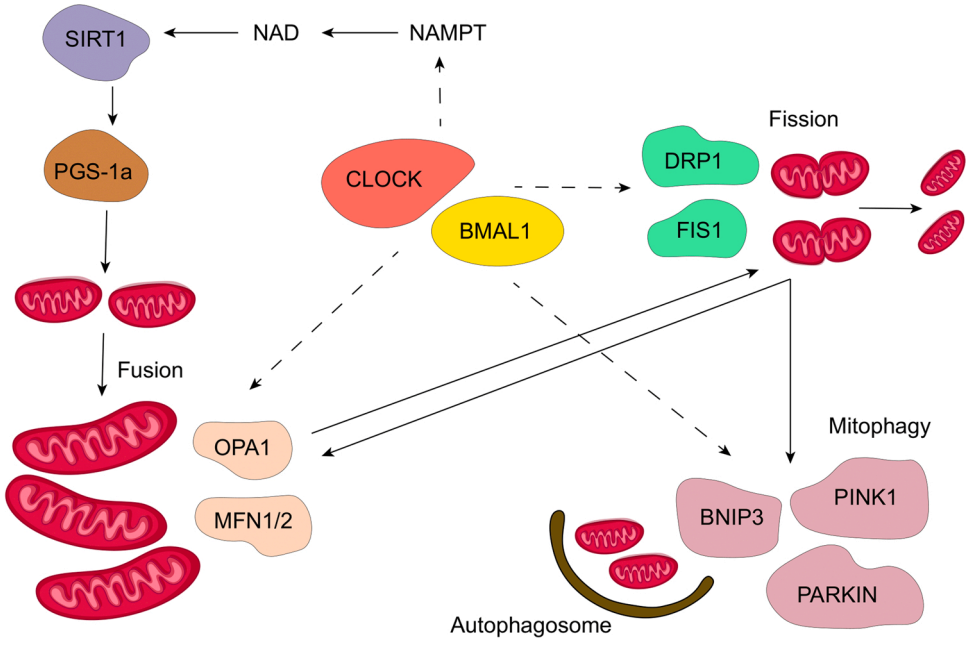

Fig. 3. Circadian interactions and mitochondrial dynamics. Clock-Bmal1 stimulates mitochondrial biogenesis by regulating mitochondrial fission and fusion. (Adapted from de Goede et al., 2018, an Open Access Article, (CC BY 4.0)).

reason, mitochondrial complex I inhibitors, a well-known source of oxidative stress, show cytotoxicity to dopaminergic neurons can cause neural apoptosis (Blesa and Przedborski, 2014; Greenamyre et al., 2010). Besides, alterations to the antioxidative SIRT1 gene have been known to affect the circadian rhythm and the expression of clock-controlled genes by deacetylating Bmal1 and Per2 proteins, which again provided an evidence of the importance of clock genes in regulating oxidative stress during PD pathogenesis (Dong et al., 2016; Wang et al., 2018a). Thus, circadian disruptions may result in increased oxidative stress, which accelerate neurodegeneration in PD (Videnovic et al., 2014a). Targeting the redox homeostasis process could therefore be a potential treatment procedure for PD (Wang et al., 2018a).

Clock genes are also implicated in the regulation of autophagy, which plays a major function in mediating the protein and cellular turnover (Hou et al., 2020). Dysfunction in autophagy can cause the accumulation of α-synuclein and the degeneration of dopaminergic neurons, which contribute to PD. It is for this reason that several autophagy-related genes, such as LRRK2, are commonly mutated in PD (Kim et al., 2019). Additionally, since autophagy also regulate immune cell homeostasis and survival, impairment in the autophagy process promotes neutrophilic infiltration, activates inflammasome and facilitates significant proinflammatory cytokine alterations (Hu et al., 2021; Qian et al., 2017). These processes lead to neuroinflammation, which is widely known to cause neurodegeneration by mediating the progressive loss of nigral dopaminergic neurons. Besides, inflammation also contributes to oxidative stress, and is in fact, exacerbated by oxidative stress; thus forming a vicious cycle with each other during the pathogenesis of PD (Pajares et al., 2020; Racanelli et al., 2018). Autophagy is not only involved in neurodegenerative diseases, but is also highly correlated with cognitive loss (Crino, 2016) and circadian rhythm dysfunction (Vaiserman et al., 2016). In addition, alterations in everyday life activities, such as sleep disturbances and the absence of circadian clock proteins, may influence the autophagy process and result in cognitive decline (Maiese, 2017). Given the importance of autophagy in PD, a recent study has demonstrated the potential of controlled autophagy induction as an efficient clinical PD therapy procedure (Ajoolabady et al., 2021). Targeting the autophagy pathway in PD therapy will thus be an interesting avenue for research in the near future.

8. Hormonal destabilization in PD involved clock genes

PD patients often show altered endocrine hormonal secretion. The SCN, which generates the circadian rhythms, is known to control the rhythmic synthesis and secretion of such hormones as melatonin and cortisol (Mlili et al., 2021). Melatonin is a natural hormone that is formed primarily in the pineal gland during the dark period. Its secretion normally starts at dusk and ends at dawn, and it has a substantial role in the sleep-wake cycle regulation and control (Kenneth et al., 2013). Since sleep disorders are one of the most common non-motor symptoms in PD patients, serum level of melatonin has been investigated in PD patients for a long time. In 1991, a study by Fertl et al. showed that the level of serum melatonin was similar between PD patients and non-PD controls (Fertl et al., 1991). However, when comparison was made between *de novo* PD patients and those treated with L-Dopa, it was found that the phase was advanced in the latter group (Fertl et al., 1993). Dopaminergic treatment enhanced the melatonin secretion cause sleep delay suggesting an uncoupling of circadian sleep regulation due to pharmacological alteration of the melatonin level (Bolitho et al., 2014). In another study examining the impact of dopaminergic treatment in PD patients on circadian melatonin secretion patterns, it was noted that the level of melatonin was decreased at night, while increased in the daytime (Bordet et al., 2003). On the other hand, a study done by Breen et al. found that the melatonin level was decreased in PD patients who were in the early disease stage and suffering from sleep disorders (Breen et al., 2014a, 2014b). In agreement with Breen et al., another study by Videnovic et al. illustrated that both the melatonin rhythm and the area-under-the-curve (AUC) in 24 h for circulating melatonin levels were dramatically lower in PD patients compared to controls (Videnovic et al., 2014b).

Since both melatonin and clock genes play a substantial role in PD, several studies have investigated the targeting of clock genes for PD treatment using melatonin. For example, Dowling et al. conducted a comparative study to assess the effect of melatonin treatment on nocturnal sleep of 40 PD patients with sleep disorders, where the patients took either 5 mg or 50 mg melatonin, or placebo, during different study periods (Dowling et al., 2005). The results showed that there was a slight improvement in night sleep when the patients received 50 mg melatonin, when compared to the placebo treatment period, although the improvement lasted for only around 10 min (Dowling et al., 2005). However, during the 5 mg melatonin treatment period, the patients showed a substantial amelioration in subjective sleep disturbance and daytime sleepiness (Dowling et al., 2005). Interestingly, in a later double-blind, randomized, placebo-controlled study conducted on 18 PD patients, a robust enhancement in subjective sleep quality was observed in patients administered 3 mg/day melatonin for 4 weeks, although the polysomnography results showed no change (Medeiros et al., 2007). Recently in 2020, Delgado-Lara et al. conducted a randomized controlled trial involving 26 PD patients to investigate the influence of melatonin administration on *PER1* and *BMAL1* genes expression. When 25 mg melatonin was administrated for a period of 3 months at noon and before sleep, increased *BMAL1* level was documented in the patients, especially in the morning, but significant changes were not observed in the level of *PER1* (Delgado-Lara et al., 2020). This suggests that melatonin improves PD symptoms by regulating *BMAL1* expression. Despite this, treatment with melatonin did not affect or delay the disease progress, insomnia, or daytime sleepiness, although it was found to enhance the perception of sleep comfort (Delgado-Lara et al., 2020). Besides, another study investigated the role of melatonin on clock genes by using male rotenone-induced PD (RIPD) Wistar rat models. The results showed that melatonin intervention restored the phase of the rPer1 daily rhythm in the RIPD models. Interestingly, when melatonin and rotenone were administered to the RIPD models for 48 days, neuroprotective effects were observed in the dark phase (Mattam and Jagota, 2015).

Cortisol is a stress hormone which is the end product of the hypothalamic-pituitary-adrenal (HPA) axis under strong circadian control. It is involved in depression, sleep disorders, and anxiety. The cortisol secretory rhythms serve as an indicator of circadian function, that is altered in PD patients as well (Mlili et al., 2021; Nandam et al., 2020). Cortisol level in the serum was found to be significantly elevated in PD patients, as demonstrated by Breen et al. (Breen et al., 2014a, 2014b). Moreover, half of the PD patients exhibited arrhythmic cortisol levels with no phase shifting, either to an earlier phase or to a delayed phase (Breen et al., 2014a, 2014b). Likewise, Hartmann et al. showed that the total plasma cortisol level was enhanced in PD patients compared to age-matched volunteers (Hartmann et al., 1997). Similarly, the salivary cortisol level was found to be higher in PD patients without impulsive compulsive behaviors compared to the non-PD controls (Djamshidian et al., 2011). It has also been observed that cortisol is involved in stress regulation, as serum cortisol levels are intimately linked to various neuropsychiatric symptoms. For example, a higher level of cortisol has been associated with longer sleep latency and a lower sleep efficiency and duration in PD patients (Breen et al., 2014a, 2014b). Another study demonstrated that cortisol levels were negatively linked to anxiety level (Růžička et al., 2015). In addition, pattern of the daily cortisol secretion has been found to be correlated with depression scores after 3 and 6 months (Seifried et al., 2013). These observations clearly demonstrate the important roles of cortisol, which is regulated by circadian clock, in PD and its symptoms. Besides, in MPTP-treated dog models of PD, an increase in the plasma cortisol level was observed, indicating that MPTP has an impact on the activity of the dog's

hypothalamic neurons (Mizobuchi et al., 1993). Animal studies have also demonstrated a link between elevated cortisol level with dopaminergic cell loss and motor handicap, which could explain why increased cortisol level is commonly found in PD patients (Djamshidian et al., 2011). A few attempts have also been made to examine the level of cortisol following PD treatments. For example, in a randomized controlled pilot study investigating the diurnal as well as the total salivary cortisol levels during short- and long-term points of tactile massage (TM), it was revealed that the salivary cortisol level was decreased after the intervention, while the diurnal cortisol level remained constant (Törnhage et al., 2013). A more recent study on 6-OHDA-treated rats found an increased cortical secretion at 06:00 following L-Dopa administration (Li et al., 2017c). Interestingly, L-Dopa treatment caused a reduction in the expression level and delayed the phase of clock genes, specifically *BMAL1* at the 4:00 ZT and 16:00 ZT time points in the SCN and at 10:00 ZT in the striatum (where the *PER2* expression was delayed to 16:00 ZT), while no changes were observed in the expression of any of the clock genes in the liver (Li et al., 2017c). It is unknown, however, whether the gene expression and phase changes were due to the direct effect of L-Dopa, or the dopamine that is converted from the former. Nonetheless, these findings suggest that the link between clock genes and cortical secretion occur in a tissue-specific manner. Besides, L-Dopa is also known to have a direct effect on clock gene regulation in PD rat model (Korshunov et al., 2017). Notably, dopamine and its receptors could have both direct and indirect effect on clock genes in the central nervous system. Additionally, dopamine can possess clock gene-like activities, like those in the retina, midbrain, and hypothalamus. In such areas, dopamine and clock genes can regulate each other (Korshunov et al., 2017). Considering these, it has now become clear that the clock genes play an undeniably important role in the pathogenesis and recovery of PD.

9. Conclusions and future perspectives

Circadian rhythm is regulated by six major clock genes, namely *CLOCK, BMAL1, PER1, PER2, CRY1* and *CRY2*. The loss of circadian rhythm, presumably due to disruptions in the levels and functions of clock genes, is a common event in the development of PD. Thus, although the role of clock genes in the pathogenesis of PD has not been extensively studied, current evidence points to the indication that they may have a significant impact on the development and progression of the disease. This assertion is corroborated by the observation in human subjects that the expression of clock genes is dysregulated in PD patients. Epigenetics, along with genetic polymorphisms, have been pinpointed as some of the possible mechanisms through which dysregulated clock gene expression is achieved. Additionally, a few polymorphisms in the clock genes have been found to be associated with risk and/or symptoms of PD. It has also been postulated that clock genes contribute to the pathogenesis of PD by disrupting the mitochondrial dynamics. Besides, abnormalities in the circadian rhythm of hormone secretion have also been noted, which can be considered as a marker of circadian regulation dysfunction. These findings provide a strong support for the potential role of clock genes in PD pathogenesis.

Despite this, several pieces of information are still missing as there are a number of limitations with the currently available studies. In gene expression analyses, for example, a number of studies normalized their expression data to a single non-validated housekeeping gene. The studies by Cai et al. (2010) and Ding et al. (2011), for example, used *18S* as the RT-PCR reference genes. Recent studies have shown that the use of common housekeeping genes for normalizing RT-PCR data is inappropriate, as the expression of these genes, contrary to the widely-held belief, is inconsistent across multiple tissue types (Fochi et al., 2021; Gu et al., 2021; Liu et al., 2020a; Tan et al., 2017; Yadav et al., 2020; Zucherato et al., 2021). Moreover, the current consensus in the scientific community is that the use of only one reference gene is not sufficient (Bustin et al., 2009). Inappropriate use of reference genes in these studies could there contribute to misleading result interpretations (Tan, 2019). In addition, none of the studies profiled the expression of all six (or more) clock genes simultaneously, thus the impact of gene-gene interactions is not well-understood. Likewise, possible gene-environment interactions are not known. Majority of epigenetics studies have also focused only on DNA methylation, even though the involvements of other epigenetic mechanisms, such as histone acetylation and microRNAs, are becoming more apparent (Jakubowski and Labrie, 2017). More research is needed to provide further insights into the roles of clock genes in PD.

Apart from that, in the current era of genomics and precision medicine, it is imperative that genome-wide (and epigenome-wide) association studies are conducted on a large scale to shed some light on the genetic variants associated with PD. Additional in vitro and in vivo functional assays should also be performed to clarify the mechanisms by which the clock genes contribute to the pathogenesis of PD (Pierce et al., 2020). Of particular interest are the studies of how the clock genes regulate mitochondrial dynamics and how abnormalities in these dynamics drive PD, since current evidence has provided a solid foundation in this field for future research. It would also be interesting to investigate the changes in the levels of hormones other than cortisol and melatonin in response to clock gene regulation.

In conclusion, it is now clear that clock genes could contribute to PD via a number of mechanisms. However, more research will be needed to provide a complete picture of the roles of clock genes in the pathogenesis of PD. These additional research data will be necessary for knowledge in this area of study to be deemed sufficiently reliable for future clinical applications.

CRediT authorship contribution statement

Anastasiia Dmytrivna Shkodina: Conceptualization, Writing – original draft, Visualization. **Shing Cheng Tan:** Writing – original draft, Writing – review & editing, Supervision, Project administration. **Mohammad Mehedi Hasan:** Writing – original draft. **Mai Abdelgawad:** Writing – original draft. **Hitesh Chopra:** Writing – original draft. **Muhammad Bilal:** Writing – original draft. **Dmytro Ivanovych Boiko:** Visualization. **Kateryna Anatoliivna Tarianyk:** Writing – original draft. **Athanasios Alexiou:** Writing – original draft.

Conflict of interest

The authors declare that they have no conflict of interest.

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