

Poster

GLOBAL DYSREGULATION OF THE SPECIALIZED PRO-RESOLVING MEDIATOR NETWORK IN PERIPHERAL MACROPHAGES OF PD PATIENTS WITH AND WITHOUT GBA1 MUTATIONS

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Objectives. Neuroinflammation is a recognized pathological hallmark of Parkinson's disease (PD). Heterozygous mutations in the *GBA1* gene represent the most frequent genetic risk factor for PD. PD carriers of *GBA1* mutations (GBA-PD) progress more rapidly, with earlier cognitive dysfunction and psychosis, greater substantia nigra terminal loss, and reduced survival [1-2]. While chronic activation of the innate immune system is well established in neurodegeneration, the mechanisms governing the "resolution of inflammation" – an active process driven by endogenous polyunsaturated lipids called Specialized Pro-resolving Mediators (SPMs) – remain largely unexplored in peripheral immune cells of PD patients[3]. Our aim, therefore, is to characterize the protein expression profiles of key SPM receptors (GPR18, GPR32, ChemR23, FPR2) and biosynthetic enzymes (15-PGDH, 15-LOX, 12-LOX, 5-LOX) in classically activated macrophages (M1-like) and alternatively activated macrophages (M2-like) across idiopathic PD, *GBA*-mutated PD and healthy controls.
Methods. Peripheral blood mononuclear cells were isolated from patients and monocytes were differentiated into macrophages M1- and M2-like. Target protein expression was quantified via flow cytometry using Mean Fluorescence Intensity (MFI). Group segregation and key driving biomarkers were identified using univariate statistics and multivariate Partial Least Squares-Discriminant Analysis (PLS-DA) with Variable Importance in Projection (VIP) scores. The phagocytic capacity of the macrophages in all experimental groups was assessed using the efferocytosis assay.
Results. Multivariate PLS-DA effectively separated the clinical groups from healthy controls, identifying 12-LOX, ChemR23 and 15-LOX as the top driving features. In macrophages M1-like, a significant downregulation of the pro-resolving receptor ChemR23 was observed in both PD and PD-GBA groups compared to controls, accompanied by an upregulated expression trend for the GPR32 receptor in idiopathic PD cases and a significant upregulation of the 12-LOX enzyme that was particularly pronounced in the PD-GBA cohort. At the same time, in M2-like macrophages, which are crucial for tissue repair and homeostasis, multivariate PLS-DA identifies ChemR23, FPR2, and the enzyme 5-LOX as the most significant discriminating biomarkers. In particular, there is a significant reduction in the expression of both pro-resolving receptors ChemR23 and FPR2 compared to controls, alongside a marked downregulation trend for GPR18 in sporadic PD. The efferocytosis assay revealed a reduced phagocytic capacity in PD macrophages compared with the controls.
Conclusions. Our results highlight a global alteration of the resolution of inflammation process in Parkinson's disease. Particular attention centers on macrophages, the key players; which in both M1- and M2-like states, and across both idiopathic PD and PD-GBA groups, showed a dysregulated expression of SPM receptors and biosynthetic enzymes compared to healthy controls. This systemic imbalance may fail to counteract chronic inflammation, thereby contributing to neurodegeneration.

References

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