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Transdifferentiation of human Mesenchymal stem cells into neuron like cells by overexpression of transcription factors

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Mesenchymal stem cells(MSCs) from bone marrow are reported to give rise not only to mesodermal lineage cells, but to adopt the fate of endodermal and neuroectodermal cell types. In this study, we are interested in mechanism controling transdifferentiation of MDSCs to neuronal fate and tried to define transcription factors to differentiate MSCs into neurons with long-term survival and specific subtypes. We also evaluated the efficacy of the cell therapy for treating brain diseases model using MSCs, and compare the efficacy with the differentiation factors for neural stem cells, We found PDGF changed the hMSC shape to bipolar with neurites, increased the expression of neuronal cell markers and AMPA receptor subunit(GluR2), specially when transfected with Nkx2.2. BDNF facillitated the differentiation into GABAegic neuron with many neurites expressing NMDA receptor(NR2A) when treated together with forskolin. Pax6 induced differentiation of hMSCs to neuron-like cells expressing neurotransmitter synthesizing enzymes and the receptors, such as neurofilament, ChAT, calbindin, NR2A as well as GluR2 but blocked differentiation to astrocyte. Interestingly, when transfected with pax6 and Olig2 or NeuroD and treated with PDGF, hMSCs changed into cholinergic like cells expressing ChAT while they differentiated into glutamatergic neurons when forskoline was treated after transfected with pax6. Transfection with olig2 induced the expression of O4 when treated with Shh. overexpression of ngn1 induced GABAegic neurons.

We developed animal models of degenerating brain disease with memory impairment histologically and behaviorally. .we transplanted human MSCs into the adult rat hippocampus. MSCs integrated into host

tissue and differentiated into neuron-like cells and glia-like cells. Preexposure to forskolin, an activator of adenylyl cyclase(AC) promoted cell survival, migration, and differentiation. Forskolin increased survival rate of MSCs over two fold by six weeks. At six weeks after transplantation, MSCs migrated laterally from dorsal region of CA1 toward CA3 region along hippocampal alveus. Preexposure of forskolin and infection of BDNF-adenovirus or to MSCs or pax6 overexpression improved learning and memory through the behavior tests, such as Y-maze task and passive avoidance test. These results suggest that human MSCs can be potentially useful as vectors for treating a variety of degenerative neurological diseases including Alzheimer's disease, Parkinson's disease, and stroke.

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