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UNSCRAMBLING THE EPITOME OF HUMAN MICROGLIAL GENE EXPRESSION DYNAMICS DURING BRAIN DEVELOPMENT FOR POTENTIAL BIOMARKER DISCOVERY

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Microglia, the native sculptors of neuronal circuits perform various crucial functions in brain milieu, including dendritic pruning, immune surveillance, phagocytizing of dead neurons and healthy neural precursors etc. In spite of these attributes, several unresolved queries exist around biomarker discovery relevant to their cellular localization, self-renewing potential and brain developmental dynamics. To ascertain microglial biomarkers in developing brain, we performed high-throughput data mining of microglia gene expression datasets. The analysis revealed a list of 3290 significant genes, out of which we have selected the top 20 dysregulated genes to be the potential markers that can be used for tracking the microglial expression in developing brain. Next, we developed a connectome of these biomarkers with their putative protein interacting partners. This demonstrated strong associations of upregulated genes like DOCK2 with early/mature microglial markers such as SPHK1, CD68 and CD45. To elucidate their anatomical habitance, we deconvoluted the BrainSpan Atlas expression data, which showed high level of expression of majority of candidate genes in microglia-dense regions (Amygdala, Hippocampus, Striatum) in the postnatal brain. Furthermore to decipher their age specific expression in human brain, we constructed a developmental dynamics map (DDM), we again deconvoluted gene expression profiles spanning prenatal to postnatal stages. Interestingly, dynamic regulation of SPHK1, PLD4 along with consistent expression of PTX3, FCAR and KLHL6 were detected. To authenticate these findings and correlate their expressions in vitro, we enforced microglial differentiation to hESC to generate microglia precursors. These microglia precursors could demonstrate expression of PTX3 and SPHK1 as well as other early stage markers, such as CD68, AIF1 (Iba1) post 30 days in vitro. In summary, our study has unraveled critical insights regarding microglial expression dynamics across the brain ages and catalogued a unique set of potential biomarkers those can be further exploited for designing of novel neurotherapeutics.

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