Modulation of Neural Stem Cell Fate by Reactive Astrocytes

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Ischemic injury causes neuronal loss and neurological deficits, challenging stroke recovery. After injury, a glial scar forms, but its regulation of neural stem cell (NSC) fate remains unclear. NSCs are multipotent cells vital for brain repair through self-renewal and generation of neurons and glia. Single-cell RNA sequencing of a mouse model showed glial scar formation increased NSC terminal differentiation and depleted the NSC pool. Reactive astrocytes are key scar components, traditionally classified as A1 (neurotoxic) or A2 (neuroprotective). TNFa, a pro-inflammatory cytokine secreted around the scar, is upregulated between NSCs and A1 astrocytes. To determine if A1 astrocytes modulate NSC fate via TNF signaling, NSCs were co-cultured with A1 astrocytes or exposed to A1-conditioned media. NSCs were biased toward NG2+ oligodendrocyte precursor cell (OPC) differentiation, which localizes to the scar periphery. TNFa alone similarly promoted OPC lineage commitment. A1 astrocytes were generated by stimulating homeostatic astrocytes with microglia-derived cytokines, leading to TNFa upregulation by RT-qPCR and sustained secretion by ELISA. Only strongly stimulated astrocytes maintained elevated TNFa after one week, indicating a threshold-dependent feedback mechanism. In contrast, astrocytes stimulated under A2 conditions (TNFa + IL-1ß) did not sustain TNFa secretion. Finally, pharmacological inhibition of astrocyte activation with dantrolene or salubrinal suppressed TNFa release, abrogating its effect on NSCs. This study suggests that A1 astrocyte–NSC interactions, mediated by TNFa-driven NSC-to-OPC conversion, contribute to the glial scar's protective architecture while limiting regeneration and depleting the NSC pool.

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