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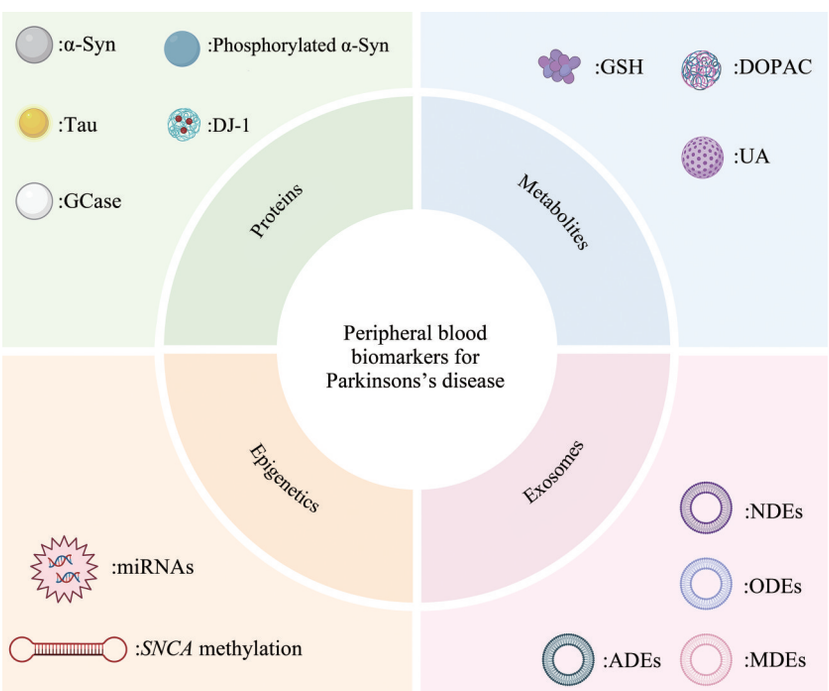
Insights on Peripheral Blood Biomarkers for Parkinson's Disease*

LI Yu-Meng**, LIU Jing-Kai**, CHEN Zi-Xuan***, DENG Yu-Lin***
(*Beijing Key Laboratory for the Separation and Analysis of Biomedical Components, School of Medical Technology, Beijing Institute of Technology, Beijing* 100081, China)

Graphical abstract



Abstract Parkinson's disease (PD) is a common neurodegenerative disorder with profound impact on patients' quality of life and long-term health, and early detection and intervention are particularly critical. In recent years, the search for precise and reliable biomarkers has become one of the key strategies to effectively address the clinical challenges of PD. In this paper, we systematically

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** These authors contributed equally to this work.
*** Corresponding author.
CHEN Zi-Xuan. Tel: 86-18519020651, E-mail: zx-chen@bit.edu.cn
DENG Yu-Lin. Tel: 86-13501125130, E-mail: deng@bit.edu.cn
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evaluated potential biomarkers, including proteins, metabolites, epigenetic markers, and exosomes, in the peripheral blood of PD patients. Protein markers are one of the main directions of biomarker research in PD. In particular, α-synuclein and its phosphorylated form play a key role in the pathological process of PD. It has been shown that aggregation of α-synuclein may be associated with pathologic protein deposition in PD and may be a potential marker for early diagnosis of PD. In terms of metabolites, uric acid, as a metabolite, plays an important role in oxidative stress and neuroprotection in PD. It has been found that changes in uric acid levels may be associated with the onset and progression of PD, showing its potential as an early diagnostic marker. Epigenetic markers, such as DNA methylation modifications and miRNAs, have also attracted much attention in Parkinson's disease research. Changes in these markers may affect the expression of PD-related genes and have an important impact on the onset and progression of the disease, providing new research perspectives for the early diagnosis of PD. In addition, exosomes, as a potential biomarker carrier for PD, are able to carry a variety of biomolecules involved in intercellular communication and pathological regulation. Studies have shown that exosomes may play an important role in the pathogenesis of PD, and their detection in blood may provide a new breakthrough for early diagnosis. It has been shown that exosomes may play an important role in the pathogenesis of PD, and their detection in blood may provide new breakthroughs in early diagnosis. In summary, through in-depth evaluation of biomarkers in the peripheral blood of PD patients, this paper demonstrates the important potential of these markers in the early diagnosis of PD and in the study of pathological mechanisms. Future studies will continue to explore the clinical application value of these biomarkers to promote the early detection of PD and individualized treatment strategies.

Key words Parkinson's disease, peripheral blood, biomarkers, early diagnosis
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1 Parkinson's disease: clinical diagnosis, etiology, and pathological mechanisms

1.1 Clinical diagnosis and treatment approaches in PD

Parkinson's disease (PD) is the most common extrapyramidal disease in the elderly. According to current research surveys, its prevalence is approximately 1% among individuals aged 65 and above, and this rate gradually increases with age[1-3]. The clinical diagnosis of PD typically involves a series of clinical assessments, symptom observation, and auxiliary examinations. Among them, the clinical symptoms of PD patients are an important basis for diagnosis, and are mainly divided into three core motor symptoms, including bradykinesia, resting tremor, and myotonia[4-6]. However, relying solely on clinical assessment may lead to misdiagnosis and missed diagnoses. Neuroimaging testing methods, such as magnetic resonance imaging (MRI) and single-photon emission computed tomography (SPECT), can help rule out other problems that may cause similar symptoms and improve the accuracy of PD diagnosis[7-10]. However, current detection methods are not yet capable of accurately diagnosing patients with early PD who do not exhibit obvious clinical symptoms. Considering the advantageous characteristics of blood biomarkers, such as non-invasiveness, low cost, and high sensitivity, the search for blood markers for early diagnosis of PD has emerged as a significant research focus.

The primary treatment for PD is medication, with levodopa preparations such as amantadine, madopar, and sulfonate considered the most effective drugs[11-12]. However, taking levodopa may increase the risk of dyskinesia, and this risk is higher with higher doses[13]. Surgical treatment serves as an adjunct to drug treatment and includes two commonly used methods: nerve core destruction and deep brain stimulation, both of which effectively reduce the motor symptoms of PD[14]. However, surgical treatment is expensive, invasive, not suitable for all PD patients, and is not a permanent solution. Although current treatments can alleviate symptoms and improve patients' quality of life, they cannot completely halt the progression of PD. Therefore, the importance of finding new early PD diagnosis and treatment targets is self-evident.

1.2 Etiological factors contributing to PD

PD is clinically categorized into two types. One type is familial PD, which is caused by known or unknown familial genetic abnormalities, mainly autosomal dominant or recessive, and accounts for 10% of all cases[15]. The other type is sporadic PD, which has no known family history and accounts for about 90% of all cases[15]. Although it has been established that PD is associated with certain genetic and cellular mechanisms, the disease is highly complex and the precise molecular mechanisms underlying it are still not fully understood. Gene mutations, epigenetic disorders, and exposure to environmental toxins are all causative factors of PD[16-17]. For familial PD, gene mutation is a key factor in the pathogenesis. So far, a number of genes have been found to be related to PD, among which *SNCA* gene is more deeply studied[18]. Krüger *et al*.[19] demonstrated that mutations in the *SNCA* gene sequence lead to the accumulation of α-synuclein (α-syn), which in turn gives rise to the formation of Lewy bodies and ultimately leads to the development of PD. The etiology of sporadic PD primarily involves environmental factors and epigenetic disorders. Extensive research has shown that environmental levels of toxins, including heavy metals, rotenone, paraquat, dichlorodiphenyltrichloroethane (DDT), 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP), and bisphenol A, have a positive correlation with the risk of developing PD[20-21]. Apart from exogenous neurotoxins, the gradual accumulation of endogenous neurotoxins within the brain can also trigger PD[22]. Previous studies have demonstrated that endogenous neurotoxins like Norsalsolinol inhibits mitochondrial activity, increase oxidative stress levels in the substantia nigra region of the brain, and up-regulate proteins associated with neuroinflammation, ultimately leading to specific damage to dopaminergic neurons[23]. PD models constructed with endogenous neurotoxins are more consistent with long-term chronic damage in PD than MPTP-induced PD models[24-25]. In addition, environmental factors have been shown to modulate epigenetic inheritance, and epigenetic disorders such as DNA methylation and dysregulated expression of small molecule RNAs also contribute to the development of sporadic PD[26-27]. Epigenetic disorders may be a bridge between environmental factors and the onset and development of PD.

1.3 Pathological mechanism underlying PD

PD is a chronic neurodegenerative disease characterized by various pathological mechanisms, including oxidative stress (OS), mitochondrial damage, neuroinflammation, abnormal protein accumulation, and protein clearance impairment[28-29]. In response to these pathological mechanisms, several hypotheses have been proposed, such as the lipopolysaccharide endotoxin hypothesis, the mitochondrial iron homeostasis hypothesis, and the immune dysfunction hypothesis[30-31]. However, due to the complexity and long-term nature of PD, these hypotheses alone are insufficient to fully explain the pathogenesis of the disease. In our previous study, we proposed and validated the triple cycle hypothesis of endogenous neurotoxins involvement in chronic injury in PD, centered on oxidative stress response, which is based on the various and complex etiologies of PD[32]. The triple cycle hypothesis proposes that continued accumulation of endogenous neurotoxins, increased mitochondrial damage, elevated levels of oxidative stress, dysregulated expression of neuroinflammation-associated proteins, and aberrant accumulation of α-syn contribute to the continued deterioration of PD[32]. Therefore, interrupting any of these cycles may alleviate the clinical symptoms of PD and potentially slow down or reverse its progression. Biological factors involved in the three cycles have the potential to serve as diagnostic markers in the development of PD, indicating the pathological stage of PD development. Some potential biomarkers for early PD have been discovered, including α-syn, certain amino acid metabolites, and non-coding RNA[33-35]. In this review, we will discuss the potential of these blood biomarkers as indicators of early PD diagnosis from the perspective of the triple cycle hypothesis (Figure 1).

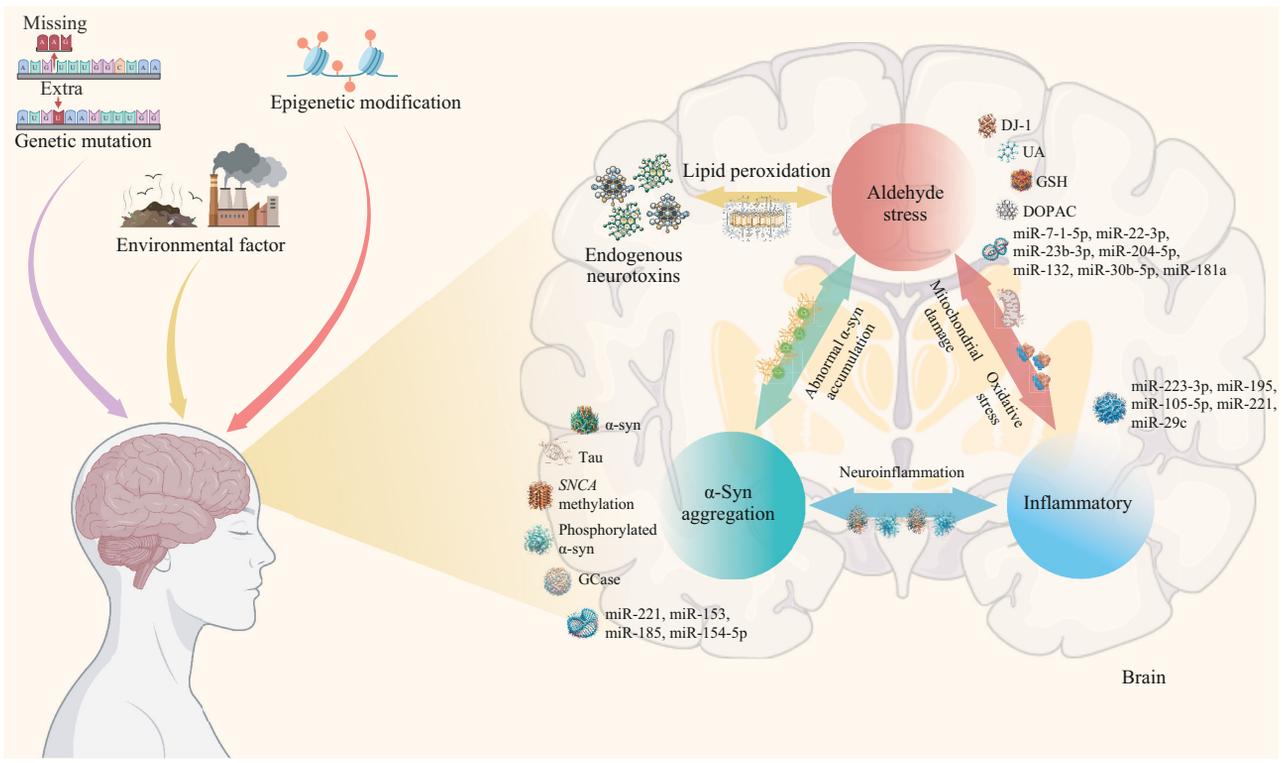

Fig. 1 Blood biomarkers implicated in the triple cycle hypothesis of Parkinson's disease

2 α-Synuclein and other protein biomarkers in PD

As a typical pathological feature PD, α-syn has been found to undergo significant changes in the body fluids of early PD patients. The level of total α-syn in the cerebrospinal fluid of patients with early PD is significantly reduced, but this downward trend is not directly correlated with the progression of the disease[36-38]. However, the α-syn content in plasma gradually increases as the condition of PD patients worsens, and the change in total α-syn content is closely associated with the degree of cognitive impairment in PD patients[39-40]. The low content of α-syn in cerebrospinal fluid may be attributed to its accumulation in nerve cells and subsequent release into the cerebrospinal fluid following cell damage[41]. Subsequently, these α-syn molecules traverse the damaged blood-brain barrier and enter the peripheral blood circulation[42]. α-syn is not exclusively associated with PD as it is also implicated in the progression of other neurodegenerative diseases such as Alzheimer's disease (AD), Lewy body disease (LBD), and multiple system atrophy (MSA) [43-45]. While the expression trends of α-syn in cerebrospinal fluid and plasma may vary, phosphorylated α-syn has been shown to exhibit high levels of up-regulation in both body fluids[46-47] . Zhang *et al.*[48] demonstrated that soluble α-syn undergoes a conformational change when phosphorylated, which in turn affects the diffusion of α-syn . Phosphorylated α-syn has been found to regulate α-syn aggregation in a conformational and phosphorylation site-specific manner, thus playing a role in the α-syn aggregation cycle[49]. Consequently, phosphorylated α-syn shows potential as a diagnostic marker for early PD.

In addition to α-syn, various proteins have been identified as contributing to the pathological progression of PD. One such protein is DJ-1, which has antioxidant properties and functions as an anti-oxidative stressor in organisms[50]. Studies have revealed that levels of DJ-1 in cerebrospinal fluid and plasma are significantly lower in PD patients compared to healthy individuals[51-53]. The DJ-1 protein exerts its antioxidative stress function by upregulating the expression of antioxidative genes, particularly through the modulation of the transcription factor Nrf2, thereby playing a role in the aldehyde stress cycle[54-55]. Tau proteins are associated with the pathology of AD and are considered potential biomarkers for AD[56]. Recent studies have revealed

that Tau protein can interact with α-syn protein, leading to changes in the fiber structure of α-syn, promoting its aggregation and precipitation, and participating in the α-syn aggregation cycle[57]. Furthermore, it has been reported that plasma levels of Tau were significantly higher in PD patients with cognitive impairment compared to healthy controls, but significantly lower compared to patients with MSA[58-59]. These findings suggest that Tau proteins may serve as potential markers of cognitive impairment in PD. The lysosomal enzyme glucocerebrosidase (GCase) is a protease encoded by the *GBA* gene that breaks down glucosylceramide sphingosine (GlcCer) and glucosylsphingosine (GlcSph) [60]. Mutations in the *GBA* gene are a common genetic mutation in PD, leading to a decrease in GCase activity. This decrease in activity results in the accumulation of GlcCer, triggering lysosomal dysfunction and promoting α-syn aggregation, which is involved in the α-syn aggregation cycle[61-62]. Previous studies have shown that GCase activity in the cerebrospinal fluid of PD patients is significantly decreased compared to healthy controls[63-65]. However, similar trends in these proteins have been observed in other neurodegenerative diseases[66-68]. Therefore, proteins such as DJ-1, Tau, and GCase may not be definitive PD diagnostic biomarkers. Further discussion is required to determine their potential as early PD diagnostic indicators.

3 Metabolite biomarkers in peripheral blood：uric acid and beyond

Elevated levels of OS are a prominent pathological feature of PD. Uric acid (UA), which is produced during purine metabolism, possesses natural antioxidant properties that aid in maintaining stable blood pressure and combating oxidative stress[69]. Recent studies conducted *in vivo* and *in vitro* have demonstrated that UA can effectively eliminate intracellular oxygen free radicals, maintain intracellular calcium ion homeostasis, and preserve mitochondrial function[70-72]. As a result, UA reduces the extent of cellular damage caused by oxidative stress. Numerous experimental results have consistently demonstrated that the levels of UA in the plasma and serum of individuals with PD are notably lower compared to those of healthy controls[73-74]. Furthermore, it has been observed that blood UA levels can differentiate between different motor subtypes of PD, such as PD patients with tremor subtype exhibiting significantly higher blood UA levels when compared to PD patients with tonic subtype[75-77]. UA is also effective in identifying other neurodegenerative diseases. Progressive supranuclear palsy (PSP) is a rare neurodegenerative disease, and recent studies have discovered that patients with PSP have significantly lower serum UA concentrations compared to patients with PD[78-79]. Therefore, UA is crucial in preventing the onset and progression of the aldehyde stress cycle in PD. Blood UA levels have the potential to serve as a diagnostic biomarker for early PD.

The aldehyde stress cycle, the inflammatory cycle, and the α-syn aggregation cycle are vital components of the triple cycle hypothesis of PD. Throughout this triple cycle, numerous metabolites are produced, which have the potential to serve as diagnostic biomarkers during the pathological progression of PD. Glutathione is an amino acid metabolite that possesses antioxidant properties. Early studies have found that glutathione acts synergistically with intracellular enzymes to reduce the production of superoxide radicals, hydroxyl radicals, and peroxynitrite[80]. Furthermore, research has indicated that plasma glutathione levels are significantly lower in PD patients than in healthy controls, suggesting that glutathione may contribute to the pathological process of PD by regulating the aldehyde stress cycle[81]. Dopamine has the ability to bind to aldehydes generated in response to oxidative stress, leading to the production of endogenous neurotoxins that contribute to the aldehyde stress cycle[32]. 3,4-Dihydroxyphenylacetic acid (DOPAC), a common dopamine oxidative metabolite, has been found to be significantly lower in the cerebrospinal fluid of patients with PD compared to healthy controls[82]. However, there is currently no clear evidence of significant differences in DOPAC levels in the blood of PD patients, and further discussion is needed to determine whether dopamine metabolites can be used as diagnostic markers for early PD.

Previous studies in metabolomics have primarily focused on specific metabolites in the pathological processes of diseases. However, the pathological mechanisms of PD are complex. Therefore, non-targeted metabolomics techniques that can provide a

comprehensive metabolic fingerprint may be helpful in the search for diagnostic and therapeutic biomarkers for early PD. Currently, researchers have demonstrated by means of untargeted metabolomics that amino acid-related metabolites (*e. g.*, threonine, tyrosine, putrescine, trans-4-hydroxyproline, dimethylglycine, dimethylarginine, and α-N-phenylacetyl-L-glutamine), glycogen-related metabolites (*e.g.*, dehydroascorbic acid, fructose), and fat-related metabolites (*e. g.*, short-chain fatty acids, long-chain fatty acids) show a consistent trend in the cerebrospinal fluid and blood of PD patients showed consistent trends[83-87]. The composition and correlation of various metabolites exhibit significant potential for diagnosis of early PD and could potentially be a groundbreaking development in the diagnosis and treatment of PD in the future[88]. Moreover, studies have demonstrated notable variations in amino acid-related metabolites, fat-related metabolites, and glycogen-related metabolites in the peripheral blood of individuals with PD and MSA. These findings suggest that metabolic molecules could serve as direct evidence for the development of distinct disease pathologies[89-90]. However, it is still unclear which specific cycle these diverse metabolites are involved in within the PD triple cycle hypothesis, as well as their regulatory role. Therefore, further investigations are necessary to explore the potential of these metabolites as diagnostic biomarkers for PD.

4 Epigenetic markers in PD：methylation modifications and non−coding RNA

Epigenetics research delves into how enduring, inheritable, and non-genetic elements can affect gene function and cellular traits. This includes aspects like non-coding RNA (ncRNA), methylation of DNA and RNA, and alterations to histones[91-92].

4.1 Methylation modifications

DNA methylation is a process that involves the covalent binding of methyl groups to the cytosine 5 carbon sites of genomic CpG dinucleotides, catalyzed by DNA methylation transferase. Extensive validation has been conducted on the phenomenon of DNA methylation modification of PD-related genes in the cerebrospinal fluid and blood of PD patients. Compared to healthy controls, PD patients exhibit a decreasing trend in DNA methylation in whole blood[93-94]. For instance, in both blood and substantia nigra regions of the brain of PD patients, the methylation of *SNCA* gene is significantly reduced[95-97]. This reduction leads to an increase in α-syn expression, which may be one of the most significant factors contributing to the promotion of the α-syn aggregation cycle. Furthermore, studies have demonstrated that as PD pathology progresses, there are significant changes in DNA methylation, and the trend of methylation changes at certain gene loci remains consistent in both the brain and blood[98].

In addition, for other neurological diseases such as MSA, PSP, and AD, the blood DNA methylation sites and changing trends will also vary as the disease progresses[99-101]. Therefore, it is crucial to investigate the DNA methylation of PD-related genes to comprehend its role in the pathological process of PD, which can aid in the diagnosis and treatment of early PD. Another form of DNA methylation is DNA hydroxymethylation, where 5-methylcytosine (5mC) is oxidized to form 5-hydroxymethylcytosine (5hmC) catalyzed by TET family enzymes[102]. Currently, the research on DNA hydroxymethylation as a biomarker for PD diagnosis is limited, but studies have found a significant increase in 5hmC levels in the cerebellum of PD patients[103]. This finding suggests the potential role of DNA hydroxymethylation, but further in-depth research is still needed to confirm its accuracy and feasibility in the diagnosis of early PD.

4.2 The non−coding RNA

microRNAs (miRNAs) are a class of non-coding, evolutionarily conserved RNA molecules that have been extensively utilized in the study of PD pathogenesis[35]. Long-term studies have demonstrated that miRNA molecules present in body fluids play a crucial role in the intricate pathogenesis and progression of PD[104-105]. Numerous experimental data revealed that miRNAs such as miR-7-1-5p, miR-105-5p, and miR-223-3p were significantly up-regulated in the blood of PD patients compared to healthy controls, while miRNAs such as miR-29c, miR-153, and miR-221 were significantly down-regulated[106-115]. Notably, some miRNAs exhibited similar expression trends in both cerebrospinal fluid and peripheral blood of PD patients. For instance, miR-433 demonstrated a significant down-regulation trend in both cerebrospinal fluid and plasma of PD

Table 1 Peripheral blood miRNA expression in patients with PD

miRNAs	miRNA expression PD *vs* HC (↑/↓)	Molecular mechanisms	The triple cycle	References
miR-7-1-5p	↑	Regulate *SNCA* transcription	α-syn aggregation cycle	［109］
miR-223-3p	↑	Negative regulator of NLRP3 expression	Inflammatory cycle	
miR-22-3p	↑	Target the GBA locus	α-syn aggregation cycle	［111］
miR-154-5p	↑	Regulate superoxide dismutase levels	Aldehyde stress cycle	
miR-23b-3p	↑	Target the 3'-UTR of *SNCA*	α-syn aggregation cycle	［115］
miR-223-3p	↑	Target the NF-κB pathway	Inflammatory cycle	［108］
miR-204-5p	↑	Regulate α-syn	α-syn aggregation cycle	［110］
miR-105-5p	↑	Target NF-κB pathway	Inflammatory cycle	［112］
miR-132	↑	Target Nurr1 nuclear protein	α-syn aggregation cycle	［114］
miR-30b-5p	↑	Regulate *SNCA* transcription	α-syn aggregation cycle	［115］
miR-195	↑	Target Rho-associated kinase 1	Inflammatory cycle	［107］
miR-185	↓	Target IGF1 and activates PI3K/AKT signaling pathway	Aldehyde stress cycle	
miR-221	↓	Inhibit expression of pro-apoptotic proteins and BIM	Aldehyde stress cycle	
miR-181a	↓	Modulate α-syn-induced DA neuronal damage	α-syn aggregation cycle	
miR-221	↓	Regulate transferrin receptor	Inflammatory cycle	［106］
miR-29c	↓	Target SP1 to inhibit inflammatory cytokines	Inflammatory cycle	
miR-153	↓	Inhibit Nrf2/ARE cascade response	Aldehyde stress cycle	［113］

“↓” indicates decrease and “↑” indicates increase. HC: healthy control.

patients[116-118]. This is one of the most important reasons for the elevated expression of α-syn in the brain of PD patients and may also serve as a potential biomarker for the early diagnosis of PD. However, miR-136-3p was significantly down-regulated in the cerebrospinal fluid and up-regulated in the plasma of PD patients[111, 118]. Some reports suggest that miR-136-3p may be associated with neuroinflammation and brain damage, but the exact mechanism requires further exploration[119]. Additionally, certain miRNAs, including miR-9-3p, miR-106b-5p, miR-223-3p, and miR-451, have the ability to distinguish PD from other neurodegenerative disorders, such as MSA, PSP, AD, and amyotrophic lateral sclerosis (ALS), with high sensitivity[108, 120-121]. Circulating miRNAs are involved in different cycles in the triple cycle hypothesis of PD injury, and their stability, tissue specificity, and ease of detection make circulating miRNAs a potential biomarker for early diagnosis of PD. These characteristics present unique opportunities to enhance the accuracy and effectiveness of early PD detection, providing crucial information for earlier intervention and treatment. A summary of studies investigating peripheral blood miRNAs for PD are listed in Table 1.

5 The exosome as novel biomarkers in PD

5.1 The total exosomes in cerebrospinal fluid and blood

Exosomes are extracellular vesicles that have a diameter of approximately 40−160 nm (with an average of around 100 nm) and contain various cellular components, including DNA, RNA, lipids, proteins, and glycoconjugates[122]. They have a crucial role in cell-to-cell communication, and their pathological transmission is closely associated with the progression of PD[123]. Exosomes can be released from intracellular multivesicular bodies (MVBs) into the extracellular space through exocytosis[124]. They have the ability to cross the blood-brain barrier and move in both directions within the cerebrospinal fluid and blood[124]. Therefore, the identification of exosome biomarkers in the cerebrospinal fluid and blood is expected to significantly contribute to the clinical auxiliary diagnosis of PD.

Studies have shown that exosomal α-syn plays a role in promoting the formation of Lewy bodies in the brain. The ratio of α-syn content in cerebrospinal fluid exosomes to the number of exosomes is significantly

lower in patients with PD compared to patients with DLB and PSP[125]. However, the concentration of α-syn in plasma exosomes of PD patients was significantly higher than in healthy controls[126-127]. Furthermore, the activity of acetylcholinesterase (AChE) in plasma exosomes of PD patients was significantly lower than in healthy controls[128]. AChE has the ability to activate nicotinic acetylcholine receptors, thereby reducing neuroinflammation and participating in cholinergic anti-inflammatory pathways[129]. Changes in acetylcholinesterase activity can regulate the anti-inflammatory effect of acetylcholine and may be involved in the inflammatory cycle in the triple cycle hypothesis of PD[130]. In addition, proteomic analysis of blood exosomes in PD patients revealed upregulation of proteins such as apolipoprotein D, gelsolin, and afamin, while proteins such as complement C1q, complement C1r, clusterin, and apolipoprotein A1 showed downregulation[131-132]. However, the precise mechanism of action of these proteins in the pathological progression of PD remains unknown, necessitating further in-depth studies to explore their potential as diagnostic and therapeutic targets for PD.

Exosomal miRNAs are protected from degradation by endoribonuclease (RNase) in body fluids due to the presence of the exosome bilayer lipid membrane, allowing them to remain stable. Consequently, plasma exosomal miRNAs have been extensively investigated as potential diagnostic biomarkers for neurodegenerative diseases[133]. In the total exosomes of body fluids of PD patients, miRNAs such as miR-10a-5p, miR-151a-3p, and miR-223-3p showed significant upregulation, whereas miRNAs such as miR-1, miR-125a-5p, and miR-423-5p exhibited significant upregulation[109, 134-139]. Among them, miR-24, miR-151a-5p, miR-214, miR-331-5p, and miR-485-5p showed an up-regulated trend in both cerebrospinal fluid and serum of PD patients[135]. Additionally, miRNAs such as miR-425-5p, miR-21-3p, miR-199a-5p, miR-135a, and miR-384 in total exosomes can effectively differentiate PD from other neurodegenerative diseases[140-141]. Therefore, the total exosomal miRNAs in peripheral circulation have the potential to diagnose early PD.

5.2 The brain−derived exosomes in blood

The brain is the primary site of pathologic injury in neurodegenerative diseases, and damage to nervous tissue accurately reflects the progression of these diseases. However, most current research primarily focuses on exosomes derived from nervous systems. While these exosomes can provide insights into the condition of various tissues and organs in the body, they are unable to accurately reflect minor brain damage and therefore cannot effectively characterize early PD damage. Therefore, a more accurate search for early PD diagnostic biomarkers can be conducted by focusing on brain-derived exosomes. Brain-derived exosomes consist of neuronal, astrocyte, microglia, and oligodendrocyte exosomes, which all play a role in different stages of the triple cycle. The method for obtaining neuronal-derived exosomes (NDEs) in plasma or serum involves using the neuronal target molecule transmembrane protein L1 cell adhesion molecule (L1CAM) for isolation[142]. Research has shown that the expression of α-syn is significantly increased in NDEs of patients with PD[143-146]. Furthermore, Zou *et al*. [147] discovered that GCase activity is notably decreased in NDEs of PD patients, and this decrease in GCase activity is negatively correlated with α-syn. The reduced GCase activity may disrupt the intracellular autophagy-lysosome system, thereby promoting the release of α-syn[147]. In order to obtain oligodendrocyte-derived exosomes (ODEs), the myeloid oligodendrocyte glycoprotein (MOG) is used as a target molecule for isolation[142]. Several studies have highlighted that differences in the expression of α-syn, pS129-α-syn, and tau proteins in NDEs and ODEs can effectively distinguish PD from other neurodegenerative diseases[148-152]. The acquisition of exosomes of astrocyte (ADEs) and microglia (MDEs) origin is instead achieved by two target molecules, glutamate aspartate transporter protein (GLAST) and transmembrane protein 119 (TMEM119) [142]. However, current research only indicates that the quantity of ADEs in the plasma of PD patients is significantly higher than that of healthy controls[149]. Further investigation is needed to explore ADEs and MDEs in the pathological process of PD.

Although only a limited number of studies have been reported, several studies have investigated the clinical diagnostic value of brain-derived exosomal miRNAs in PD. Researchers have observed that miR-155 and miR-4639-5p were significantly up-regulated

in NDEs from PD patients, while miR-212 and miR-132 were significantly down-regulated in AD patients[153-155]. miR-155 is involved in the aggregation of α-syn protein, while miR-4639-5p affects the expression and translation of DJ-1. These two miRNAs play crucial roles in regulating the pathological progression of PD[155-156]. More research is needed to determine whether brain-derived exosomal miRNA can be a reliable clinical diagnostic indicator for PD. However, there have been no studies reported on exosomal miRNAs derived from other nervous tissue in the blood or cerebrospinal fluid of PD patients. Exosomal biomarkers secreted by central nervous system (CNS) cells in the blood are involved in different cycles of the three cycles of the PD injury hypothesis, and the changes of these biomarkers reflect the changes in the central nervous system, which to a certain extent reflect the physiopathological state of different types of cells in the CNS, which is an important indicator for monitoring the pathological progression of PD, and may be an important direction of research for realizing the early diagnosis of PD (Figure 2).

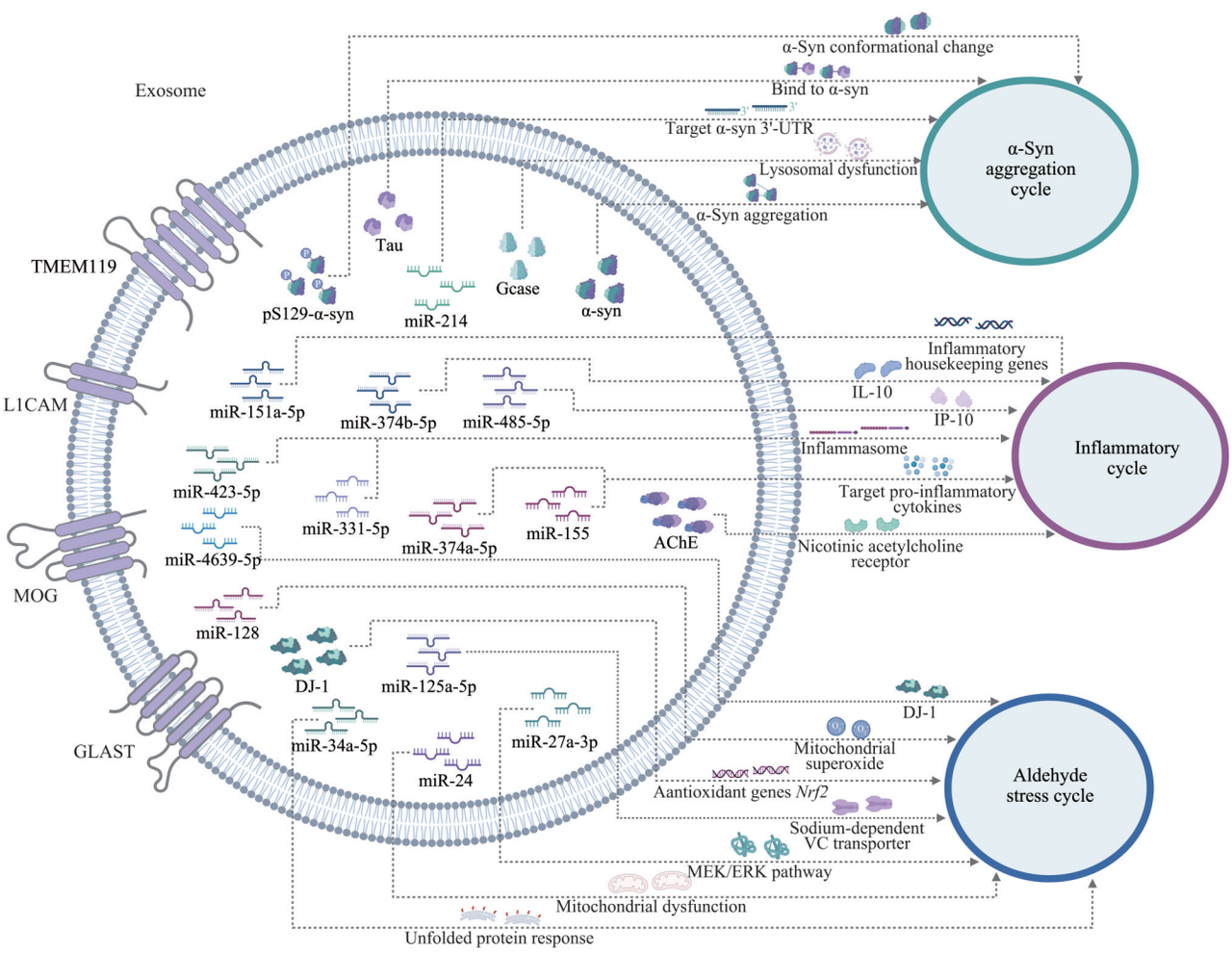

Fig. 2　Exosomal biomarkers are involved in different stages of the triple cycle hypothesis of Parkinson's disease

6　Conclusion

Early diagnosis and treatment of PD have always faced significant challenges, particularly in the selection and application of biomarkers. Various biomarkers such as α-syn, phosphorylated α-syn, DJ-1, Tau, GCase, UA, other metabolites, DNA methylation sites, and miRNA in blood have been

considered for diagnosing PD. There is a strong link between protein markers, metabolite markers, and epigenetic markers. abnormal aggregation of α-syn may lead to changes in the intracellular environment, affecting the levels of metabolites such as glutathione and uric acid, which interact to reflect the complex pathology of PD. Epigenetic changes may affect the expression of proteins such as α-syn, which in turn are involved in the pathologic process. At the same time, regulation of non-coding RNAs may also affect the function and expression of these proteins. Environmental factors, by affecting epigenetic markers, may indirectly influence metabolite levels, reflecting the interaction between environmental and genetic factors in PD. However, there are still issues with the diagnostic accuracy of these markers, especially in early PD patients. Furthermore, their ability to effectively and accurately distinguish PD from other neurodegenerative diseases requires further investigation. In the current study, it was found that brain-derived exosomes may hold promise as more accurate markers for distinguishing PD from other neurodegenerative diseases. However, their potential as diagnostic biomarkers for early PD still requires further exploration.

The complex nature of the pathomechanisms of PD presents challenges in identifying accurate early diagnostic markers. However, focusing on the pathomechanisms of PD may help in identifying precise diagnostic and therapeutic targets during the development of PD pathology. Currently, most PD pathology models used are MPTP-based polar injury models, which do not accurately mimic the chronic injury process of PD. A chronic injury model induced by endogenous neurotoxins could provide a more accurate simulation of the pathological development process of PD. Therefore, exploring chronic injury models could be an important direction in the search for diagnostic markers of early PD.

In addition, due to the complex pathologic mechanisms of PD, the complexity of PD biomarkers has also increased. It is now understood that a single biomarker may not be sufficient to accurately diagnose PD. Therefore, the future development trend is towards the combined use of multiple diagnostic markers. Based on research utilizing big data, the integration of diverse omics data and large-scale cohort study findings may facilitate the discovery and validation of biomarkers for the early diagnosis of PD.

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帕金森病外周血生物标志物：见解与展望*

李雨萌**　刘经凯**　陈姿喧***　邓玉林***

（北京理工大学，医学技术学院，生物医药成分分离与分析北京市重点实验室，北京 100081）

摘要　帕金森病（Parkinson’s disease，PD）是一种常见的神经退行性疾病，对患者的生活质量和长期健康造成深远影响，早期发现和干预尤为关键。近年来，寻找精确可靠的生物标志物成为有效应对PD临床挑战的重要策略之一。本文系统评估了PD患者外周血中潜在的生物标志物，包括蛋白质、代谢产物、表观遗传标志物和外泌体。蛋白质标志物是PD生物标志物研究的主要方向之一。特别是α突触核蛋白及其磷酸化形式，在PD的病理过程中起着关键作用。研究表明，α突触核蛋白的聚集可能与PD的病理性蛋白质沉积相关联，可能成为PD早期诊断的潜在标志物。代谢产物方面，尿酸作为一种代谢产物，在PD的氧化应激和神经保护中扮演重要角色。研究发现，尿酸水平的变化可能与PD的发病和病情进展相关，显示其作为早期诊断标志物的潜力。表观遗传标志物，如DNA甲基化修饰和miRNA，在PD研究中也引起了广泛关注。这些标志物的变化可能影响PD相关基因的表达，对疾病的发生和发展产生重要影响，为PD的早期诊断提供了新的研究视角。另外，外泌体作为一种潜在的PD生物标志物载体，能够携带多种生物分子参与细胞间通讯和病理调控。研究表明，外泌体在PD的发病机制中可能发挥重要作用，其在血液中的检测可能为早期诊断提供新的突破。综上所述，通过深入评估PD患者外周血中的生物标志物，本文展示了这些标志物在PD早期诊断和病理机制研究中的重要潜力。未来的研究将继续探索这些生物标志物的临床应用价值，推动PD的早期发现和个体化治疗策略的实现。

关键词　帕金森病，外周血，生物标志物，早期诊断

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** 并列第一作者。

*** 通讯联系人。

陈姿喧　Tel：18519020651，E-mail：zx-chen@bit.edu.cn

邓玉林　Tel：13501125130，E-mail：deng@bit.edu.cn

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