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Bone Marrow-Derived Cell Therapies to Heal Long-Bone Nonunions: A Systematic Review and Meta-Analysis-Which Is the Best Available Treatment?

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Abstract

Nonunions represent one of the major indications for clinical settings with stem cell-based therapies. The objective of this research was to systematically assess the current evidence for the efficacy of bone marrow-derived cell-based approaches associated or not with bone scaffolds for the treatment of nonunions. We searched MEDLINE (PubMed) and CENTRAL up to July 2019 for clinical studies focused on the use of cell-based therapies and bone marrow derivatives to treat bone nonunions. Three investigators independently extracted the data and appraised the risk of bias. We analysed 27 studies including a total number of 347 participants exposed to four interventions: bone marrow concentrate (BMAC), BMAC combined with scaffold (BMAC/Scaffold), bone marrow-derived mesenchymal stromal cells (BMSCs), and BMSC combined with scaffold (BMSC/Scaffold). Two controlled studies showed a positive trend in bone healing in favour of BMAC/Scaffold or BMSC/Scaffold treatment against bone autograft, although the difference was not statistically significant (RR 0.11, 95% CI -0.05; 0.28). Among single cohort studies, the highest mean pooled proportion of healing rate was reported for BMAC (77%; 95% CI 63%-89%; 107 cases, *n* = 8) and BMAC/Scaffold treatments with (71%; 95% CI 50%-89%; 117 cases, *n* = 8) at 6 months of follow-up. At 12 months of follow-up, an increasing proportion of bone healing was observed in all the treatment groups, ranging from 81% to 100%. These results indicate that BMAC or BMAC/Scaffold might be considered as the primary choice to treat nonunions with a successful healing rate at a midterm follow-up. Moreover, this meta-analysis highlighted that the presence of a scaffold positively influences the healing rate at a long-term follow-up. More case-control studies are still needed to support the clinical improvement of cell-based therapies against autografts, up to now considered as the gold standard for the treatment of nonunions.

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Mesenchymal stem cells used as carrier cells of oncolytic adenovirus results in enhanced oncolytic virotherapy.

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Abstract

Mesenchymal stem cells (MSCs) loaded with oncolytic viruses are presently being investigated as a new modality of advanced/metastatic tumors treatment and enhancement of virotherapy. MSCs can, however, either promote or suppress tumor growth. To address the critical question of how MSCs

loaded with oncolytic viruses affect virotherapy outcomes and tumor growth patterns in a tumor microenvironment, we developed and analyzed an integrated mathematical-experimental model. We used the model to describe both the growth dynamics in our experiments of firefly luciferase-expressing Hep3B tumor xenografts and the effects of the immune response during the MSCs-based virotherapy. We further employed it to explore the conceptual clinical feasibility, particularly, in evaluating the relative significance of potential immune promotive/suppressive mechanisms induced by MSCs loaded with oncolytic viruses. We were able to delineate conditions which may significantly contribute to the success or failure of MSC-based virotherapy as well as generate new hypotheses. In fact, one of the most impactful outcomes shown by this investigation, not inferred from the experiments alone, was the initially counter-intuitive fact that using tumor-promoting MSCs as carriers is not only helpful but necessary in achieving tumor control. Considering the fact that it is still currently a controversial debate whether MSCs exert a pro- or anti-tumor action, mathematical models such as this one help to quantitatively predict the consequences of using MSCs for delivering virotherapeutic agents in vivo. Taken together, our results show that MSC-mediated systemic delivery of oncolytic viruses is a promising strategy for achieving synergistic anti-tumor efficacy with improved safety profiles.

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Bone Regeneration, Reconstruction and Use of Osteogenic Cells; from Basic Knowledge, Animal Models to Clinical Trials.

Hutchings G[1,2], Moncrieff L[1,3], Dompe C[1,3], Janowicz K[1,2], Sibiak R[4], Bryja A[2], Jankowski M[2], Mozdziak P[5], Bukowska D[6], Antosik P[7], Shibli JA[8], Dyszkiewicz-Konwińska M[2,9], Bruska M[2], Kempisty B[2,3,10], Piotrowska-Kempisty H[11].

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Abstract

The deterioration of the human skeleton's capacity for self-renewal occurs naturally with age. Osteoporosis affects millions worldwide, with current treatments including pharmaceutical agents that target bone formation and/or resorption. Nevertheless, these clinical approaches often result in long-term side effects, with better alternatives being constantly researched. Mesenchymal stem cells (MSCs) derived from bone marrow and adipose tissue are known to hold therapeutic value for the treatment of a variety of bone diseases. The following review summarizes the latest studies and clinical trials related to the use of MSCs, both individually and combined with other methods, in the treatment of a variety of conditions related to skeletal health. For example, some of the most recent works noted the advantage of bone grafts based on biomimetic scaffolds combined with MSC and growth factor delivery, with a greatly increased regeneration rate and minimized side effects for patients. This review also highlights the continuing research into the mechanisms underlying bone homeostasis, including the key transcription factors and signalling pathways responsible for regulating the differentiation of osteoblast lineage. Paracrine factors and specific miRNAs are also believed to play a part in MSC differentiation.

Furthering the understanding of the specific mechanisms of cellular signalling in skeletal remodelling is key to incorporating new and effective treatment methods for bone disease.

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Acquisition of stem associated-features on metastatic osteosarcoma cells and their functional effects on mesenchymal stem cells.

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Abstract

BACKGROUND:

Osteosarcoma (OS) is the most frequent malignant bone tumor, affecting predominantly children and young adults. Metastases are a major clinical challenge in OS. In this context, 20% of OS patients are diagnosed with metastatic OS, but near 80% of all OS patients could present non-detectable micrometastasis at the moment of diagnosis.

METHODS:

Osteogenic differentiation; doxorubicin exclusion assay; fluorescence microscopy; RT-qPCR; proteomic analysis.

RESULTS:

Our results suggest that metastatic OS cells posses a diminished osteoblastic differentiation potential with a gain of metastatic traits like the capacity to modify intracellular localization of chemodrugs and higher levels of expression of stemness-related genes. On the opposite hand, non-metastatic OS cells possess bone-associated traits like higher osteoblastic differentiation and also an osteoblastic-inducer secretome. OS cells also differ in the nature of their interaction with mesenchymal stem cells (MSCs), with opposites impacts on MSCs phenotype and behavior.

CONCLUSIONS:

All this suggests that a major trait acquired by metastatic cells is a switch into a stem-like state that could favor its survival in the pulmonary niche, opening new possibilities for personalized chemotherapeutic schemes.

GENERAL SIGNIFICANCE:

Our work provides new insights regarding differences among metastatic and non-metastatic OS cells, with particular emphasis on differentiation potential, multidrug resistance and interaction with MSCs.

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Senescent mesenchymal stem cells remodel extracellular matrix driving breast cancer cells to a more-invasive phenotype.

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Abstract

Mesenchymal stem cells (MSCs) are essential for the regenerative process; however, biological aging and environmental stress can induce senescence - an irreversible state of growth arrest - that not only affects the behavior of cells but also disrupts their ability to restore tissue integrity. While abnormal tissue properties, including increased extracellular matrix stiffness, are linked with the risk of developing breast cancer, the role and contribution of senescent MSCs to the disease progression to malignancy are not well understood. Here, we investigated senescence-associated biophysical changes in MSCs and how this influences cancer cell behavior in a 3D matrix interface model. Although senescent MSCs were far less motile than pre-senescent MSCs, they induced an invasive breast cancer phenotype, characterized by increased spheroid growth and cell invasion in collagen gels. Further analysis of collagen gels using second-harmonic generation showed increased collagen density when senescent MSCs were present, suggesting that senescent MSCs actively remodel the surrounding matrix. This study provides direct evidence of the pro-malignant effects of senescent MSCs in tumors.

Ann Transl Med. 2019 Nov;7(22):693. doi: 10.21037/atm.2019.11.66.

The potential roles of stem cell-derived extracellular vesicles as a therapeutic tool.

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Abstract

Extracellular vesicles (EVs) of mesenchymal stem cells (MSCs) are secreted by live cells and possess the same regenerative potential and immunomodulatory ability as their parental cells. Clinical applications of MSC-EVs could overcome the shortage of MSCs for treatment of cancer and other diseases and impact the field of regenerative medicine from cellular to acellular therapy. For use of MSC-EVs as a clinical agent, various engineered EVs have been manufactured and their therapeutic effects on various diseases demonstrated in preclinical studies and clinical trials. However, MSC-EVs are heterogeneous, and many of their characteristics are still unknown. Many barriers still need to be surmounted before MSC-EVs can be used as biomedical agents.

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Endothelial cells support osteogenesis in an in vitro vascularized bone model developed by 3D bioprinting.

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Abstract

Bone is a highly vascularized tissue, in which vascularization and mineralization are concurrent processes during skeletal development. Indeed, both components should be included in any reliable and adherent in vitro model platform for the study of bone physiology and pathogenesis of skeletal disorders. To this end, we developed an in vitro vascularized bone model, using a gelatin-nanohydroxyapatite (gel-nHA) 3D bioprinted scaffold. First, we seeded human mesenchymal stem cells (hMSCs) on the scaffold which underwent osteogenic differentiation for two weeks. Then, we included lentiviral-GFP transfected human umbilical vein endothelial cells (HUVECs) within the 3D bioprinted scaffold macropores to form a capillary-like network during two more weeks of culture. We tested three experimental conditions: Condition 1, bone constructs with HUVECs cultured in 1:1 osteogenic medium (OM):endothelial medium (EM); Condition 2, bone constructs without HUVECs cultured in 1:1 OM:EM; Condition 3: bone construct with HUVECs cultured in 1:1 growth medium:EM. All samples resulted in engineered bone matrix. In Conditions 1 and 3, HUVECs formed tubular structures within the bone constructs, with the assembly of a complex capillary-like network visible by fluorescence microscopy in the live tissue and histology. CD31 immunostaining confirmed significant vascular lumen formation. Quantitative real-time PCR was used to quantify osteogenic differentiation and endothelial response. Alkaline phosphatase and runt-related transcription factor 2 upregulation confirmed early osteogenic commitment of hMSCs. Even when OM was removed under Condition 3, we observed clear osteogenesis, which was notably accompanied by upregulation of osteopontin, vascular endothelial growth factor, and collagen type I. These findings indicate that we have successfully realized a bone model with robust vascularization in just four weeks of culture and we highlighted how the inclusion of endothelial cells more realistically supports osteogenesis. The approach reported here resulted in a biologically inspired in vitro model of bone vascularization, simulating de novo morphogenesis of capillary vessels occurring during tissue development.