Exploring Neutrophil-Associated Proteomic Alterations in Parkinson\'s Disease: Bridging Inflammation and Neurodegeneration

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Introduction: Parkinson\'s disease (PD) is the second most prevalent neurodegenerative disorder, with its etiopathogenesis remaining largely unknown. Numerous hypotheses have been proposed to elucidate the mechanisms underlying neurodegeneration in PD, including the role of inflammation. Alterations in leukocytes and their subpopulations, both quantitatively and qualitatively, have been documented in PD patients. Neutrophils, as the primary effector cells of the innate immune system and the most abundant leukocyte subpopulation, serve as the initial line of defense in the body. In the context of neurodegeneration, neutrophils infiltrate the central nervous system, and their detrimental actions exacerbate neuronal damage. A deeper understanding of neutrophil involvement in PD is crucial for elucidating the disease pathology. Methods: This study involved 37 PD patients admitted to the Neurology Department of Clementino Fraga Filho University Hospital (HUCFF) and 42 healthy controls (HC), including patients\' companions and/or individuals admitted to the Internal Medicine Department of HUCFF. Individuals with histories of autoimmune diseases, stroke, or other neurological disorders that could confound the results were excluded. Blood samples were collected in EDTA tubes, and neutrophils were isolated using a Ficoll gradient. For subsequent shotgun proteomic analysis, neutrophils from 20 PD patients and 20 HC were subjected to LC-MS/MS (Q-Exactive Plus, EASY-nLCII). The data-independent acquisition (DIA) method was employed for the proteomic analysis, and the data were analyzed using bioinformatics tools. Results and Discussion: Approximately 600 proteins were identified in neutrophil samples from both patients and controls. Among the differentially expressed proteins, members of the Ras GTPase family and leukotriene A4 hydrolase, which converts leukotriene A4 to B4—a product released by endothelial cells that enhances neutrophil activation—were noted. Additionally, calcium-binding proteins from the S100 family were identified. The presence of selectins suggests that pro-inflammatory cytokines may be upregulating these proteins, leading to a delayed neutrophil arrival and increased activation through additional factors, as well as enhanced adhesion to endothelial cells. The pathways and biological processes associated with the identified proteins predominantly reflect mechanisms aimed at regulating inflammatory and oxidative stress responses, as well as cytokine and chemokine release, which may amplify neutrophil activation and contribute to neuroinflammation in PD. Proteins involved in cytoskeletal reorganization were also identified, potentially indicating a role in phagosomal maturation processes.Conclusion: Neutrophils are integral to both the initiation and resolution of inflammatory responses and are involved in functions beyond microbial eradication. Contrary to their previous characterization as static, terminally differentiated cells, neutrophils exhibit significant transcriptional and translational activity. Advances in understanding these changes at the protein level will enhance our comprehension of neutrophil functions in both health and disease.

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