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Pro-neural conversion of human bone marrow stromal cells for regenerative therapy of Parkinson's disease

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Introduction:

Current pharmacotherapy of Parkinson's disease does improve symptoms and extends the patients life expectancy, but does not provide a cure for this detrimental disease. Alternative approaches include cell replacement therapy. Human bone marrow stromal cells (MSC) are not capable of neuroectodermal differentiation *per se*. Though, in recent years several reports have claimed to achieve a neural transdifferentiation of these easily accessible stem cells. Here we report our protocol to *epigenetically convert* MSC into neural stem cell-like cells (MSC-NSC) using conditions similar to neural stem cell (NSC) culture.

Materials and Methods:

Upon trypsination MSC are cultured in suspension in serum-free P48F medium with 5 μ M heparin, FGF2, and EGF (20 ng/ml each), under 3% oxygen (instead of 21%).

Results:

Initially, we identified changes of gene expression upon conversion of MSC by mRNA gene chip analysis. In respect to their genome-wide transcriptome, both MSC and MSC-NSC were similar to each other, but differed significantly from adult human NSC. On closer examination we could identify several "neural" genes (e.g. EAAT1, GFAP, MAOA, MAP2, MBP, NES, NOT1, NSE, PAX6, PTCH, SNCB) and dopaminergic genes (e.g. Nurr1, TH) being up-regulated in MSC-NSC and confirmed these data by real-time RT-PCR. Further investigations revealed that these changes were due to the specific culture conditions (suspension, serum-withdrawal, and hypoxia). Additionally, several neurotrophic factors (e.g. HGF, VEGFa) are up-regulated on both mRNA and protein level, reaching concentrations significantly higher than in human adult cortex. Though lacking therapeutic effects in a mouse model of amyotrophic lateral sclerosis due to limited survival of intrathecally transplanted cells, we observed a directed migration of MSC-NSC *in vivo* complying with *in vitro* experiments.

Discussion and Conclusions:

Based on their neural gene expression profile MSC-NSC share noticeable similarities with adult human NSC arguing for a partial transdifferentiation. The converted cells release neurotrophic factors at high concentrations and further investigations will reveal whether the cells synthesize and release dopamine. Presenting a relatively simple epigenetic protocol to induce a cell phenotype with potentially improved neurotherapeutic properties, MSC-NSC might be a valuable resource for future treatment of neurodegenerative diseases by autologous transplantation.

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