Biomed Pharmacother. 2018 Sep 12;108:111-118. doi: 10.1016/j.biopha.2018.09.040. [Epub ahead of print]

Uptake-release by MSCs of a cationic platinum(II) complex active in vitro on human malignant cancer cell lines.

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Author information

Abstract

In this study, the in vitro stability of cisplatin (CisPt) and cationic platinum(II)-complex (caPt(II)-complex) and their in vitro activity (antiproliferative and anti-angiogenic properties) were investigated against three aggressive human tumor cell lines. caPt(II)-complex shown a high stability until 9 days of treatment and displayed a significant and higher activity than CisPt against both NCI-H28 mesothelioma (19.37 ± 9.57 μM versus 34.66 ± 7.65 μM for CisPt) and U87 MG glioblastoma (19.85 ± 0.97 μM versus 54.14 ± 3.19 for CisPt). Mesenchymal Stromal Cells (AT-MSCs) showed a significant different sensitivity (IC_{50} = 71.9 ± 15.1 μM for caPt(II)-complex and 8.7 ± 4.5 μM for CisPt) to the antiproliferative activity of caPt(II)-complex and CisPt. The ability of MSCs to uptake both the drugs in a similar amount of 2.49 pM /cell, suggested a possible development of new therapies based on cell mediated drug delivery.

Cancer Res Treat. 2018 Sep 14. doi: 10.4143/crt.2018.364. [Epub ahead of print]

A Potential Therapy Using Engineered Stem Cells Prevented Malignant Melanoma in Cellular and Xenograft Mouse Models.

Heo JR[1], Hwang KA[1], Kim SU[2], Choi KC[1,3].

Author information

Abstract

PURPOSE:

In the present study, human neural stem cells (hNSCs) with tumor-tropic behavior were used as drug delivery vehicle to selectively target melanoma. A human neural stem cell line (HB1.F3) was transduced into two types: one expressed only the cytosine deaminase (CD) gene (HB1.F3.CD) and the other expressed both CD and human interferon-β (IFN-β) genes (HB1.F3.CD.IFN-β).

MATERIALS AND METHODS:

This study verified the tumor-tropic migratory competence of engineered hNSCs on melanoma (A375SM) using a modified Boyden chamber assay in vitro and CM-DiI staining in vivo. The antitumor effect of HB1.F3.CD and HB1.F3.CD.IFN-β on melanoma was also confirmed using an MTT assay in vitro and xenograft mouse models.

RESULTS:

A secreted form of interferon-β from the HB1.F3.CD.IFN-β cells modified the epithelial-mesenchymal transition (EMT) process and metastasis of melanoma. 5-fluorouracil (5-FU) treatment also accelerated

the expression of the pro-apoptotic protein BAX and decelerated the expression of the anti-apoptotic protein Bcl-xL on melanoma cell line.

CONCLUSION:

Our results illustrate that engineered hNSCs prevented malignant melanoma cells from proliferating in the presence of the prodrug, and the form that secreted interferon-β intervened in the EMT process and melanoma metastasis. Hence, neural stem cell-directed enzyme/prodrug therapy is a plausible treatment for malignant melanoma.

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Am J Cancer Res. 2018 Aug 1;8(8):1332-1342. eCollection 2018.

Engineering exosomes: a new direction for anticancer treatment.

You B[1], Xu W[1], Zhang B[2].

Author information

Abstract

Currently, lacks of specificity and effectiveness remain the main drawbacks of clinical cancer treatment. Despite therapeutic advances in recent decades, clinical outcomes remain poor. Exosomes are nanosized particles with great potential for enhancing anticancer responses and targeted drug delivery. Exosomes modified through genetic or nongenetic methods can augment the cytotoxicity and targeting ability of therapeutic agents, thus improving their efficacy in killing cancer cells. In this review, we summarize recent research on engineering exosomes-based cancer therapy and discuss exosomes derived from tumors, mesenchymal stem cells, dendritic cells, HEK293T cells, macrophages, milk, and other donor cells. The antitumor effects of engineered-exosomes are highlighted and the potential adverse effects are considered. A comprehensive understanding of exosomes modification may provide a novel strategy for cancer therapy.

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J Cancer. 2018 Aug 6;9(17):3129-3137. doi: 10.7150/jca.25376. eCollection 2018.

Mesenchymal Stem Cell Derived Exosomes in Cancer Progression, Metastasis and Drug Delivery: A Comprehensive Review.

Zhou J[1], Tan X[2], Tan Y[1], Li Q[1], Ma J[1], Wang G[3].

Author information

Abstract

With the development of cancer treatments, it has become a popular research focus that mesenchymal stem (or stromal) cells (MSCs) have the functional mechanisms that influence cancer progression. One of the underestimated mechanisms is secretion of highly specialized double-membrane structures called exosomes. Mesenchymal stem cells generate several exosomes that may act as paracrine mediators by exchanging genetic information. MSC-derived exosomes are microvesicles ranging from approximately 60-200 nm in size and detected in various body fluids. It has been demonstrated that MSC-derived exosomes are involved in tumor growth, angiogenesis, metastasis, and invasion.

Furthermore, emerging evidence suggests that as natural nanocarriers, MSC-exosomes are responsible for multidrug resistance mechanisms, reverse effect of radiation injury, and immune regulation, which can be used in clinical applications for cancer therapy. The present review aims to briefly describe the properties and biological functions of MSC-exosomes in cancer progression and its possible clinical applications in the future.

Transfusion. 2018 Sep 10. doi: 10.1111/trf.14805. [Epub ahead of print]

Characterization and cost-benefit analysis of automated bioreactor-expanded mesenchymal stem cells for clinical applications.

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Author information

Abstract

BACKGROUND:

Expanding quantities of mesenchymal stem cells (MSCs) sufficient to treat large numbers of patients in cellular therapy and regenerative medicine clinical trials is an ongoing challenge for cell manufacturing facilities.

STUDY DESIGN AND METHODS:

We evaluated options for scaling up large quantities of bone marrow-derived MSCs (BM-MSCs) using methods that can be performed in compliance with Good Manufacturing Practices (GMP). We expanded BM-MSCs from fresh marrow aspirate in αMEM supplemented with 5% human platelet lysate using both an automated cell expansion system (Quantum, Terumo BCT) and a manual flask-based method using multilayer flasks. We compared MSCs expanded using both methods and assessed their differentiation to adipogenic and osteogenic tissue, capacity to suppress T-cell proliferation, cytokines, and growth factor secretion profile and cost-effectiveness of manufacturing enough BM-MSCs to administer a single dose of 100×10^6 cells per subject in a clinical trial of 100 subjects.

RESULTS:

We have established that large quantities of clinical-grade BM-MSCs manufactured with an automated hollow-fiber bioreactor were phenotypically (CD73, CD90, CD105) and functionally (adipogenic and osteogenic differentiation and cytokine and growth factor secretion) similar to manually expanded BM-MSCs. In addition, MSC manufacturing costs significantly less and required less time and effort when using the Quantum automated cell expansion system over the manual multilayer flasks method.

CONCLUSION:

MSCs manufactured by an automated bioreactor are physically and functionally equivalent to the MSCs manufactured by the manual flask method and have met the standards required for clinical application.

Curr Rheumatol Rep. 2018 Sep 10;20(11):67. doi: 10.1007/s11926-018-0776-7.

Evaluating the Current Literature on Treatments Containing Adipose-Derived Stem Cells for Osteoarthritis: a Progress Update.

Ranmuthu CDS[1], Ranmuthu CKI[1], Khan WS[2,3].

Author information

Abstract

PURPOSE OF REVIEW:

Recent studies have investigated the effect of treatments containing adipose-derived mesenchymal stem cells (ADMSCs) on human osteoarthritis. These have mostly used biologic adjuvants which may influence results. Thus, the purpose of this systematic review is to evaluate the current literature on these treatments when used in isolation.

RECENT FINDINGS:

Five studies in this review used cultured ADMSCs, while four studies used stromal vascular fraction and three used micro-fragmented adipose tissue to deliver ADMSCs. No studies reported serious treatment-related adverse effects and all reported improvements in clinical measures for at least one dose. This was not necessarily reflected in imaging evaluations nor were improvements always maintained. Current low-level evidence is limited due to variability in study methodology but indicates that treatments containing ADMSCs, when used in isolation, are safe and have the potential to reduce pain and improve function. Randomized controlled trials are now needed.

Methods Mol Biol. 2018;1842:93-103. doi: 10.1007/978-1-4939-8697-2_7.

3D Bioprinting and Stem Cells.

Moore CA[1], Shah NN[2], Smith CP[1], Rameshwar P[3].

Author information

Abstract

Three-dimensional (3D) in vitro modeling is increasingly relevant as two-dimensional (2D) cultures have been recognized with limits to recapitulate the complex endogenous conditions in the body. Additionally, fabrication technology is more accessible than ever. Bioprinting, in particular, is an additive manufacturing technique that expands the capabilities of in vitro studies by precisely depositing cells embedded within a 3D biomaterial scaffold that acts as temporary extracellular matrix (ECM). More importantly, bioprinting has vast potential for customization. This allows users to manipulate parameters such as scaffold design, biomaterial selection, and cell types, to create specialized biomimetic 3D systems.The development of a 3D system is important to recapitulate the bone marrow (BM) microenvironment since this particular organ cannot be mimicked with other methods such as organoids. The 3D system can be used to study the interactions between native BM cells and metastatic breast cancer cells (BCCs). Although not perfect, such a system can recapitulate the BM microenvironment. Mesenchymal stem cells (MSCs), a key population within the BM, are known to communicate with BCCs invading the BM and to aid in their transition into dormancy. Dormant BCCs are cycling quiescent and resistant to chemotherapy, which allows them to survive in the BM to resurge

even after decades. These persisting BCCs have been identified as the stem cell subset. These BCCs exhibit self-renewal and can be induced to differentiate. More importantly, this BCC subset can initiate tumor formation, exert chemoresistance, and form gap junction with endogenous BM stroma, including MSCs. The bioprinted model detailed in this chapter creates a MSC-BC stem cell coculture system to study intercellular interactions in a model that is more representative of the endogenous 3D microenvironment than conventional 2D cultures. The method can reliably seed primary BM MSCs and BC stem cells within a bioprinted scaffold fabricated from CELLINK Bioink. Since bioprinting is a highly customizable technique, parameters described in this method (i.e., cell-cell ratio, scaffold dimensions) can easily be altered to serve other applications, including studies on hematopoietic regulation.

Stem Cell Res Ther. 2018 Sep 14;9(1):235. doi: 10.1186/s13287-018-0969-z.

Linking cell function with perfusion: insights from the transcatheter delivery of bone marrow-derived CD133$^+$ cells in ischemic refractory cardiomyopathy trial (RECARDIO).

Bassetti B[1], Carbucicchio C[2], Catto V[2], Gambini E[1], Rurali E[1], Bestetti A[3], Gaipa G[4,5], Belotti D[4,6], Celeste F[7], Parma M[8], Righetti S[9], Biava L[10], Arosio M[11], Bonomi A[12], Agostoni P[13,14], Scacciatella P[10], Achilli F[9], Pompilio G[15,16].

Author information

Abstract

BACKGROUND:

Cell therapy with bone marrow (BM)-derived progenitors has emerged as a promising therapeutic for refractory angina (RA) patients. In the present study, we evaluated the safety and preliminary efficacy of transcatheter delivery of autologous BM-derived advanced therapy medicinal product CD133$^+$ cells (ATMP-CD133) in RA patients, correlating perfusion outcome with cell function.

METHODS:

In the phase I "Endocavitary Injection of Bone Marrow Derived CD133$^+$ Cells in Ischemic Refractory Cardiomyopathy" (RECARDIO) trial, a total of 10 patients with left ventricular (LV) dysfunction (ejection fraction ≤ 45%) and evidence of reversible ischemia, as assessed by single-photon emission computed tomography (SPECT), underwent BM aspiration and fluoroscopy-based percutaneous endomyocardial delivery of ATMP-CD133. Patients were evaluated at 6 and 12 months for safety and preliminary efficacy endpoints. ATMP-CD133 samples were used for in vitro correlations.

RESULTS:

Patients were treated safely with a mean number of $6.57 \pm 3.45 \times 10^6$ ATMP-CD133. At 6-month follow-up, myocardial perfusion at SPECT was significantly ameliorated in terms of changes in summed stress (from 18.2 ± 8.6 to 13.8 ± 7.8, p = 0.05) and difference scores (from 12.0 ± 5.3 to 6.1 ± 4.0, p = 0.02) and number of segments with inducible ischemia (from 7.3 ± 2.2 to 4.0 ± 2.7, p = 0.003). Similarly, Canadian Cardiovascular Society and New York Heart Association classes significantly improved at follow-up vs baseline (p ≤ 0.001 and p = 0.007, respectively). Changes in summed stress score changes positively

correlated with ATMP-CD133 release of proangiogenic cytokines HGF and PDGF-bb ($r = 0.80$, $p = 0.009$ and $r = 0.77$, $p = 0.01$, respectively) and negatively with the proinflammatory cytokines RANTES ($r = -0.79$, $p = 0.01$) and IL-6 ($r = -0.76$, $p = 0.02$).

CONCLUSION:

Results of the RECARDIO trial suggested safety and efficacy in terms of clinical and perfusion outcomes in patients with RA and LV dysfunction. The observed link between myocardial perfusion improvements and ATMP-CD133 secretome may represent a proof of concept for further mechanistic investigations.

TRIAL REGISTRATION:

ClinicalTrials.gov, NCT02059681 . Registered 11 February 2014.