

Regulation of cell proliferation by ion channels in human mesenchymal stem cells

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Introduction: Human bone marrow-derived mesenchymal stem cells (hMSCs) are a promising cell source for regenerative medicine; however, cellular physiology is not fully understood in hMSCs. The present study was to determine the potential role of the dominant functional ion channels, large-conductance Ca^{2+} -activated K^+ (BKCa) channel, human ether-à-go-go K^+ (hEAG1) channel, and Na^+ channel, in regulating proliferation of hMSCs.

Methods: Ionic currents were recorded using a whole-cell patch-clamp technique. Cell proliferation assay was made with MTT and ^3H -thymidine incorporation approaches. Cell cycle distribution was determined by flow cytometry.

Results: We found that the BKCa channel blocker paxilline (1 μM) almost fully inhibited BKCa current (from 6.76 ± 0.99 pA/pF of control, to 0.02 ± 0.09 pA/pF at +100 mV, $n=5$, $P<0.05$) in hMSCs. The hEAG1 channel blocker astemizole (0.5 μM) significantly reduced hEAG1 current from 4.28 ± 1.86 pA/pF to 1.40 ± 1.13 pA/pF at +50 mV, $n=6$, $P<0.05$). The MTT experiment showed that paxilline at 0.3, 1.0, and 3.0 μM reduced cell proliferation to 97.2, 84.4, and 48.7% of control, respectively, and astemizole at 0.3, 0.5, and 1 μM decreased cell proliferation to 96.5, 80.5, and 45.8%, respectively. However, the Na^+ channel blocker tetrodotoxin (1 μM , fully blocked Na^+ current) had no effect on proliferation in hMSCs. Both paxilline and astemizole reduced DNA synthesis rate in a concentration-dependent manner. Inhibition of BKCa channel with 1 μM paxilline or hEAG1 channel with 0.5 μM astemizole accumulated cells at G0/G1 phase (from control 68.9% to 80.5% for paxilline; to 79.2% for astemizole).

Conclusion: Our results demonstrate that BKCa and hEAG1 channels, but not Na^+ channel, participate in the regulation of cell proliferation by promoting G0/G1 cells into cell cycling progression.

Human embryonic stem cells-derived mesenchymal stem cells functionally attenuate monocrotaline-induced pulmonary arterial hypertension in mice

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Introduction: Transplantation of bone marrow (BM)-derived mesenchymal stem cells (MSCs) has been shown to attenuate pulmonary arterial hypertension (PAH). However, the effect of human embryonic stem cells (hESCs)-derived MSC which may have higher proliferative capacity than BM-MSCs on the pulmonary vascular bed in monocrotaline (MCT)-induced animal model of PAH has not been determined. In the present study, the effects of hESC-MSCs versus BM-MSCs transplantation on MCT-induced pulmonary arterial hypertension (PAH) were compared in mice.

Methods: PAH was induced in adult mice (ICR strain) by intraperitoneal injection of 400 mg/kg MCT. As the negative control, mice received saline instead of MCT (control group, $n=6$). One week after MCT administration, the animals were randomised to receive intravenous administration of: (1) PBS (MCT group, $n=6$); (2) 3.0×10^6 BM-MSCs (BMC group, $n=6$); or (3) 3.0×10^6 hESC-MSCs (hESC group, $n=6$) via tail vein. All animals were treated with cyclosporine (15 mg/kg) daily after transplantation. Invasive haemodynamic assessment and immunohistological studies were performed at 3 weeks after transplantation.

Results: Administration of either hESC-MSCs or BM-MSCs significantly attenuated elevated RV systolic pressure and reduced RV hypertrophy. After 1 week of transplantation, both hESC-MSCs and BM-MSCs not only retained in the wall of pulmonary vessels and in lung parenchyma, but also underwent vascular differentiation and cytokine release. However, after 3 weeks of transplantation, both BM-MSCs and hES-MSCs were undetectable in lung tissues as confirmed by immunostaining for human nuclear antigen (HNA) and PCR. Both hESC-MSCs and BM-MSCs were able to reduce microvascular wall thickness and increase density of pulmonary capillary to augment MCT-induced PAH.

Conclusion: We conclude hESC-MSCs are as functional as BM-MSCs to attenuate MCT-induced PAH. Despite hESC-MSCs have a higher proliferative capacity, both cell types are poor to long-term survive well in injured lung environments.