Inhibition of BMP-Smad1 Signaling and Neural Stem Cell Transplantation for Enhanced Brain Repair from Ischemia-reperfusion Injury

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Stroke is a leading cause of disability and mortality in adult population worldwide. Our previous study has revealed inhibition of Bone morphogenetic protein (BMP) signaling can attenuate the brain injury from ischemia-reperfusion. Smad1, the downstream of BMP signaling, has been implicated in the stroke pathology and neural stem cells' (NSCs) activation, migration and differentiation. Therefore we investigate whether a strategy combining Smad1 inhibition with pharmaceutical approach and NSCs transplantation through carotid artery can attenuate stroke-induced brain injury and promote functional recovery from endogenous and exogenous NSCs. C57B6 mice at the age of 8weeks received 1h ischemia using a silicone rubber coated filament nylon suture, and then were randomly assigned into 4 groups: 1. i.p. injection of vehicle solution for 10days; 2. Injection of DMH1 (Smad1 inhibitor, 5mg/kg); 3. Injection of vehicle solution + NSCs delivery; and 4. Injection of DMH1 solution + NSCs delivery. NSCs were isolated from embryonic cortex of E18 eYFP (+) mice and expanded until delivery. At day3 post-stroke, 106 eYFP+ NSCs in PBS were injected through ipsilateral carotid artery to mice from group 3 and 4. The stroke volume, motor function, survival of NSCs were examined at 10days and 2months post-stroke. Our preliminary data showed that inhibition of Smad1 signaling with DMH1 or transplant of NSCs mitigate brain injury; while in the group4, DMH1 treatment also prompted NSCs' survival and neuronal differentiation in the stroke area. Taken together, our results suggest the translational potential of a regimen for stroke including both Smad1 inhibition and NSCs therapy.