Expert Opin Ther Pat. 2018 Sep 24:1-9. doi: 10.1080/13543776.2018.1528234. [Epub ahead of print]

Novel platinum agents and mesenchymal stromal cells for thoracic malignancies: state of the art and future perspectives.

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Author information

Abstract

Non-small cell lung cancer and malignant pleural mesothelioma represent two of the most intriguing and scrutinized thoracic malignancies, presenting interesting perspectives of experimental development and clinical applications. Areas covered: In advanced non-small cell lung cancer, molecular targeted therapy is the standard first-line treatment for patients with identified driver mutations; on the other hand, chemotherapy is the standard treatment for patients without EGFR mutations or ALK rearrangement or those with unknown mutation status. Once considered an ineffective therapy in pulmonary neoplasms, immunotherapy has been now established as one of the most promising therapeutic options. Mesenchymal stromal cells are able to migrate specifically toward solid neoplasms and their metastatic localizations when injected intravenously. This peculiar cancer tropism has opened up an emerging field to use them as vectors to deliver antineoplastic drugs for targeted therapies. Expert opinion: Molecular targeted therapy and immunotherapy are the new alternatives to standard chemotherapy. Mesenchymal stromal cells are a new promising tool in oncology and-although not yet utilized in the clinical practice, we think they will represent another main tool for cancer therapy and will probably play a leading role in the field of nanovectors and molecular

NPJ Regen Med. 2018 Sep 17;3:15. doi: 10.1038/s41536-018-0041-8. eCollection 2018.

Effectiveness of mesenchymal stem cells for treating patients with knee osteoarthritis: a meta-analysis toward the establishment of effective regenerative rehabilitation.

Iijima H[#1,2,3], Isho T[#2,4], Kuroki H[2], Takahashi M[1], Aoyama T[2].
Author information

Abstract

This systematic review with a meta-analysis aimed to summarize the current evidence of the effectiveness of mesenchymal stem cell (MSC) treatment for knee osteoarthritis (OA) and to examine whether rehabilitation is an effect modifier of the effect estimate of MSC treatment. A literature search yielded 659 studies, of which 35 studies met the inclusion criteria ($n = 2385$ patients; mean age: 36.0-74.5 years). The meta-analysis results suggested that MSC treatment through intra-articular injection or arthroscopic implantation significantly improved knee pain (standardized mean difference [SMD]: -1.45, 95% confidence interval [CI]: -1.94, -0.96), self-reported physical function (SMD: 1.50, 95% CI: 1.09, 1.92), and cartilage quality (SMD: -1.99; 95% CI: -3.51, -0.47). However, the MSC treatment efficacy on

cartilage volume was limited (SMD: 0.49; 95% CI: -0.19, 1.16). Minor adverse events (knee pain or swelling) were reported with a wide-ranging prevalence of 2-60%; however, no severe adverse events occurred. The evidence for these outcomes was "very low" to "low" according to the Grades of Recommendation, Assessment, Development and Evaluation system because of the poor study design, high risk of bias, large heterogeneity, and wide 95% CI of the effects estimate. Performing rehabilitation was significantly associated with better SMD for self-reported physical function (regression coefficient: 0.881, 95% CI: 0.049, 1.712; $P = 0.039$). We suggest that more high quality randomized controlled trials with consideration of the potential rehabilitation-driven clinical benefit would be needed to facilitate the foundation of effective MSC treatment and regenerative rehabilitation for patients with knee OA.

Biomaterials. 2018 Sep 18;185:194-204. doi: 10.1016/j.biomaterials.2018.09.027. [Epub ahead of print]

Improved in situ seeding of 3D printed scaffolds using cell-releasing hydrogels.

Whitely M[1], Cereceres S[2], Dhavalikar P[3], Salhadar K[4], Wilems T[5], Smith B[6], Mikos A[7], Cosgriff-Hernandez E[8].
Author information

Abstract

The design of tissue engineered scaffolds based on polymerized high internal phase emulsions (polyHIPEs) has emerged as a promising bone grafting strategy. We previously reported the ability to 3D print emulsion inks to better mimic the structure and mechanical properties of native bone while precisely matching defect geometry. In the current study, redox-initiated hydrogel carriers were investigated for in situ delivery of human mesenchymal stem cells (hMSCs) utilizing the biodegradable macromer, poly(ethylene glycol)-dithiothreitol. Hydrogel carrier properties including network formation time, sol-gel fraction, and swelling ratio were modulated to achieve rapid cure without external stimuli and a target cell-release period of 5-7 days. These in situ carriers enabled improved distribution of hMSCs in 3D printed polyHIPE grafts over standard suspension seeding. Additionally, carrier-loaded polyHIPEs supported sustained cell viability and osteogenic differentiation of hMSCs post-release. In summary, these findings demonstrate the potential of this in situ curing hydrogel carrier to enhance the cell distribution and retention of hMSCs in bone grafts. Although initially focused on improving bone regeneration, the ability to encapsulate cells in a hydrogel carrier without relying on external stimuli that can be attenuated in large grafts or tissues is expected to have a wide range of applications in tissue engineering.

Biomaterials. 2018 Sep 13;185:155-173. doi: 10.1016/j.biomaterials.2018.09.007. [Epub ahead of print]

Bioinstructive microparticles for self-assembly of mesenchymal stem Cell-3D tumor spheroids.

Ferreira LP[1], Gaspar VM[2], Mano JF[3].
Author information

Abstract

3D multicellular tumor spheroids (3D-MCTS) that closely mimic in vitro the complex lung tumor microenvironment (TME) are highly desirable for screening innovative anti-cancer therapeutics. Despite significant improvements in mimicking lung TME, few models have combined tumor-infiltrating mesenchymal stem cells from bone marrow (hBM-MSCs) with heterotypic 3D tumor spheroid models containing ECM mimetic components. Herein, we engineered hybrid 3D-MCTS that combine, for the first time, A549:fibroblasts:hBM-MSCs in heterotypic tri-culture, with bioinstructive hyaluronan microparticles that act as tumor-ECM mimetics and as cell-anchoring hotspots. The obtained results indicated that 3D microspheres provided proper support for cells to self-assemble into compact 3D microtissues and promoted an increase in CD44 expression, emulating the presence of native-ECM hyaluronan. 3D-MCTS size and sphere-like morphology was reproducible and tri-culture models presented the characteristic solid tumors necrotic core. Mesenchymal stem cells tracking demonstrated that hBM-MSCs migrate to different regions in 3D microtumors mass exhibiting dynamic interactions with cancer cells and stromal fibroblasts, alike in human tumors. Importantly, doxorubicin administration revealed hBM-MSCs effect on cytotoxic responses in 3D tri-culture models and in dual cultures of hBM-MSCs:A549 at 10:1 ratio. Such findings evidence the relevance of including hBM-MSCs in combination with cancer-stromal fibroblasts in 3D in vitro tumor models and the importance to test different cell-to-cell ratios to mimic tumor heterogeneity. In addition, bioinstructive hyaluronan-microparticles were also effective as cell-agglomerating scaffolds and showed potential to be used as an enabling technology for including different ECM components in 3D in vitro models in the future.

Onco Targets Ther. 2018 Sep 12;11:5753-5762. doi: 10.2147/OTT.S173110. eCollection 2018.

Targeted cancer therapy using engineered exosome as a natural drug delivery vehicle.

Gomari H[1], Forouzandeh Moghadam M[1], Soleimani M[2].
Author information

Abstract

PURPOSE:

Exosomes are small 30-100 nm vesicles secreted by various cell types. They are released by most cell types, indicating their important role in physiological and pathological processes, including signaling pathways, cell-to-cell communication, tumor progression, and molecule transferring. As natural nanovesicles, exosomes can be a good candidate for drug delivery due to low immunogenicity and ability to enter tissues and even cross the blood-brain barrier. In an effort to improve the efficiency of exosomes for targeted drug delivery with minimal effect on normal cells, we expressed ligands against HER2+ cells.

METHODS:

To purify exosomes, transduced mesenchymal stromal cells were cultured to reach 80% confluency. Next, the cells were cultured in serum-free media for 48 hours and the supernatant was harvested to purify exosomes. These exosomes were then labeled with PKH67 and added to BT-474, SKBR3 (HER2+), and MDA-MB231 (HER2-), cell lines and their binding to HER2+ was evaluated by flow

cytometry. Exosomes were loaded with doxorubicin and quantified using intrinsic fluorescence of doxorubicin at 594 nm.

RESULTS:

Targeted exosomes were preferably uptaken by HER2+ cells. Therefore, untargeted exosomes showed lower binding to HER2+ cells compared to their targeted counterparts. MTT assay was performed to analyze cytotoxic effect of exo-DOX (exosome encapsulated with doxorubicin). Efficiency of exo-DOX and free DOX (doxorubicin) delivery with different concentrations, to the BT-474 cell line, was compared, and no significant difference was observed.

CONCLUSION:

Our results imply that targeted exosomes are preferentially uptaken by HER2+ cells relative to HER2- cells and have the potential to be used as an efficient drug delivery system.

Cells Tissues Organs. 2018 Sep 26:1-9. doi: 10.1159/000493210. [Epub ahead of print]

Peripheral Blood Mesenchymal Stem Cells Combined with Modified Demineralized Bone Matrix Promote Pig Cartilage Defect Repair.

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Author information

Abstract

OBJECTIVE:

To investigate the mobilization of peripheral blood mesenchymal stem cells (PBMSCs) and whether a combination of PBMSCs and modified demineralized bone matrix (DBM) promoted the repair of cartilage lesions in a pig model.

METHODS:

Pig PBMSCs were mobilized by the combined administration of granulocyte colony-stimulating factor (G-CSF) and the CXCR4 antagonist AMD3100. Colony formation was detected by the fibroblast colony-forming unit (CFU-F) count and the percentage of the CD45-CD90+ cell population by flow cytometry. The mobilized cells were identified as MSCs by their morphological characteristics, surface markers, and differentiation potentials. The composite scaffolds carrying BMP-2 and TGF-β3 chitosan sustained-release microspheres/DBM were prepared by emulsion cross-linking and the Urist method, and scanning electron microscopy (SEM) observation was performed. The model of pig cartilage defect was prepared, and gross observation, histological examination, immunohistochemistry, and O'Driscoll scoring were performed 4, 8, and 12 weeks postoperation.

RESULTS:

After mobilization, the number of CFU-Fs in the peripheral blood in the experimental group (G-CSF + AMD3100) was significantly increased compared with the control group ($p < 0.05$). The proportion and total number of CD45-CD90+ cells were increased ($p < 0.05$). The mobilized stem cells had MSC

characteristics. SEM of the new tissue-engineered cartilage showed that PBMSCs were evenly grown on the surface of the scaffold and microsphere morphology had no obvious change. Gross observation, histological examination, immunohistochemistry, and O'Driscoll score were better in the experimental group than in the other groups ($p < 0.05$).

CONCLUSION:

G-CSF + AMD3100 is an effective mobilization agent for PBMSCs. The new tissue-engineering cartilage constructed by two-factor sustained-release microspheres/DBM composite PBMSCs effected good repair of the cartilage defect in pigs.

Onco Targets Ther. 2018 Sep 12;11:5753-5762. doi: 10.2147/OTT.S173110. eCollection 2018.

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CONCLUSION:

Our results imply that targeted exosomes are preferentially uptaken by HER2+ cells relative to HER2- cells and have the potential to be used as an efficient drug delivery system

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Cell-Based Therapies: The Nonresponder.

Caplan AI[1].
Author information

Abstract

Cell-based therapies have come of age and several phase III trials are now being conducted. Cell-based therapies, especially involving mesenchymal stem cells (MSCs), have substantial nonresponder rates as have been reported in some current clinical trials. This high rate is expected as the MSCs are neither tuned for each of the diseases that are being treated nor for the huge variance in the genetics and response characteristics of the individual patients being treated. Such nonresponders might be used as a control group, and thus eliminating the need for placebo controls. Stem Cells Translational Medicine 2018.