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Exosomes from adipose tissue-derived mesenchymal stem cells ameliorate histone-induced acute lung injury by activating the PI3K/Akt pathway in endothelial cells

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Abstract

Background: Mesenchymal stem cells (MSCs), including adipose-derived mesenchymal stem cells (ADSCs), have been shown to attenuate organ damage in acute respiratory distress syndrome (ARDS) and sepsis; however, the underlying mechanisms are not fully understood. In this study, we aimed to explore the potential roles and molecular mechanisms of action of ADSCs in histone-induced endothelial damage.

Methods: Male C57BL/6 N mice were intravenously injected with ADSCs, followed by histones or a vehicle. The mice in each group were assessed for survival, pulmonary vascular permeability, and histological changes. A co-culture model with primary human umbilical vein endothelial cells (HUVECs) exposed to histones was used to clarify the

paracrine effect of ADSCs. Overexpression and inhibition of miR-126 ADSCs were also examined as causative factors for endothelial protection.

Results: The administration of ADSCs markedly improved survival, inhibited histone-mediated lung hemorrhage and edema, and attenuated vascular hyper-permeability in mice. ADSCs were engrafted in the injured lung and attenuated histone-induced endothelial cell apoptosis. ADSCs showed endothelial protection (via a paracrine effect) and Akt phosphorylation in the histone-exposed HUVECs. Notably, increased Akt phosphorylation by ADSCs was mostly mediated by exosomes in histone-induced cytotoxicity and lung damage. Moreover, the expression of miR-126 was increased in exosomes from histone-exposed ADSCs. Remarkably, the inhibition of miR-126 in ADSCs failed to increase Akt phosphorylation in histone-exposed HUVECs.

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Biostimulative effect of laser on growth of mesenchymal stem/stromal cells *in vitro*

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Abstract

Introduction: Human adipose tissue-derived mesenchymal stem/stromal cells (hAT-MSCs) are multipotent stromal cells with a high potential application in tissue engineering and

regenerative medicine. Laser irradiation of the place where the cells were implanted can stimulate their proliferation, increase the secretion of growth factors and thus increase the therapeutic effect.

Aim: To evaluate the influence of two lasers: Er:YAG and diode on the growth of hAT-MSCs *in vitro*.

Material and methods: hAT-MSCs were isolated from human subcutaneous adipose tissue. Immunophenotype of hAT-MSCs was confirmed by flow cytometry. Multipotency of hAT-MSCs was confirmed by differentiation into adipogenic, osteogenic and chondrogenic lineages. hAT-MSCs were irradiated with Er:YAG laser (wavelength 2940 nm, frequency 5, 10 Hz, doses: 0.1-1.2 J/cm^2) for 2 s and 4 s and diode laser (wavelength 635 nm and doses: 1-8 J/cm^2) for 5, 10, 20, 30 and 40 s. Cell viability was analysed 24 h after the exposure using MTT assay.

Results: Growth stimulation of hAT-MSCs after 5 Hz Er:YAG laser exposure, 0.1 J/cm^2 dose for 4 s and 0.3 J/cm^2 dose for 4 s was shown in comparison with the control group. Significant growth stimulation of hAT-MSCs after diode laser irradiation in doses of 1-4 J/cm^2 was demonstrated compared to the control group.

Conclusions: The presented results indicate that both lasers, Er:YAG and diode can be used to stimulate stem/stromal cell growth *in vitro*. The biostimulative effect of laser therapy on stromal cells may be used in the future in aesthetic dermatology in combined laser and cell therapy.

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Exosomes derived from three-dimensional cultured human umbilical cord mesenchymal stem cells ameliorate pulmonary fibrosis in a mouse silicosis model

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Abstract

Background: Silicosis is an occupational respiratory disease caused by long-term excessive silica inhalation, which is most commonly encountered in industrial settings. Unfortunately, there is no effective therapy to delay and cure the progress of silicosis. In the recent years, stem cell therapy has emerged as an attractive tool against pulmonary fibrosis (PF) owing to its unique biological characteristics. However, the direct use of stem cells remains limitation by many risk factors for therapeutic purposes. The exclusive utility of exosomes secreted from stem cells, rather than cells, has been considered a promising alternative to overcome the limitations of cell-based therapy while maintaining its advantages.

Methods and results: In this study, we first employed a three-dimensional (3D) dynamic system to culture human umbilical cord mesenchymal stem cell (hucMSC) spheroids in a microcarrier suspension to yield exosomes from serum-free media. Experimental silicosis was induced in C57BL/6J mice by intratracheal instillation of a silica suspension, with/without exosomes derived from hucMSC (hucMSC-Exos), injection via the tail vein afterwards. The results showed that the gene expression of collagen I (COL1A1) and fibronectin (FN) was upregulated in the silica group as compared to that in the control group; however, this change decreased with hucMSC-Exo treatment. The value of FEV0.1 decreased in the silica group as compared to that in the control group, and this change diminished with hucMSC-Exo treatment. These findings suggested that hucMSC-Exos could inhibit silica-induced PF and regulate pulmonary function. We also performed in vitro experiments to confirm these findings; the results revealed that hucMSC-Exos decreased collagen deposition in NIH-3T3 cells exposed to silica.

Conclusions: Taken together, these studies support a potential role for hucMSC-Exos in ameliorating pulmonary fibrosis and provide new evidence for improving clinical treatment induced by silica.

Cell Tissue Res

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Comparison of bone regenerative capacity of donor-matched human adipose-derived and bone marrow mesenchymal stem cells

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Abstract

Adipose-derived stem cells (ASC) have been used as an alternative to bone marrow mesenchymal stem cells (BMSC) for bone tissue engineering. However, the efficacy of ASC in bone regeneration in comparison with BMSC remains debatable, since inconsistent results have been reported. Comparing ASC with BMSC obtained from different individuals might contribute to this inconsistency in results. Therefore, this study aimed to compare the bone regenerative capacity of donor-matched human ASC and BMSC seeded onto poly(L-lactide-co-ε-caprolactone) scaffolds using calvarial bone defects in nude rats. First, donor-matched ASC and BMSC were seeded onto the co-polymer scaffolds to evaluate their in vitro osteogenic differentiation. Seeded scaffolds and scaffolds without cells (control) were then implanted in calvarial defects in nude rats. The expression of osteogenesis-related genes was examined after 4 weeks. Cellular activity was investigated after 4 and 12 weeks. Bone formation was evaluated radiographically and histologically after 4, 12, and 24 weeks. In vitro, ASC and BMSC demonstrated mineralization. However, BMSC showed higher alkaline phosphatase activity than ASC. In vivo, human osteogenesis-related genes Runx2 and collagen type I were expressed in defects with scaffold/cells. Defects with scaffold/BMSC had higher cellular activity than defects with scaffold/ASC. Moreover, bone formation in defects with scaffold/BMSC was greater than in defects with scaffold/ASC, especially at the early time-point. These results suggest that although ASC have the potential to regenerate bone, the rate of bone regeneration with ASC may be slower than with BMSC. Accordingly, BMSC are more suitable for bone regenerative applications.

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Inclusion of a 3D-printed Hyperelastic Bone mesh improves mechanical and osteogenic performance of a mineralized collagen scaffold

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Abstract

Regenerative repair of craniomaxillofacial bone injuries is challenging due to both the large size and irregular shape of many defects. Mineralized collagen scaffolds have previously been shown to be a promising biomaterial implant to accelerate craniofacial bone regeneration in vivo. Here we describe inclusion of a 3D-printed polymer or ceramic-based mesh into a mineralized collagen scaffold to improve mechanical and biological activity. Mineralized collagen scaffolds were reinforced with 3D-printed Fluffy-PLG (ultraporous polylactide-co-glycolide co-polymer) or Hyperelastic Bone (90wt% calcium phosphate in PLG) meshes. We show degradation byproducts and acidic release from the printed structures have limited negative impact on the viability of mesenchymal stem cells. Further, inclusion of a mesh formed from Hyperelastic Bone generates a reinforced composite with significantly improved mechanical performance (elastic modulus, push-out strength). Composites formed from the mineralized collagen scaffold and either Hyperelastic Bone or Fluffy-PLG reinforcement both supported human bone-marrow derived mesenchymal stem cell osteogenesis and new bone formation. This was observed by increased mineral formation in Fluffy-PLG composites and increased cell viability and upregulation of RUNX2, Osterix, and COL1A2 genes in both composites. Strikingly, composites reinforced with Hyperelastic Bone mesh elicited significantly increased secretion of osteoprotegerin, a soluble glycoprotein and endogenous inhibitor of osteoclast activity. These results suggest that architectured meshes can be integrated into collagen scaffolds to boost mechanical performance and actively instruct cell processes that aid osteogenicity; specifically, secretion of a factor crucial to inhibiting osteoclast-mediated bone resorption. Future work will focus on further adapting the polymer mesh architecture to confer improved shape-

fitting capacity as well as to investigate the role of polymer reinforcement on MSC-osteoclast interactions as a means to increase regenerative potential.