Gene Set Enrichment Analysis (GSEA) of injury models and evaluation of potential biomarkers in PBMC from PD patients

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Abstract: Neurological disorders including Parkinson's disease (PD), stroke, and mood disorders are caused by several pathogenetic mechanisms, some of which may be common, such as neuroinflammation and impaired metabolism. The emerging idea of a peripheral origin linked to systemic inflammation and metabolic changes, is gaining interest, as well as the idea that identifying peripheral biomarkers could provide early diagnosis and improve therapeutic interventions. We used gene set enrichment analysis (GSEA) on transcriptomic datasets of astrocytes from mice treated with LPS or MCAO, as well as on PBMC datasets from PD patients to identify common gene and pathway alterations. The immune response and hemostasis were upregulated both in the mice models and in PD-PBMCs. Inflammasome and cytokines receptors/signaling (IL-6 family) upregulation was a common factor, in agreement with the increase of Interleukin-6 receptor subunit beta Precursor (IL6ST) and of the Complement C1q tumor necrosis factor-related protein 6 precursor (C1QTNF6) observed in our PD-PBMC samples. Downregulation of metabolic pathways related to TCA cycle and respiratory electron transport chain was unique to MCAO. However, these changes might well correspond to the downregulated mitochondrial protein translation machinery found in the PD-PBMC dataset, knowing that 13 mitochondrial genes encode for electron transport chain complexes. Furthermore, we analyzed gene expression data from murine primary cortical neurons treated with rotenone for 24h, a toxicity-PD model. We found alterations in metabolism as well as alterations in the levels of various interleukins. Again, overlapping analysis between PD-PBMCs and rotenone-treated neurons revealed common altered pathways (mitochondrial protein translation and IL-10 signaling).Overall, these data support the concept that integrating computational analysis with experimental data can 1)provide a better understanding of multifactorial disorders, 2)support the translational value of commonly used models of disease and 3)help identify potential biomarkers of neurodegenerative diseases.