Symposia

[1S03m]Regulation and manipulation of neural stem/progenitor cells in the brain

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*Videos are available throughout the meeting period.

[1S03m-03]Direct reprogramming of microglia into functional neurons in the adult mouse brain

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Lineage-specific transcription factors enable the switch from one cell type into another, with potential applications in disease modeling and regenerative therapy. Microglia, the major immune cells in the CNS, converge at injured sites and become a predominant cell type within the glial scar in response to injury. Furthermore, a recent report has shown that even after selective elimination of most microglia in the adult mouse brain, the population can be rapidly replenished from the few surviving microglia. Thus, microglia that have accumulated at injured sites should be suitable for restoring lost neurons by direct reprogramming, without exhaustion of the source in the brain.

Here, we show that NeuroD1 achieves direct neuronal reprogramming from mouse microglia both in vitro and in vivo. Exogenous NeuroD1 initially occupies closed chromatin regions associated with bivalent H3K4me3 and H3K27me3 marks in microglia to induce neuronal gene expression. These regions are resolved to a monovalent H3K4me3 mark at later stages of the reprogramming to establish neuronal identity. Furthermore, after transient middle cerebral artery occlusion (tMCAO) in mouse brain, we also found that forced expression of NeuroD1 in microglia in the injured striatum enables the reprogramming into neurons that functionally integrate into the brain circuits. NeuroD1-mediated in vivo neuronal reprogramming significantly improves neurological function after tMCAO, and the ablation of newly generated neurons abolishes gained functional recovery. Thus, our findings demonstrate that NeuroD1 rearranges transcriptional and epigenetic profiles to execute microglia-neuron reprogramming, and this reprogramming contributes directly to the functional recovery after tMCAO.