



Title	Both ion channels and calcium signals regulate proliferation in human adult mesenchymal stem cells from bone marrow
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Thursday Poster Abstracts

Poster Board Number: 3015

HUMAN ADULT DENTAL PULP STEM CELLS: SURVIVAL, MIGRATION AND DIFFERENTIATION FOLLOWING TRANSPLANTATION INTO STROKE RAT BRAIN

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Human dental pulp stem cells (DPSCs), derived from adult third molar teeth, are multipotent and have the capacity to differentiate into neurons under inductive conditions both *in vitro* and following transplantation into the mesencephalon of the avian embryo. In this study, focal cerebral ischemia was induced via reversible intraluminal middle cerebral artery occlusion in a rodent model, and human DPSCs were transplanted intracerebrally 24 hours post-stroke into the peri-infarct region at 2 stereotaxic coordinates: half each into the cortex and the striatum. We then evaluated the behavior of the engrafted cells. An average of 2.3% of the original 600,000 transplanted DPSCs survived in the rodent brain at 4 weeks after treatment. While the majority of the DPSCs demonstrated targeted migration toward the infarct, some travelled considerable distances into the contralateral hemisphere. Engrafted cells around the lesion expressed the mature neuron-specific nuclear protein NeuN as well as the astrocytic marker glial fibrillary acidic protein. A number of cells also appeared to engraft into the wall of blood vessels with morphological appearances suggesting differentiation into smooth muscle and endothelial cells. The present data substantiates the long-range migration, neural and angiogenic differentiation potential of human DPSCs in the ischemic brain. These engrafted cell behaviors may represent cellular mechanisms of actions underlying the enhancement of post-stroke functional recovery following cell therapy.

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BOTH ION CHANNELS AND CALCIUM SIGNALS REGULATE PROLIFERATION IN HUMAN ADULT MESENCHYMAL STEM CELLS FROM BONE MARROW

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Background: It has been recognized that human bone marrow-derived mesenchymal stem cells (MSCs) are present within the bone marrow cavity and serve as a reservoir for the continuous renewal of various mesenchymal tissues. However, their cellular biology is not fully understood, especially on the regulation of their cellular activities by ion channels and cytosolic free calcium ion (Ca²⁺). The present study was designed to investigate the potential roles of Ca²⁺ signals and ion channels in regulating proliferation in human MSCs. Methods: Whole-cell patch voltage-clamp, confocal microscopy, cell proliferation assay, and Western blot analysis were used to determine membrane currents, Ca²⁺ signals, cell proliferation, and intracellular kinase activity, respectively, in cultured human MSCs. Results: Large-conductance Ca²⁺-activated potassium (BKCa) channel, ether-à-go-go potassium (hEAG1) channel, and voltage-gated sodium channel (INa) were present in human MSCs, and suppressed respectively by paxilline, astemizole and tetrodotoxin (TTX). Paxilline or astemizole, but not TTX, decreased cell

proliferation and DNA synthesis rate in a concentration-dependent manner. Silencing BKCa or hEAG1 channel with the specific shRNA also inhibited proliferation. Flowcytometry analysis showed that paxilline and astemizole accumulated human MSCs at G₀/G₁ phase, and decreased cell population of S phase. In addition, spontaneous Ca²⁺ oscillations exhibited in most human MSCs were inhibited by the IP₃R inhibitor aminoethoxydiphenyl borate (2-APB) and the SERCA inhibitor cyclopiazonic acid (CPA), while enhanced by cyclic ADP ribose. Interestingly, cell proliferation was suppressed by 2-APB or CPA, whereas promoted by cyclic ADP ribose via decreasing or increasing ERK1/2 phosphorylation. Conclusion: These results demonstrate that in addition to BKCa and hEAG1 channels (but not INa), intracellular Ca²⁺ signals regulate cell proliferation in human MSCs, indicating that both ion channels and Ca²⁺ signals most likely play a crucial role in maintaining *in situ* physiological renewal of human bone marrow.

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ROLES OF PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR GAMMA ON PROLIFERATION STATE OF MOUSE EMBRYONIC STEM CELLS DUE TO THE ABSENCE OR PRESENCE OF LEUKEMIA INHIBITORY FACTOR

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Embryonic stem cells have drawn particular interest due to their ability to differentiate into all three embryonic lineages while maintaining their other characteristic, self-renewal. These characteristics have made them a powerful model for investigating the mechanisms of cell survival and differentiation in early embryonic development. There are several factors like Leukemia inhibitory factor (LIF) which modulate the self-renewal and stem cell differentiation. Peroxisome Proliferator-Activated Receptor γ (PPAR γ) is belong to nuclear receptor dependent ligand-activated transcription factors that regulates expression many genes involvement in metabolism, cell differentiation, adipogenesis, inflammation and apoptosis. In this study we demonstrated that activation of PPAR γ by its agonists (Rosiglitazone and Ciglitazone) increased mESCs proliferation state in presence of LIF, while in absence of LIF, PPAR γ agonist decreased proliferation state of these cells. In both situations, PPAR γ antagonist (GW9662) reversed the effects caused by PPAR γ agonists. Moreover, data indicated that LIF increased PPAR γ expression. In the absence of LIF, PPAR γ agonist reduced Nanog expression as one of the pluripotent markers while had not any effect on Oct4 expression level. These results suggest that pivotal roles of PPAR γ on proliferative state of mouse embryonic stem cells depend on presence and absence of LIF.