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Ex-vivo Therapy Using Mesenchymal Stem Cells as Vehicles for the Gene Delivery into the Brain

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Mesenchymal stem cells (MSCs) are non-hematopoietic bone marrow cells that are able to differentiate into mesodermal lineage cells such as osteocytes, chondrocytes, adipocytes and myocytes [1]. In addition, MSCs can trans-differentiate into non-mesodermal lineage cells. Specifically, MSCs can give rise to neural lineage cells including neurons and astrocytes. After transplantation into the rat brain, MSCs were found to migrate along known neural progenitor cell pathways and engraft into the brain parenchyma [2]. Similarly, after systemic injection of whole bone marrow, donor-derived cells were found in the brain of immunodeficient mice [3, 4]. In both cases, most of the cells differentiated into non-neuronal glial cells, with a smaller number of neuron-like cells observed. This neurogenic potential of MSCs makes them good candidates for auto-transplantation in various cell and gene therapies for the neurological diseases.

Furthermore, MSCs have a great potential to migrate selectively into damaged areas in the brain after systemic or intracranial implantation in the rat model [5, 6]. The molecular signals governing rMSC migration in vivo is of major importance for understanding the MSC-mediated cell therapy for traumas and diseases in the central nervous system (CNS). The interaction between chemokines and their receptors [fractalkine and its receptor CX_3CR1, stromal cell-derived factor 1 and its receptor CXCR4; interleukin-8] partially mediate the trafficking of MSCs to the impaired sites in the unilateral nerve injury model [7,8].

Here, we show that pre-conditioning of MSCS with a neurogenic transcription factor could yield higher rates in transdifferentiation into neuronal cells in vitro as well as in therapeutic effects in vivo. We found that transplantation of the pre-conditioned MSCs had higher therapeutic effects than MSCs as tested in the rat brain ischemic model. The pre-conditioned MSCs reduced the infarct volume in the rat MCAo brain and partially restored the motor deficits two weeks after implantation. The pre-conditioned MSCs differentiated into neurons at higher rates in the ischemic core region. We also utilized MSCs as vehicles for delivering the suicide genes into the rat brain tumor. The MSCs carrying the suicide genes migrated away from the implantation site and toward the glioma where the cells

infiltrated into the tumor tissue. Inactive prodrug was converted into active form by the suicide genes in the MSCs and caused cell death of adjacent glioma cells. The anti-tumor effects finally led to regression of glioma.

Compared to other stem cells, MSCs have few practical, ethical, or immunological barriers to their clinical application, since they can be aspirated from patients and easily expanded *in vitro*. In addition, their ability to propagate easily in vitro and differentiate into neuronal cells make these autologous cells a potentially important cell source for future treatment of neural dysfunctions.

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