Cellular Reprogramming for Understanding and Facilitating Neuroregeneration

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We showed that FGF1 gene 1B promoter-driven green fluorescence protein (F1B-GFP) is active in NSCs. We developed a novel approach to isolate neuronal progenitor cells from mouse and human brain tissues using F1B-GFP reporter plasmid. We showed that F1B-GFP$^+$ NSCs, when combined with FGF1 and nerve conduit, could promote the repair of damaged sciatic nerves in mice and rats. These studies could shed light on the role of FGF1 in neurogenesis and neural repair. We further showed that adaptor protein SH2B1, when combined with miRNA124, BRN2 and MYT1L (IBM), can enhance neurite outgrowth of iNeurons reprogrammed from adult human fibroblasts. These SH2B1-enhanced iNeurons (S-IBM) showed typical neuronal morphology, expressed canonical neuronal markers and functional proteins for neurotransmitter release. Importantly, SH2B1 accelerated mature process of functional neurons and exhibited action potentials as early as Day 14. Without SH2B1, the IBM-iNeurons do not exhibit proper action potentials until Day 28. Our data demonstrate that SH2B1 can enhance neurite outgrowth and accelerate the maturation of human iNeurons under defined condition. This reprogramming approach with SH2B1 could facilitate the application of iNeurons in regenerative medicine, *in vitro* disease modeling, and new drug discovery.

To further identify the function of F1B promoter in the brain, we generated F1B-GFP transgenic mice. Immunohistochemistry results from brain sections of 12-week old mice showed F1B-GFP$^+$ cells were expressed in two distinct populations. One population was ependymal cells of ventricular system, including lateral ventricles (LV), dorsal third ventricle (D3V), third ventricle (3V), aqueduct (Aq) and central canal (CC). The second population of F1B-GFP$^+$ cells was neurons throughout the brain. We found that a part of F1B-GFP$^+$ cells can express tyrosine hydroxylase, the marker for dopaminergic neurons. In addition, we showed that F1B-Cre transgenic mice, mated with Rosa26 transgenic mice to detect β-galactosidase activity, also exhibited the same expression pattern as F1B-GFP mice. Taken together, we successfully used mouse as an animal model to activate human FGF1 gene promoter F1B. The F1B-GFP$^+$ cells are ependymal and neuronal cells. Since neural stem cells are known to localize in the ventricular ependymal, the F1B-GFP transgenic mice could provide a novel tool to understand the function of FGF1 in brain development and in neuroregeneration.