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Photobiomodulation effect on the proliferation of adipose tissue mesenchymal stem cells.

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Abstract

The use of mesenchymal stem cells (MSCs) in tissue engineering has been extensively investigated. The greater the proliferation of this cellular group, the greater the regenerative and healing capacity of the tissue to which they belong. In this context, photobiomodulation (PBM) is an efficient technique in proliferation of distinct cell types. However, its parameters and mode of action are still unclear and require further investigation. This study aimed to evaluate the PBM action with different energies in MSCs of adipose tissue (hASCs). We used hASCs, seeded in 24-well plates, with 3×10^4 cells per well, in culture media. We used a total of four experimental groups, one with hASCs and simulated PBM and three other groups, which received PBM irradiation at 24, 48, and 72 h, with a 660-nm laser and power of 40 mW and energy of 0.56, 1.96, and 5.04 J. We performed analyses of MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromidefor) and trypan blue to evaluate cell proliferation and viability, 1 h after PBM irradiation. Software Graph PadPrism 7.0 was used. Intergroup comparisons were performed with ANOVA two-way and we used the Tukey post hoc test. Mitochondrial activity evaluated by MTT revealed the statistical difference in the first 24 h for group with more high energy when compared to control group; and in the 72 h for two irradiated groups when compared to the control group. The trypan blue test showed significant differences at the end of the experiment for two irradiated groups LG1 ($4.52 \times 10^4 \pm 0.2$) and LG2 ($4.85 \times 104 \pm 0.8$), when compared to the control group ($1.87 \times 10^4 \pm 0.7$). Both tests failed to be statistically different at the end of the experiment for groups LG1 and LG2 and observed a reduction in cellular mitochondrial growth and activity for group LG3. We conclude that PBM with energy close to 0.56 and 1.96 J promote proliferation of hASCs, and higher energy, such as 5.04 J, can be harmful.

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Dosage and composition of bioactive glasses differentially regulate angiogenic and osteogenic response of human MSCs.

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Abstract

Vascularization of the fracture site and cell-mediated deposition of the mineralized matrix are crucial determinants for successful bone regeneration after injury. Ceramic biomaterials such as bioactive glasses (BAGs) that release bioactive ions have shown promising results in bone defect regeneration.

However, it remains unclear how the dosage and composition of bioactive ions influence the angiogenic and osteogenic behavior of primary human mesenchymal stromal cells (MSCs). Here, we show that exposure to ionic dissolution products from 1393 and 45S5 BAGs can evoke distinct angiogenic and osteogenic responses from primary MSCs in a dose- and composition-dependent manner. Significantly higher concentrations of the pro-angiogenic factors VEGF, HGF, PIGF, angiopoietin, and angiogenin were detected in conditioned media (CM) from MSCs exposed to 45S5, but not 1393, BAGs. Application of this CM to human umbilical vein endothelial cells (HUVECs) resulted in robust 2D tube formation in vitro. Osteogenic differentiation of MSCs was assessed by gene expression analysis and mineralization assays. Low concentrations (0.1% w/v) of 1393 BAGs significantly enhanced the gene expression of RUNX2 and ALP and induced an earlier onset of matrix mineralization compared to all other groups. We further tested whether simultaneous exposure to both BAGs would improve both angiogenic secretion and osteogenic differentiation of MSCs, and did not find evidence to support this hypothesis. Our results provide evidence of BAG composition-dependent enhancement of primary human MSCs' regenerative function, besides also underlining the importance of an in vitro evaluation of the dose-response relationship to translate BAG based approaches into safe and effective clinical therapies.

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Engineering mesenchymal stem cells to improve their exosome efficacy and yield for cell-free therapy.

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Abstract

Through traditional medicine, there were diseases and disorders that previously remained untreated or were simply thought to be incurable. Since the discovery of mesenchymal stem cells (MSCs), there has been a flurry of research to develop MSC-based therapy for diseases and disorders. It is now well-known that MSCs do not typically engraft after transplantation and exhibit their therapeutic effect via a paracrine mechanism. In addition to secretory proteins, MSCs also produce extracellular vesicles (EVs), membrane-bound nanovesicles containing proteins, DNA and RNA. The secreted vesicles then interact with target cells and deliver their contents, imparting their ultimate therapeutic effect. Unlike the widely studied cancer cells, the yield of MSC-exosomes is a limiting factor for large-scale production for cell-free therapies. Here we summarise potential approaches to increase the yield of such vesicles while maintaining or enhancing their efficacy by engineering the extracellular environment and intracellular components of MSCs.

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Characterization and potential roles of bone marrow-derived stromal cells in cancer development and metastasis.

Kawai H[1], Tsujigiwa H[2], Siar CH[3], Nakano K[1], Takabatake K[1], Fujii M[1], Hamada M[1], Tamamura R[4], Nagatsuka H[1].
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Abstract

Background: The tumor microenvironment and its stromal cells play an important role in cancer development and metastasis. Bone marrow-derived cells (BMDCs), a rich source of hematopoietic and mesenchymal stem cells, putatively contribute to this tumoral stroma. However their characteristics and roles within the tumor microenvironment are unclear. In the present study, BMDCs in the tumor microenvironment were traced using the green fluorescent protein (GFP) bone marrow transplantation model. **Methods:** C57BL/6 mice were irradiated and rescued by bone marrow transplantation from GFP-transgenic mice. Lewis lung cancer cells were inoculated into the mice to generate subcutaneous allograft tumors or lung metastases. Confocal microscopy, immunohistochemistry for GFP, α-SMA, CD11b, CD31, CD34 and CD105, and double-fluorescent immunohistochemistry for GFP-CD11b, GFP-CD105 and GFP-CD31 were performed. **Results:** Round and dendritic-shaped GFP-positive mononuclear cells constituted a significant stromal subpopulation in primary tumor peripheral area (PA) and metastatic tumor area (MA) microenvironment, thus implicating an invasive and metastatic role for these cells. CD11b co-expression in GFP-positive cells suggests that round/dendritic cell subpopulations are possibly BM-derived macrophages. Identification of GFP-positive mononuclear infiltrates co-expressing CD31 suggests that these cells might be BM-derived angioblasts, whereas their non-reactivity for CD34, CD105 and α-SMA implies an altered vascular phenotype distinct from endothelial cells. Significant upregulation of GFP-positive, CD31-positive and GFP/CD31 double-positive cell densities positively correlated with PA and MA (P<0.05). **Conclusion:** Taken together, *in vivo* evidence of traceable GFP-positive BMDCs in primary and metastatic tumor microenvironment suggests that recruited BMDCs might partake in cancer invasion and metastasis, possess multilineage potency and promote angiogenesis.

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allograft tumors or lung metastases. Confocal microscopy, immunohistochemistry for GFP, α-SMA, CD11b, CD31, CD34 and CD105, and double-fluorescent immunohistochemistry for GFP-CD11b, GFP-CD105 and GFP-CD31 were performed. **Results:** Round and dendritic-shaped GFP-positive mononuclear cells constituted a significant stromal subpopulation in primary tumor peripheral area (PA) and metastatic tumor area (MA) microenvironment, thus implicating an invasive and metastatic role for these cells. CD11b co-expression in GFP-positive cells suggests that round/dendritic cell subpopulations are possibly BM-derived macrophages. Identification of GFP-positive mononuclear infiltrates co-expressing CD31 suggests that these cells might be BM-derived angioblasts, whereas their non-reactivity for CD34, CD105 and α-SMA implies an altered vascular phenotype distinct from endothelial cells. Significant upregulation of GFP-positive, CD31-positive and GFP/CD31 double-positive cell densities positively correlated with PA and MA (P<0.05). **Conclusion:** Taken together, *in vivo* evidence of traceable GFP-positive BMDCs in primary and metastatic tumor microenvironment suggests that recruited BMDCs might partake in cancer invasion and metastasis, possess multilineage potency and promote angiogenesis.