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Amelioration of the neuroinhibitory local environment after ischemic injury through in situ astrocyte-to-neuron conversion

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Ischemic injury in central nervous system (CNS) often causes severe neuronal loss and activates glial cells. We showed earlier that NeuroD1-mediated astrocyte-to-neuron (AtN) conversion can regenerate a substantial proportion of neurons (~40% of the total) and reconstruct the ischemic injured neural circuits. In this study, we focus on glial changes and blood vessel recovery following AtN conversion. Specifically, we found that ectopic expression of NeuroD1 in the reactive astrocytes after ischemic injury significantly reduced glial reactivity, as shown by less hypertrophic morphology, along with reduced secretion of neuroinhibitory factors such as CSPG and LCN2. As for microglia, we found less amoeboid shape of reactive microglia with reduced inflammatory factors such as IL-1β, TNFα. Moreover, blood vessels in the injured areas were repaired after AtN conversion and the blood-brain-barrier structure was restored. Whole tissue transcriptome sequencing identified significantly reduced reactive astrocyte genes and proinflammatory genes, as well as an upregulation of neurogenesis pathway and angiogenesis genes. Together, we demonstrate that NeuroD1-mediated astrocyte-to-neuron (AtN) conversion can alleviate glial scarring and inflammation to create a more neuropermissive micro-environment for functional recovery.