ML 13-18 (05/04/2018)

Mol Cancer Ther. 2018 Mar 28. pii: molcanther.0682.2017. doi: 10.1158/1535-7163.MCT-17-0682. [Epub ahead of print]

Nano-engineered mesenchymal stem cells increase therapeutic efficacy of anticancer drug through true active tumor targeting.

Layek B[1], Sadhukha T[2], Panyam J[2], Prabha S[3].
Author information

Abstract

Tumor-targeted drug delivery has the potential to improve therapeutic efficacy and mitigate non-specific toxicity of anticancer drugs. However, current drug delivery approaches rely on inefficient passive accumulation of the drug carrier in the tumor. We have developed a unique, truly active tumor targeting strategy that relies on engineering mesenchymal stem cells (MSCs) with drug-loaded nanoparticles. Our studies using the A549 orthotopic lung tumor model show that nano-engineered MSCs carrying the anticancer drug paclitaxel (PTX) home to tumors and create cellular drug depots that release the drug payload over several days. Despite significantly lower doses of PTX, nano-engineered MSCs resulted in significant inhibition of tumor growth and superior survival. Anticancer efficacy of nano-engineered MSCs was confirmed in immunocompetent C57BL/6 albino female mice bearing orthotopic Lewis Lung Carcinoma (LL/2-luc) tumors. Further, at doses that resulted in equivalent therapeutic efficacy, nano-engineered MSCs had no effect on white blood cell count whereas PTX solution and PTX nanoparticle treatments caused leukopenia. Biodistribution studies showed that nano-engineered MSCs resulted in greater than 9-fold higher AUClung of PTX (1.5 µg.day/g) than PTX solution and nanoparticles (0.2 and 0.1 µg.day/g tissue, respectively) in the target lung tumors. Furthermore, the lung-to-liver and the lung-to-spleen ratios of PTX were several folds higher for nano-engineered MSCs relative to those for PTX solution and nanoparticle groups, suggesting that nano-engineered MSCs demonstrate significantly less off-target deposition. In summary, our results demonstrate that nano-engineered MSCs can serve as an efficient carrier for tumor specific drug delivery and significantly improved anti-cancer efficacy of conventional chemotherapeutic drugs.

Stem Cells. 2018 Mar 31. doi: 10.1002/stem.2829. [Epub ahead of print]

MSC Cross-Talk with Cancer Cells Provides Therapeutic Potential.

Melzer C[1], von der Ohe J[1], Hass R[1].
Author information

Abstract

Various direct and indirect cellular interactions between multi-functional mesenchymal stroma/stem-like cells (MSC) and cancer cells contribute to increasing plasticity within the tumor tissue and its microenvironment. Direct and tight communication between MSC and cancer cells is based on

membrane protein interactions and the exchange of large plasma membrane fragments also known as trogocytosis. An ultimate but rare direct interaction resumes in fusion of these two cellular partners resulting in the formation of new cancer hybrid cell populations. Alternatively, indirect interactions are displayed by the release of membranous vesicle-encapsulated miRNAs and proteins or soluble components such as molecular growth factors, hormones, chemo-/cytokines and metabolites. Released single molecules as well as multivesicular bodies including exosomes and microvesicles can form local concentration gradients within the tumor microenvironment and are incorporated not only by adjacent neighboring cells but also affect distant target cells. The present review will focus on vesicle-mediated indirect communication and on cancer cell fusion with direct contact between MSC and cancer cells.These different types of interaction are accompanied by functional interference and mutual acquisition of new cellular properties. Consequently, alterations in cancer cell functionalities paralleled by the capability to re-organize the tumor stroma can trigger changes in metastatic behavior and promote retrodifferentiation to develop new cancer stem-like cells. However, exosomes and microvesicles acting over long distances may also provide a tool with therapeutic potential when loaded with anti-tumor cargo.

Biomaterials. 2017 Nov 21. pii: S0142-9612(17)30755-X. doi: 10.1016/j.biomaterials.2017.11.023. [Epub ahead of print]

Strategies for MSC expansion and MSC-based microtissue for bone regeneration.

Bunpetch V[1], Zhang ZY[2], Zhang X[1], Han S[1], Zongyou P[1], Wu H[1], Hongwei O[3].
Author information

Abstract

Mesenchymal stem cells (MSCs) have gained increasing attention as a potential approach for the treatment of bone injuries due to their multi-lineage differentiation potential and also their ability to recognize and home to damaged tissue sites, secreting bioactive factors that can modulate the immune system and enhance tissue repair. However, a wide gap between the number of MSCs obtainable from the donor site and the number required for implantation, as well as the lack of understanding of MSC functions under different in vitro and in vivo microenvironment, hinders the progression of MSCs toward clinical settings. The clinical translation of MSCs pre-requisites a scalable expansion process for the biomanufacturing of therapeutically qualified cells. This review briefly introduces the features of implanted MSCs to determine the best strategies to optimize their regenerative capacity, as well as the current MSC implantation for bone diseases. Current achievements for expansion of MSCs using various culturing methods, bioreactor technologies, biomaterial platforms, as well as microtissue-based expansion strategies are also discussed, providing new insights into future large-scale MSC expansion and clinical applications.

Bull Math Biol. 2018 Mar 29. doi: 10.1007/s11538-018-0416-4. [Epub ahead of print]

Size Matters: Metastatic Cluster Size and Stromal Recruitment in the Establishment of Successful Prostate Cancer to Bone Metastases.

Araujo A[1], Cook LM[2], Lynch CC[2], Basanta D[3].
Author information

Abstract

Prostate cancer (PCa) impacts over 180,000 men every year in the USA alone, with 26,000 patients expected to succumb to the disease (cancer.gov). The primary cause of death is metastasis, with secondary lesions most commonly occurring in the skeleton. Prostate cancer to bone metastasis is an important, yet poorly understood, process that is difficult to explore with experimental techniques alone. To this end we have utilized a hybrid (discrete-continuum) cellular automaton model of normal bone matrix homeostasis that allowed us to investigate how metastatic PCa can disrupt the bone microenvironment. Our previously published results showed that PCa cells can recruit mesenchymal stem cells (MSCs) that give rise to bone-building osteoblasts. MSCs are also thought to be complicit in the establishment of successful bone metastases (Lu, in Mol Cancer Res 4(4):221-233, 2006). Here we have explored the aspects of early metastatic colonization and shown that the size of PCa clusters needs to be within a specific range to become successfully established: sufficiently large to maximize success, but not too large to risk failure through competition among cancer and stromal cells for scarce resources. Furthermore, we show that MSC recruitment can promote the establishment of a metastasis and compensate for relatively low numbers of PCa cells seeding the bone microenvironment. Combined, our results highlight the utility of biologically driven computational models that capture the complex and dynamic dialogue between cells during the initiation of active metastases.

Biomed Rep. 2018 Mar;8(3):207-214. doi: 10.3892/br.2018.1054. Epub 2018 Jan 31.

Exosomes as a novel pathway for regulating development and diseases of the skin.

Liu Y[1], Wang H[1], Wang J[2].
Author information

Abstract

Exosomes are one of the most potent intercellular communicators, which are able to communicate with adjacent or distant cells. Exosomes deliver various bioactive molecules, including membrane receptors, proteins, mRNA and microRNA, to target cells and serve roles. Recent studies have demonstrated that exosomes may regulate the functions and diseases of the skin, which is the largest organ of the human body. The abnormal functions of the skin lead to the progression of scleroderma, melanoma, baldness and other diseases. A previous study has demonstrated that epithelial progenitor cells are rich in several subunits of exosomes that may maintain the proliferative capacity of these epithelial progenitor cells, which is essential for the development of the epidermis. Exosomes derived from human adipose mesenchymal stem cells accelerate skin wound healing by optimizing fibroblast properties; this is beneficial for the recovery of postoperative and other wounds. Exosomes derived from adipocytes

promote melanoma migration and invasion through fatty acid oxidation; therefore, in the clinic, it may be possible to improve the prognosis of patients with melanoma by reducing their body fat content. Exosomes derived from keratinocytes modulate melanocyte pigmentation, which has been utilized as a novel mechanism for the regulation of pigmentation in conditions including Moynahan syndrome and albinism. Meanwhile, scleroderma patients with vascular abnormalities may experience decreased serum exosome levels; it may therefore be possible to detect the exosome content in sera in order to diagnose and treat scleroderma. In addition, the use of exosomes has been suggested to promote or enhance hair growth, which has been demonstrated to be highly effective. These studies have provided new opportunities and therapeutic strategies for understanding how exosomes regulate intercellular communication in pathological processes of the skin.

Biomaterials. 2018 Mar 19. pii: S0142-9612(18)30205-9. doi: 10.1016/j.biomaterials.2018.03.033. [Epub ahead of print]

Feasibility and safety of treating non-unions in tibia, femur and humerus with autologous, expanded, bone marrow-derived mesenchymal stromal cells associated with biphasic calcium phosphate biomaterials in a multicentric, non-comparative trial.

Gómez-Barrena E[1], Rosset P[2], Gebhard F[3], Hernigou P[4], Baldini N[5], Rouard H[6], Sensebé L[7], Gonzalo-Daganzo RM[8], Giordano R[9], Padilla-Eguiluz N[10], García-Rey E[10], Cordero-Ampuero J[10], Rubio-Suárez JC[10], Stanovici J[2], Ehrnthaller C[3], Huber-Lang M[3], Flouzat-Lachaniette CH[4], Chevallier N[6], Donati DM[5], Ciapetti G[5], Fleury S[7], Fernandez MN[8], Cabrera JR[8], Avendaño-Solá C[8], Montemurro T[9], Panaitescu C[11], Veronesi E[12], Rojewski MT[13], Lotfi R[13], Dominici M[12], Schrezenmeier H[13], Layrolle P[14].

Author information

Abstract

BACKGROUND:

ORTHO-1 is a European, multicentric, first in human clinical trial to prove safety and feasibility after surgical implantation of commercially available biphasic calcium phosphate bioceramic granules associated during surgery with autologous mesenchymal stromal cells expanded from bone marrow (BM-hMSC) under good manufacturing practices, in patients with long bone pseudarthrosis.

METHODS:

Twenty-eight patients with femur, tibia or humerus diaphyseal or metaphyso-diaphyseal non-unions were recruited and surgically treated in France, Germany, Italy and Spain with 100 or 200 million BM-hMSC/mL associated with 5-10 cc of bioceramic granules. Patients were followed up during one year. The investigational advanced therapy medicinal product (ATMP) was expanded under the same protocol in all four countries, and approved by each National Competent Authority.

FINDINGS:

With safety as primary end-point, no severe adverse event was reported as related to the BM-hMSC. With feasibility as secondary end-point, the participating production centres manufactured the BM-hMSC as planned. The ATMP combined to the bioceramic was surgically delivered to the non-unions, and 26/28 treated patients were found radiologically healed at one year (3 out of 4 cortices with bone bridging).

INTERPRETATION:

Safety and feasibility were clinically proven for surgical implantation of expanded autologous BM-hMSC with bioceramic.

FUNDING:

EU-FP7-HEALTH-2009, REBORNE Project (GA: 241876).

Int J Nanomedicine. 2018 Mar 19;13:1653-1664. doi: 10.2147/IJN.S159404. eCollection 2018.

Imaging of extracellular vesicles derived from human bone marrow mesenchymal stem cells using fluorescent and magnetic labels.

Dabrowska S[1], Del Fattore A[2], Karnas E[3,4], Frontczak-Baniewicz M[5], Kozlowska H[6], Muraca M[7], Janowski M[1,8], Lukomska B[1].

Author information

Abstract

BACKGROUND:

Mesenchymal stem cells have been shown therapeutic in various neurological disorders. Recent studies support the notion that the predominant mechanism by which MSCs act is through the release of extracellular vesicles (EVs). EVs seem to have similar therapeutic activity as their cellular counterparts and may represent an interesting alternative standalone therapy for various diseases. The aim of the study was to optimize the method of EV imaging to better understand therapeutic effects mediated by EVs.

METHODS:

The fluorescent lipophilic stain PKH26 and superparamagnetic iron oxide nanoparticles conjugated with rhodamine (Molday ION Rhodamine B™) were used for the labeling of vesicles in human bone marrow MSCs (hBM-MSCs). The entire cycle from intracellular vesicles to EVs followed by their uptake by hBM-MSCs has been studied. The identity of vesicles has been proven by antibodies against: anti-CD9, -CD63, and -CD81 (tetraspanins). NanoSight particle tracking analysis (NTA), high-resolution flow cytometric analysis, transmission electron microscopy (TEM), ELYRA PS.1 super-resolution microscopy, and magnetic resonance imaging (MRI) were used for the characterization of vesicles.

RESULTS:

The PKH26 and Molday ION were exclusively localized in intracellular vesicles positively stained for EV markers: CD9, CD63, and CD81. The isolated EVs represent heterogeneous population of various sizes as confirmed by NTA. The TEM and MRI were capable to show successful labeling of EVs using ION. Co-culture of EVs with hBM-MSCs revealed their uptake by cells in vitro, as visualized by the co-localization of PKH26 or Molday ION with tetraspanins inside hBM-MSCs.

CONCLUSION:

PKH26 and Molday ION seem to be biocompatible with EVs, and the labeling did not interfere with the capability of EVs to re-enter hBM-MSCs during co-culture in vitro. Magnetic properties of IONs provide an additional advantage for the imaging of EV using TEM and MRI.

Osteoarthritis Cartilage. 2018 Mar 23. pii: S1063-4584(18)31127-0. doi: 10.1016/j.joca.2018.03.006. [Epub ahead of print]

Sheep as a model for evaluating mesenchymal stem/stromal cell (MSC)-based chondral defect repair.

Music E[1], Futrega K[2], Doran MR[3].
Author information

Abstract

Osteoarthritis results from the degradation of articular cartilage and is one of the leading global causes of pain and immobility. Cartilage has a limited capacity for self-repair. While repair can be enhanced through surgical intervention, current methods often generate inferior fibrocartilage and repair is transient. The development of tissue engineering strategies to improve repair outcomes is an active area of research. While small animal models such as rodents and rabbits are often used in early pre-clinical work, larger animals that better recapitulate the anatomy and loading of the human joint are required for late-stage preclinical evaluation. Because of their physiological similarities to humans, and low cost relative to other large animals, sheep are routinely used in orthopedic research, including cartilage repair studies. In recent years, there has been considerable research investment into the development of cartilage repair strategies that utilize mesenchymal stem/stromal cells (MSC). In contrast to autologous chondrocytes derived from biopsies of articular cartilage, MSC offer some benefits including greater expansion capacity and elimination of the risk of morbidity at the cartilage biopsy site. The disadvantages of MSC are related to the challenges of inducing and maintaining a stable chondrocyte-like cell population capable of generating hyaline cartilage. Ovine MSC (oMSC) biology and their utility in sheep cartilage repair models have not been reviewed. Herein, we review the biological properties of MSC derived from sheep tissues, and the use of these cells to study articular cartilage repair in this large animal model