[BIOINFO 2023]

Single-cell profiling unveils molecular insights and region-specific heterogeneity in the hippocampus during global ischemia

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Ischemic stroke, a widespread global affliction, annually affects over 12 million individuals, resulting in enduring physical and cognitive impairments. Glial cells, including microglia, astrocytes, and oligodendrocytes, form the peri-infarct environment in the central nervous system, playing pivotal roles in the progression of stroke pathophysiology. This study aimed to contrast the hippocampal CA1 region, recognized for its vulnerability to ischemia, with the adjacent CA3-DG region to elucidate alterations in glial characteristics both pre- and post-ischemic insult. Single-cell RNA sequencing was conducted both in the normal rats and the four-vessel occlusion (4-VO) surgery, which served as a transient global ischemia model. Clustering 43,202 cells in both sham and ischemic hippocampi revealed 7 distinct cell lineages and 18 clusters. Comparative analyses unveiled changes in gene expression and subpopulation composition based on region and ischemic insults. Our data substantiated an elevation in pro-inflammatory microglial subtypes following a stroke, accompanied by distinct distribution differences in microglial pathways, depending on regional discrepancies. Furthermore, we discerned a distinctive oligodendrocyte subtype in the post-ischemic hippocampus, notably absent in normal conditions. Our results demonstrated differences in cellular functions and compositions during global ischemia. It also highlighted the diversities of molecular signatures of individual cells based on the specific hippocampal region, which had not been comprehensively studied before. This research may resolve, at least in part, the questions on the regional differences of vulnerability to ischemia in the hippocampus in terms of glial heterogeneity. Also, this comprehension may have the potential to streamline applications such as drug development by providing insights into the mechanisms associated with ischemic stroke.