The proteomics behind clinical and temporal changes in Parkinson's Disease: a literature review

A proteômica por trás das alterações clínicas e temporais na Doença de Parkinson: uma revisão de literatura

La proteómica detrás de los cambios clínicos y temporales en la Enfermedad de Parkinson: una revisión sistemática

Abstract
Parkinson's disease (PD) is characterized by the dopaminergic neuron's progressive neurodegeneration, which is chronic and results in movement and behavioral disorders. There are still many gaps in the PD etiology and pathogenesis. Thus, aiming to strengthen the evidence that serves as a tool for diagnostic aid and future treatments, this systematic review aims to relate and analyze studies on the PARK proteomics, that is, the class of expressed park proteins that are associated with pathogenesis, PD clinical changes, and temporal effects. 261 papers were selected for eligibility analysis based on their title and abstract, resulting in 56 papers, with a full reading, included in this study. The observed result leads to the understanding of gene expression for a class of proteins that participate in cellular metabolic pathways associated with the PD etiology. Genetic studies applied to proteomics investigated disease-linked loci of PARK genes and their gene expression to relate the cellular pathways that contribute to PD. It was observed that PARK proteins corroborate the PD pathogenesis, highlighting the hypothesis of change in perception over time. Therefore, exploratory, and systematic studies can guide future investigations and strengthen clinically applied evidence.

Keywords: Parkinson's Disease; PARK Proteins; Time perception.

Resumo
A Doença de Parkinson (DP) é caracterizada pela neurodegeneração progressiva dos neurônios dopaminérgicos, de caráter crônico e resultante em distúrbios do movimento e comportamentais. Ainda há muitas lacunas sobre a etiologia e patogenia da DP. Desse modo, visando fortalecer evidências que sirvam de ferramenta para auxílio diagnóstico e futuros tratamentos, esta revisão sistemática tem como objetivo relacionar e analisar estudos de
proteômica das PARK, ou seja, da classe de proteínas parks expressas que estejam associadas a patogênese, alterações clínicas e temporais da DP. Foram selecionados 261 trabalhos para análise de elegibilidade com base em seu título e resumo, resultando em 56 trabalhos, com leitura completa, incluídos nesse estudo. O resultado observado direciona para a compreensão da expressão genética para uma classe de proteínas que participam das vias metabólicas celulares associadas à etiologia da DP. Estudos genéticos aplicados a proteômica investigaram loci ligados à doença dos genes PARK e sua expressão gênica para assim relacionar as vias celulares que contribuem para a DP. Observou-se que as proteínas PARK corroboram para a patogenia da DP, destacamos a hipótese de alteração na percepção do tempo. Portanto, estudos exploratórios e sistemáticos podem direcionar futuras investigações e fortalecer evidências aplicadas à clínica.

**Palavras-chave:** Doença de Parkinson; Proteínas PARK; Percepção temporal.

### 1. Introduction

Parkinson's disease (PD) is the most common neurodegenerative movement disorder in the world. Risk factors include age, sex, and some environmental factors. The etiology of the disease in most patients is unknown, but different genetic predictions have been reported. The PD cardinal motor symptoms are tremor, rigidity, bradykinesia/akinesia, and postural instability, but the clinical picture includes other motor and non-motor symptoms, which include behavioral and temporal changes. Its diagnosis is primarily clinical, although specific investigations can assist in the differential diagnosis with other parkinsonism forms. Pathologically, PD is characterized by the α-synuclein protein (αSyn) accumulation and the dopaminergic neurons progressive deficit of the substantia nigra pars compacta, which is found in intracytoplasmic inclusions called Lewy bodies. Currently, available drug treatments offer good motor symptoms control but do not prevent the disease progression (Teixeira et al., 2016; Magalhaes et al., 2018; Balestrino & Schapira, 2020; Terriente-Felix et al., 2020; Balestrino and Schapira, 2020 Kesh, Kannan et al., 2021).

Scientific evidence that seeks to understand the proteins’ gene expression involved in the Parkinson’s disease pathogenesis, so that biomarkers can be identified, is one of the strands that seek to minimize the effects resulting from long-term pharmacotherapy since the individual profile will direct possible metabolic and clinical variations of the patient. Thus, classes of related proteins have been described in addition to αSyn, most notably PARK (Pan et al., 2014; Panicker et al., 2021), which encode proteins DJ1, LRRK2, ATP13A2, HtrA2, and FBXO7 (Dave et al., 2014; Riley et al., 2014; Park et al., 201 Xiong et al., 2014; Cha et al., 2015; Kim et al., 2016; Hwang et al., 2017; 5; Park & Sue, 2017; Park & Sue, 2017; Yoon et al., 2017; Larsen et al., 2018; Terriente-Felix et al., 2020; Kesh et al., 2021). Studies show that alterations related to this class of proteins may be associated with dopamine-responsive dystonia, rapid-onset dystonia-parkinsonism, X-linked dystonia-parkinsonism, and young-onset dystonia-parkinsonism, which are monogenic combination dystonias with parkinsonian features associated with polymorphisms related to the PARK loci (Weissbach et al., 2021).

Recent studies point out relations between alterations in the PARK proteins gene expression, and thus functional
alterations of these proteins are related to neuroinflammation and, consequently, PD neurodegeneration resulting (Berwick & Harvey, 2014; Pan et al., 2014; Panicker et al., 2021). Thus, the present study is characterized as a systematic review and aims to relate and analyze PARK protein proteomic studies and their association with the PD pathogenesis, clinical and temporal changes.

2. Methodology

The study consists of a systematic review of english language articles on the following relationship: Parkinson Disease Associated PARK Proteins and Time Perception. We included in our study: reviews, meta-analyses, case reports, and original articles. No restrictions on publication dates or status will be imposed. Exclusion criteria: dissertations, book reviews, conferences or publishing works. The results will be analyzed and those documents that were deemed relevant and of acceptable quality will be included in the analysis.

2.1. Information Sources

Online searches in Science Direct, Pubmed/Medline, and ISI Web of Knowledge databases (2013 to 2021) were conducted in August 2021 using relevant terms and associations highlighted in the MeSH: [Parkinson's Disease] [PARK Proteins], [Parkinson's Disease] [Serine Protease HTRA2], [Parkinson's Disease] [PARK8 Protein], [Parkinson's Disease] [PARK7 Protein], [Parkinson's Disease] [DJ1 Protein], [Parkinson's Disease] [PARK5 Protein], [Parkinson's Disease] [Ubiquitin C-Terminus Hydrolase], [Parkinson's Disease] [Time Perception]. Through these, we highlighted a total of 334 papers, and subsequently, the abstracts were examined for references to the research question, if the study appeared relevant, the full text was retrieved, and the reference lists of identified papers were searched for additional studies. A total of 261 papers were selected for eligibility analysis based on their title and abstract, and where necessary, the full-text publication was reviewed. Thus, after the analysis of the studies, 249 papers were selected for full reading, following the pre-established eligibility criteria, resulting in 55 papers included in this study, published in the last eight years, summarized in Figure 1.
2.2 Study Selection

Studies will be included if they meet the following inclusion criteria: Initially, documents retrieved from each database were compared to remove duplicate records. Documents were screened for eligibility based on title and abstract, and if necessary, the full-text publication was reviewed. We included studies if they investigated the relationship between Parkinson's Disease-Associated Proteins and Time Perception. Also included will be studies investigating the PARK class of proteins, experimental animal models associated with time perception tasks, and metabolic modulation and pharmacogenetics pathways, related to the main thrust of the research.

In summary, study design: case reports, meta-analyses, original articles, and reviews will be included. Population: population-based study consisting of healthy and/or Parkinson's disease individuals (young, middle-aged, and older adults). Also, "organism models"/experimental using rats or mice. Intervention: neurobiological interventions were defined as any intervention with the ability to influence time perception through tasks (tasks: time estimation, temporal reproduction, motor reproduction, temporal discrimination) associated with experimental models and metabolic pathways involved with the class of parks proteins. Results: The primary outcome measure was the investigation of the class of Parkinson's disease-associated proteins, the PARK proteins, their functions and pathways of cellular interactions, and changes in time perception in pre-set tasks that modify neural synchrony in cognition, as well as characteristic altered metabolic pathways that distort time perception in Parkinson's disease.

3. Results and Discussion

In the analysis of the selected papers, it was observed the direction towards the gene expression understanding for a class of proteins that participate in cellular metabolic pathways associated with the PD etiology. From this premise, genetic studies applied to proteomics investigate loci linked to the disease (PARK 1 to 18) and their gene expression to relate the
cytotoxicity. BNIP3L ubiquitination by PARK2 recruits NBR1 to mitochondria, targeting mitochondria for cellular stress-induced degradation and neurodegeneration (Hwang et al., 2017). Mitochondrial dysfunction correlates to PD pathogenesis are a process directly related to dopaminergic neuronal survival (Gao et al., 2015).

Furthermore, studies have been showing that mutated genes, most prominently PARK1, PARK2, PARK7, PARK9, PARK13, and PARK15, are related to autosomal recessive early-onset PD (Dave et al., 2014). Protein kinase (PINK1) or in E3 ubiquitin ligase parkin (PARK2) function together to clear damaged mitochondria (Yoon et al., 2017). PINK1 phosphorylates both parkin and ubiquitin to stimulate proteins ubiquitination on the mitochondria membrane surface (Klosowiak et al., 2016; Terrriente-Felix, Wilson, and Whitworth, 2020). Already, parkin (PARK2) is also related to p21, responsible for proteasomal degradation, which binds directly with parkin and is ubiquitinated resulting in the neural cell deficit differentiation capacity (Park et al., 2017). Recently, it has been reported that PD-associated PINK1 genes expressing products, α-synuclein, LRRK2, and DJ-1 (PARK7) as well as PARKINs associate with lipid rafts, suggesting that dysfunction of these proteins in lipid rafts may be a causative factor in PD. To understand this interaction, caveolin-1 (cav-1) and flotillin-1 (flt-1), the main lipid rafts constituents in the plasma membrane, seem to function as a substrate for parkin. In addition, total cholesterol level and membrane fluidity were altered by parkin deficiency, causing dysregulation of lipid raft-dependent endocytosis (Cha et al., 2015, Kim et al., 2016).

It was reported that the DJ-1 protein total level was significantly reduced in the PD substantia nigra patients, suggesting that the DJ-1 abnormal expression may contribute to the PD pathogenesis from the DJ-1 expression (PARK7) (Xiong et al., 2014) corroborating with studies showing that mutations in genes are associated with familial, autosomal recessive early-onset Parkinson's disease (Bonilha et al., 2015; Culleton et al., 2015; Taipa et al., 2016; Singh et al., 2020), and this being pointed out as a biomarker since the oxidized DJ-1 protein (oxDJ-1) level in RBCs by ELISA and demonstrating a sensitivity of 81% in patients and can be used for differential diagnosis (Ogawa et al., 2014; An et al., 2018; Yamagishi et al., 2018). Studies have also observed that DJ-1 (PARK7) protein is also associated with lipid rafts. Lipopolysaccharide (LPS) induced DJ-1 localization to lipid rafts in astrocytes via LPS-TLR4 signaling was further increased in DJ-1 knockout astrocytes by TLR4 endocytosis impairment (Kim et al., 2013; Parsanejad et al., 2014; Khang et al., 2015; Choi et al., 2020).

Other studies point out that reactive oxygen species (ROS) induce DJ-1 aggregation in neural cells and consequently DJ-1 protein stimulates pro-inflammatory protein expression, STAT1 (p-STAT1) phosphorylation in response to interferon-gamma (IFN-γ) (Kim et al., 2018), as well as innate immune cells (Singh et al., 2020), as it is a protein with antioxidant function modulating multiple cells signaling pathways (Culleton et al., 2015; Sánchez-Lanzas & Castaño, 2021). Other evidence points to the involvement of DJ-1 in the gut-brain axis’s maintenance and may be used as a PD biomarker (Singh et al., 2020).

Another protein also related to PD is leucine-rich LRRK2 (PARK8), which is responsible for signaling and transport related to Wnt pathway and cellular organization (Daniel and Moore, 2015; Manzoni et al., 2015) and related to dopaminergic neurons neurogenesis (Berwick & Harvey, 2013), and alterations resulted in aberrant protein aggregation and cell cycle dysregulation (Feng et al., 2015). Studies further point out that mutations in the LRRK2 (PARK8) gene represent the most commonly known cause of hereditary PD with late dominant inheritance. Disease-causing mutations located in the kinase domain increase kinase activity, while clustering mutations within the Roc-COR tandem domain impair GTPase activity (Tsika & Moore, 2013; Steger et al., 2016). LRRK2 mutations commonly induce neuronal toxicity that, at least for the frequent
G2019S variant, is kinase activity-dependent (Tsika et al., 2015; Janković et al., 2015) and according to the study by Janković and colleagues (2015) that performed comprehensive mutation screening of selected LRRK2 exons in 486 PD patients, the observed frequency was equivalent to European population (1.23%) with penetrance dependent on the study population, being important for efficient genetic testing strategy and counseling. Furthermore, studies have shown that mutations in PARK1 negatively regulate LRRK2 expression (if gene here leaves in italics) thus correlating the relationship between the mitochondrial homeostasis regulation and the Parkinson's disease pathogenesis (Azkona et al., 2018; Kesh et al., 2021).

Other investigations have pointed out that alterations in the ATP13A2 (PARK9) protein expression, involved in the metabolic pathway related to Zn2+ homeostasis, result in molecular consequences such as lysosomal impairment, α-synuclein accumulation, and mitochondrial dysfunction (Kong et al., 2014; Park et al., 2014; Riley et al., 2014; Park et al., 2015; Park and Sue, 2017; Larsen et al., 2018). Another protein regulated by the PARK class is the human mitochondrial serine protease (HtrA2/PARK13, which participates in the apoptosis process as it regulates proteolytic activity in vitro and cells from the thermostable feature and control of conformational changes characterized by "loops" in the active site and thus studies correlate it to PD (Goo et al., 2017; Merski et al., 2017). Mutations in the F-box7 protein gene (FBXO7/PARK15), on the other hand, are associated with a severe form of PD early-onset autosomal recessive, because this protein responds to stress and can play both cytoprotective and neurotoxic roles. Under stress, endogenous F-box7 becomes regulated, in the mitochondrial milieu, forming F-box7 aggregates in the microenvironment (Zhou et al., 2015; Yoon et al., 2017).

The polymorphisms or mutations’ presence in the PARK proteins class causes an imbalance in the optimal microenvironment homeostasis, for maintenance of essential metabolic pathways and cellular responses, predisposing to PD nigral neurodegeneration, with a high penetrance rate and thus clinical motor and non-motor phenotypic variations (Berwick & Harvey, 2014; da Silva et al., 2015; Koentjoro et al., 2017; Magalhaes et al., 2018; Balestrino & Schapira, 2020; Panicker, Ge, Dawson and Dawson, 2017; Weissbach et al., 2021). The brain areas involved in Parkinson's disease pathogenesis are also correlated to the temporal perception control (Teixeira et al., 2016). In general, the PD pathophysiology has been described as a dysfunction in the basal nuclei and cortical areas, related to the “internal clock” hypothesized to be a multisensory integration station (Lucas et al., 2013). Clinical and experimental evidence on PARK protein expression and its association with temporal processing, point to neural networks dysfunction involving movement disorders such as dystonia and bradykinesia in PD (Avanzino et al. 2016; De Miranda et al., 2018).

4. Final Considerations

Therefore, exploratory, and systematic studies are presented as tools to help substantiate the evidence applied to clinical research in an individualized way. Thus, allowing influence in pathogenesis clarification from the gene PARK protein class expression and their relationship with motor and non-motor, behavioral and temporal phenotypes of PD patients, because these are also associated with the brain areas activation pathways maintenance involved with the time perception. Thus, the approach brings new possibilities to be investigated for better PD understanding and enabling future new studies focused on evidence applied to the clinic as a diagnostic aid, individualized treatment, and thus better prognosis and quality of life for patients, since the disease presents progressive and neurodegenerative clinical picture.

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