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EDITORIAL

Biomarker Discovery in Parkinson's Disease: Present Challenges and Future Opportunities

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Parkinson's disease (PD) is the second most common neurodegenerative disorder affecting more than 1% of the older population. Histopathologically, PD is characterized by a severe loss of dopaminergic neurons in the substantia nigra and cytoplasmic inclusions composed of insoluble protein aggregates (Lewy bodies), which lead to a progressive movement disorder including the classic triad of tremor, bradykinesia, and rigidity.

Significant motor impairments are the core symptoms of this disease but usually occur at the middle to late stage after the majority of dopaminergic neuronal loss. Therefore, the diagnosis of this disease is largely delayed, causing difficulty in its management. Early pre-motor diagnosis seems to be essential to prevent the disease or delay its onset. Current research interest is therefore to optimize diagnosis in the prodromal stage and to propose personalized therapeutic solutions to individual patients. The new clinical diagnostic procedure combining various biological, clinical, and imaging biomarkers is a major step toward a "precise" diagnosis and predicts the prognosis. However, many challenging issues are still subjects of debate, providing future research directions:

1. There is considerable debate on the appropriate and optimal use of non-motor biomarkers – when and how (alone or in combination) to use them.
2. How can biological biomarkers be measured in the most reliable way? The standardization of protocols for sampling, storing, transporting, and quality control should be addressed. Moreover, the comparison of different analytical methodologies (immunoassays, single and multiplex assays, and mass spectrometry) should also be addressed.
3. How can the biological diagnosis of PD (in terms of sensitivity, specificity, or differentiation from other neurodegenerative disorders) be improved with the help of other newly discovered biomarkers?
4. Detecting PD biomarkers in the CSF is of limited use in screening or monitoring patients conveniently and rapidly. The standardization of protocols for blood sampling/assays for putative PD biological biomarkers need to be specifically addressed.
5. How are the current and novel biomarkers, especially molecular biomarkers and imaging markers, related to the understanding of the pathophysiology of PD?

Since the first description of PD as a neurological disorder by James Parkinson (1755–1824) in 1817, many important discoveries have been made during this 200-year history of PD research [1]. In this special issue on Biomarker Discovery in Parkinson's Disease, some of the challenges listed above are addressed. For example, Le *et al.* discuss the feasibility of current biomarkers, i.e., clinical, molecular, biological, and imaging biomarkers for the possible early diagnosis of PD [2]. As iron is commonly found to accumulate in the substantia nigra pars compacta

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in PD, region-specific iron quantification using magnetic resonance imaging may be used as a potential marker for PD in both clinical and prodromal stages [3]. Then, Cen *et al.* focus on the use of peripheral lymphocytes to detect specific markers for PD [4]. At the molecular level, several transcription factors that may have neuroprotective effects against dopaminergic neuron degeneration are proposed to be PD biomarkers [5]. Wang *et al.* systematically summarize the changes of miRNA expression profiles in PD patients, highlighting their putative roles in the diagnosis and treatment of this devastating disease [6]. In addition, Tang *et al.* provide a systemic review of the application of cerebral dopamine neurotrophic factor in PD treatment [7]. Zhong *et al.* characterized the age-dependent morphological alterations and aggregation of α-synuclein, the primary protein component in Lewy bodies and Lewy neuritis, in the enteric nervous system in an α-synuclein transgenic mouse model [8].

Typical Parkinsonian symptoms consist of bradykinesia plus rigidity and/or resting tremor. However, before the appearance of these symptoms, pre-motor symptoms such as hyposmia, constipation, REM sleep behavior disorder, and depression may have been present for years. In this issue, Reichmann described the main clinical features of these pre-motor symptoms as biomarkers for PD [9]. Jin *et al.* specifically focus on the clinical significance of REM sleep behavior disorders for Parkinsonism [10]. Olfactory impairment has a high prevalence among PD patients, and its assessment is easy and of low cost. Fullard *et al.* discuss the potential utility of olfaction dysfunction as a biomarker for early or differential diagnosis of PD [11].

PD is a multifactorial disease, and genetic defects play an important role in its pathogenesis. In this issue, Yuan *et al.* analyze four paralogs of the recessive F-box protein 7 gene (FBXO7), mutations of which have been reported to cause hereditary Parkinsonism, in Han Chinese patients with sporadic PD. They have detected significant differences in the genotypic and allelic frequencies of the FBXO2 variant rs9614, suggesting its potential as a biomarker for PD [12]. Zeng *et al.* have conducted a longitudinal resting-state fMRI study to evaluate changes in local spontaneous brain activity with time in PD patients, and report that regional homogeneity may be a suitable non-invasive marker of PD progression in comparison to voxel-based-morphometry [13]. Finally, Lotankar *et al.* provide a comprehensive update on research on PD biomarkers [14].

In conclusion, "Biomarker discovery in Parkinson's disease" is a very interesting topic that is valuable for the diagnosis and therapeutics of PD. There is a strong need to develop highly accurate, sensitive, and reliable biomarkers for PD diagnosis, especially at the prodromal stage. The combination of biological biomarkers with other diagnostic strategies including pre-motor symptoms and imaging techniques will in fact help early diagnosis, the prediction of therapeutic effects, and prognosis. In addition, although experimental evidence has shown the promising potential of PD biomarkers, future studies are warranted to validate the sensitivity and specificity of these potential biomarkers, and to confirm their high correlation with disease development and progression. Furthermore, big data analysis and artificial intelligence should be introduced and encouraged for biomarker discovery and development.

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