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Engineered microtissues for the bystander therapy against cancer

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Abstract

Thymidine kinase expressing human adipose mesenchymal stem cells (TK-hAMSCs) in combination with ganciclovir (GCV) are an effective platform for antitumor bystander therapy in mice models. However, this strategy requires multiple TK-hAMSCs administrations and a substantial number of cells. Therefore, for clinical translation, it is necessary to find a biocompatible scaffold providing TK-hAMSCs retention in the implantation site against their rapid wash-out. We have developed a microtissue (MT) composed by TKhAMSCs and a scaffold made of polylactic acid microparticles and cell-derived extracellular matrix deposited by hAMSCs. The efficacy of these MTs as vehicles for TK-hAMSCs/GCV bystander therapy was evaluated in a rodent model of human prostate cancer. Subcutaneously implanted MTs were integrated in the surrounding tissue, allowing neovascularization and maintenance of TK-hAMSCs viability. Furthermore, MTs implanted beside tumors allowed TK-hAMSCs migration towards tumor cells and, after GCV administration, inhibited tumor growth. These results indicate that TK-hAMSCs-MTs are promising cell reservoirs for clinical use of therapeutic MSCs in bystander therapies.

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Reduced graphene oxide coating enhances osteogenic differentiation of human mesenchymal stem cells on Ti surfaces

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Free article

Abstract

Background: Titanium (Ti) has been utilized as hard tissue replacement owing to its superior mechanical and bioinert property, however, lack in tissue compatibility and biofunctionality has limited its clinical use. Reduced graphene oxide (rGO) is one of the graphene derivatives that possess extraordinary biofunctionality and are known to induce osseointegration in vitro and in vivo. In this study, rGO was uniformly coated by meniscus-dragging deposition (MDD) technique to fabricate rGO-Ti substrate for orthopedic and dental implant application.

Methods: The physicochemical characteristics of rGO-coated Ti (rGO-Ti) substrates were evaluated by atomic force microscopy, water contact angle, and Raman spectroscopy. Furthermore, human mesenchymal stem cells (hMSCs) were cultured on the rGO-Ti substrate, and then their cellular behaviors such as growth and osteogenic differentiation were determined by a cell counting kit-8 assay, alkaline phosphatase (ALP) activity assay, and alizarin red S staining.

Results: rGO was coated uniformly on Ti substrates by MDD process, which allowed a decrease in the surface roughness and contact angle of Ti substrates. While rGO-Ti substrates significantly increased cell proliferation after 7 days of incubation, they significantly promoted ALP activity and matrix mineralization, which are early and late differentiation markers, respectively.

Conclusion: It is suggested that rGO-Ti substrates can be effectively utilized as dental and orthopedic bone substitutes since these graphene derivatives have potent effects on

stimulating the osteogenic differentiation of hMSCs and showed superior bioactivity and osteogenic potential.

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The Potential Function of Super Enhancers in Human Bone Marrow Mesenchymal Stem Cells during Osteogenic Differentiation

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Abstract

Super enhancers (SEs) are large clusters of transcriptional activity enhancers, which drive and control the expression of cell identity genes, as well as differentiation of specific cell types. SEs have great application potential in pathogenic mechanism studies in developmental biology, cancer, and other diseases. However, the potential function and regulatory mechanism of SEs in the osteogenic differentiation of human bone marrow mesenchymal stem cells (hBMSCs) are unknown. Therefore, this study investigated the potential function of SEs in the osteogenic differentiation of hBMSCs and their target genes. Osteogenesis was induced in three hBMSCs groups for 14 days. Further, ChIP-seq was performed on cells before and after osteogenic differentiation. Two target genes were then selected from cells before and after osteogenic differentiation for RT-qPCR. Finally, the selected SE target genes were analyzed by bioinformatics. In total, 1,680 SEs were identified in hBMSCs. After 14 days of osteogenic induction, only 342 SEs were detected in

cells, among which 1,380 unique SEs were detected in hBMSCs, 42 unique SEs were found in cells induced by osteoblast differentiation after 14 days, and 300 SEs were common in both groups. Further, 1,680 genes were found to be regulated by SEs in hBMSCs, including 1,094 genes with protein-coding function and 586 noncoding genes. Additionally, 342 genes were regulated by SEs in cells after 14 days of osteogenic differentiation induction, of which 223 and 119 had protein-coding and noncoding functions, respectively. KEGG analysis of SE target genes before and after osteogenic differentiation showed the TGF-β, PI3K-Akt, and ECM receptor signaling pathways as highly enriched and closely related to osteogenic differentiation. Further, RT-qPCR results of four selected target genes confirmed the sequencing results. Taken together, osteogenic differentiation of hBMSCs involves changes in multiple SEs, which may regulate the osteogenic differentiation of hBMSCs by regulating the expression of target genes.

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Functional Regulatory Mechanisms Underlying Bone Marrow Mesenchymal Stem Cell Senescence During Cell Passages

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Abstract

Mesenchymal stem cell (MSC) transplantation is an effective periodontal regenerative therapy. MSCs are multipotent, have self-renewal ability, and can differentiate into periodontal cells. However, senescence is inevitable for MSCs. In vitro, cell senescence can be induced by long-term culture with/without cell passage. However, the regulatory mechanism of MSC senescence remains unclear. Undifferentiated MSC-specific transcription factors can regulate MSC function. Herein, we identified the regulatory transcription factors involved in MSC senescence and elucidated their mechanisms of

action. We cultured human MSCs (hMSCs) with repetitive cell passages to induce cell senescence and evaluated the mRNA and protein expression of cell senescence-related genes. Additionally, we silenced the cell senescence-induced transcription factors, GATA binding protein 6 (GATA6) and SRY-box 11 (SOX11), and investigated senescence-related signaling pathways. With repeated passages, the number of senescent cells increased, while the cell proliferation capacity decreased; GATA6 mRNA expression was upregulated and that of SOX11 was downregulated. Repetitive cell passages decreased Wnt and bone morphogenetic protein (BMP) signaling pathway-related gene expression. Silencing of GATA6 and SOX11 regulated Wnt and BMP signaling pathway-related genes and affected cell senescence-related genes; moreover, SOX11 silencing regulated GATA6 expression. Hence, we identified them as pair of regulatory transcription factors for cell senescence in hMSCs via the Wnt and BMP signaling pathways.

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Mesenchymal stem cells and oncolytic viruses: joining forces against cancer

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Free article

Abstract

The development of oncolytic viruses (OVs) has increased significantly in the past 20 years, with many candidates entering clinical trials and three of them receiving approval for some indications. Recently, OVs have also gathered interest as candidates to use in combination with immunotherapies for cancer due to their immunogenic properties, which include immunogenic cell death and the possibility to carry therapeutic transgenes in their genomes. OVs transform non-immunogenic 'cold' tumors into inflamed immunogenic 'hot' tumors, where immunotherapies show the highest efficacy. However, in monotherapy or in combination with immunotherapy, OVs face numerous challenges that limit their

successful application, in particular upon systemic administration, such as liver sequestration, neutralizing interactions in blood, physical barriers to infection, and fast clearance by the immune system. In this regard, the use of mesenchymal stem cells (MSCs) as cells carrier for OV delivery addresses many of these obstacles acting as virus carriers and factories, expressing additional transgenes, and modulating the immune system. Here, I review the current progress of OVs-loaded MSCs in cancer, focusing on their interaction with the immune system, and discuss new strategies to improve their therapeutic efficacy.