Transplantation of heterospheroids of islet cells and mesenchymal stem cells for effective angiogenesis and anti-apoptosis.

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Abstract

Although islet transplantation has been suggested as an alternative therapy for type 1 diabetes, there are efficiency concerns that are attributed to poor engraftment of transplanted islets. Hypoxic condition and delayed vasculogenesis induce necrosis and apoptosis of the transplanted islets. To overcome these limitations in islet transplantation, heterospheroids (HSs), which consist of rat islet cells (ICs) and human bone marrow-derived mesenchymal stem cells (hMSCs) were transplanted to kidney and liver. The HSs cultured under hypoxic condition system exhibited a significant increase in anti-apoptotic gene expression in ICs. hMSCs in the HSs secreted angiogenic and anti-apoptotic proteins. With the HS system, ICs and hMSCs were successfully located in the same area of liver after transplantation of HSs via portal vein, whereas the transplantation of islets and the dissociated hMSCs did not result in localization of transplanted ICs and hMSCs in the same area. HS transplantation resulted in an increase in angiogenesis at the transplantation area and a decrease in the apoptosis of transplanted ICs after transplantation into the kidney subcapsule compared to transplantation of islet cell clusters. Insulin production levels of ICs were higher in the HS transplantation group compared to the ICC transplantation group. The HS system may be a more efficient transplantation method than the conventional methods for the treatment of type 1 diabetes.

Expression and Significance of DLL4--Notch Signaling Pathway in the Differentiation of Human Umbilical Cord Derived Mesenchymal Stem Cells into Cardiomyocytes Induced by 5-Azacytidine.

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Abstract

hUCMSCs were isolated and purified from the umbilical cords of normal or cesarean term deliveries under sterile conditions. Flow cytometry analysis revealed that CD13, CD29, CD44, CD90, and CD105 were highly expressed on the surface of passage-3 hUCMSCs, but negative for CD31, CD34, CD45, and HLA-DR. Immunocytochemistry showed that 5-azacytidine (5-aza) could induce the cTnI expression of hUCMSCs. RT-PCR showed that a stable higher level expression of DLL4 and Notch1 gene in 5-aza-induced group was observed compared to that in the control group. There was a higher expression level in the induced group. Compared with control group, the expression levels of Notch1 were, respectively, increased 6.60, 7.36, 7.595, and 7.805 times at 1, 3, 5, and 7 days after intervention of 5-aza. Statistically higher Ct value of Notch1 mRNA in induced group was observed in comparison with that of the control group (0.51 ± 0.21 vs 7.85 ± 0.35, t = 35.98, P < 0.01). The expression level of DLL4 increased stably compared with the control group. Compared with control group, the expression levels of DLL4 were, respectively, increased 11.53, 10.1, 10.17, and 11.46 times at 1, 3, 5, and 7 days after intervention of 5-aza. There was a significant difference of
DLL4 Ct value between the 5-aza-induced group and the control group (1.60 ± 0.49 vs 12.42 ± 0.73, t = 11.71, P < 0.01). In conclusion, hUCMSCs can be differentiated into myocardial cells in vitro. The DLL4-Notch signaling pathway may be involved in the differentiation of hUCMSCs into cardiomyocytes induced by 5-aza.

**Lung.** 2014 Oct 26. [Epub ahead of print]

**Infusion of Mesenchymal Stem Cells Protects Lung Transplants from Cold Ischemia-Reperfusion Injury in Mice.**


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**Abstract**

**BACKGROUND:**

Cold ischemia-reperfusion injury (IRI) is a major cause of graft failure in lung transplantation. Despite therapeutic benefits of mesenchymal stem cells (MSCs) in attenuating acute lung injury, their protection of lung transplants from cold IRI remains elusive. The present study was to test the efficacy of MSCs in the prevention of cold IRI using a novel murine model of orthotopic lung transplantation.

**METHODS:**

Donor lungs from C57BL/6 mice were exposed to 6 h of cold ischemia before transplanted to syngeneic recipients. MSCs were isolated from the bone marrows of C57BL/6 mice for recipient treatment. Gas exchange was determined by the measurement of blood oxygenation, and lung injury and inflammation were assessed by histological analyses.

**RESULTS:**

Intravenously delivered MSC migration/trafficking to the lung grafts occurred within 4-hours post-transplantation. As compared to untreated controls, the graft arterial blood oxygenation (PaO₂/FiO₂) capacity was significantly improved in MSC-treated recipients as early as 4 h post-reperfusion and such improvement continued over time. By 72 h, oxygenation reached normal level that was not seen in controls. MSCs treatment conferred significant protection of the grafts from cold IRI and cell apoptosis, which is correlated with less cellular infiltration, a decrease in proinflammatory cytokines (TNF-α, IL-6) and toll-like receptor 4, and an increase in anti-inflammatory TSG-6 generation.

**CONCLUSIONS:**

MSCs provide significant protection against cold IRI in lung transplants, and thus may be a promising strategy to improve outcomes after lung transplantation.

**Oncotarget.** 2014 Sep 6. [Epub ahead of print]

**RNA-seq analysis reveals significant effects of EGFR signalling on the secretome of mesenchymal stem cells.**

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Abstract

Bone marrow-derived mesenchymal stem cells (MSCs) contribute to breast cancer progression by releasing soluble factors that sustain tumor progression. MSCs express functional epidermal growth factor receptor (EGFR) and breast cancer cells secrete EGFR-ligands including transforming growth factor-α (TGFα). Using RNA-sequencing, we analysed the whole transcriptome of MSCs stimulated with TGFα. We identified 1,640 highly differentially regulated genes: 967 genes up-regulated with Fold Induction (FI)≥1.50 and 673 genes down-regulated with FI≤0.50. When highly regulated genes were categorized according to GO molecular function classification and KEGG pathways analysis, a large number of genes coding for potentially secreted proteins or surface receptors resulted enriched following TGFα treatment, including VEGFA, IL6, EREG, HB-EGF, LIF, NGF, NRG1, CCL19, CCL2, CCL25 and CXCL3. Secretion of corresponding proteins was confirmed for selected factors. Finally, we identified 4,377 and 4,262 alternatively spliced genes in untreated and TGFα-treated MSCs, respectively. Among these, an unannotated splice variant of VEGFA coding for a secreted VEGF protein of 172 aminoacids (VEGFA172), was found only in MSCs stimulated with TGFα. These findings suggest that EGFR activation in MSCs leads to a significant change in the expression of a wide array of genes coding for secreted proteins that can significantly enhance tumor progression.