PARKINSON'S DISEASE: MITOCHONDRIAL DYSFUNCTION, PROTEIN MISFOLDING AND NEUROINFLAMMATION AS BIOMARKER PATHWAYS

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Abstract: *To explore the relationship between mitochondrial dysfunction, protein misfolding, and neuroinflammatory markers in patients with Parkinson's disease (PD) and to assess their potential as diagnostic biomarkers.*

Keywords: *Parkinson's disease, mitochondrial dysfunction, protein misfolding, neuroinflammation, biomarkers, α-synuclein, tau.*

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by the loss of dopaminergic neurons in the substantia nigra and the accumulation of misfolded proteins, including α-synuclein and phosphorylated tau. Although the etiology of PD is multifactorial, growing evidence points to mitochondrial dysfunction, protein misfolding, and neuroinflammation as central contributors to disease pathogenesis (Schapira & Gegg, 2011; Exner et al., 2012).

Mitochondrial impairment, particularly deficits in complex I activity and increased reactive oxygen species (ROS) production, has been linked to neuronal death in PD (Schapira, 2010). Simultaneously, the misfolding and aggregation of α-synuclein and tau proteins exacerbate oxidative stress and trigger microglial activation, creating a feedback loop of neurodegeneration (Bellucci et al., 2012; Goedert et al., 2017). Chronic neuroinflammation, characterized by elevated proinflammatory cytokines such as TNF-α, IL-1β, and IL-6, further contributes to dopaminergic neuronal loss (Tansey & Goldberg, 2010).

Given the interplay between mitochondrial dysfunction, protein misfolding, and neuroinflammation, identifying reliable biomarkers reflecting these pathways may improve early diagnosis, disease monitoring, and therapeutic targeting in PD (Kalia & Lang, 2015). Exploring these mechanisms together provides a comprehensive understanding of PD pathophysiology and may inform the development of novel therapeutic strategies.

Methods: The study enrolled 50 patients diagnosed with Parkinson's disease (mean age 64 ± 7 years) and 25 age- and sex-matched healthy controls. Mitochondrial

function was evaluated using peripheral blood mononuclear cell (PBMC) assays for ATP production and reactive oxygen species (ROS) levels. Levels of misfolded α-synuclein and phosphorylated tau were quantified in serum using ELISA. Neuroinflammatory status was assessed by measuring TNF-α, IL-1β, and IL-6. Clinical assessment included the Unified Parkinson's Disease Rating Scale (UPDRS) and Hoehn and Yahr staging. Statistical analyses were performed using SPSS 26.0; $p < 0.05$ was considered significant.

Results: PD patients demonstrated significantly impaired mitochondrial function, indicated by decreased ATP production and increased ROS levels ($p < 0.01$). Serum concentrations of misfolded α-synuclein and phosphorylated tau were elevated in PD patients compared to controls ($p < 0.01$) and positively correlated with disease severity (UPDRS score, $r = 0.52$, $p < 0.05$). Proinflammatory cytokines (TNF-α, IL-1β, IL-6) were also significantly increased and correlated with both mitochondrial dysfunction and protein misfolding markers. Patients with combined abnormalities showed more severe motor and non-motor symptoms.

Conclusion: The findings suggest that mitochondrial dysfunction, protein misfolding, and neuroinflammation are interrelated mechanisms contributing to Parkinson's disease progression. The combined assessment of these biomarkers may improve early diagnosis and patient stratification. Future research targeting these interconnected pathways could inform the development of novel therapeutic strategies.

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