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 ^{3}H-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) $3.0x10^6$ BM-MSCs (BMC group, n=6); or (3) $3.0x10^6$ 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.