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Cell-based Therapy to Reduce Mortality From COVID-19: Systematic Review and Meta-Analysis of Human Studies on Acute Respiratory Distress Syndrome

Wenchun Qu[1,2], Zhen Wang[3,4], Joshua M Hare[5], Guojun Bu[2,6], Jorge M Mallea[7], Jorge M Pascual[7], Arnold I Caplan[8], Joanne Kurtzberg[9], Abba C Zubair[2,10], Eva Kubrova[11], Erica Engelberg-Cook[1], Tarek Nayfeh[3,4], Vishal P Shah[12], James C Hill[12], Michael E Wolf[12], Larry J Prokop[13], M Hassan Murad[3,4,12], Fred P Sanfilippo[14]
Affiliations expand

- PMID: 32472653

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Free article

Abstract

Severe cases of COVID-19 infection, often leading to death, have been associated with variants of acute respiratory distress syndrome (ARDS). Cell therapy with mesenchymal stromal cells (MSCs) is a potential treatment for COVID-19 ARDS based on preclinical and clinical studies supporting the concept that MSCs modulate the inflammatory and remodeling processes and restore alveolo-capillary barriers. The authors performed a systematic literature review and random-effects meta-analysis to determine the potential value of MSC therapy for treating COVID-19-infected patients with ARDS. Publications in all languages from 1990 to March 31, 2020 were reviewed, yielding 2691 studies, of which nine were included. MSCs were intravenously or intratracheally administered in 200 participants, who were followed for 14 days to 5 years. All MSCs were allogeneic from bone marrow, umbilical cord, menstrual blood, adipose tissue, or unreported sources. Combined mortality showed a favorable trend but did not reach statistical significance. No related

serious adverse events were reported and mild adverse events resolved spontaneously. A trend was found of improved radiographic findings, pulmonary function (lung compliance, tidal volumes, PaO_2 /FiO_2 ratio, alveolo-capillary injury), and inflammatory biomarker levels. No comparisons were made between MSCs of different sources.

J Biol Eng

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High-throughput Screening of Clinically Approved Drugs That Prime Nonviral Gene Delivery to Human Mesenchymal Stem Cells

Tyler Kozisek[1], Andrew Hamann[1], Albert Nguyen[1], Michael Miller[2], Sarah Plautz[1], Angela K Pannier[1]
Affiliations expand

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- PMCID: PMC7238544
- DOI: 10.1186/s13036-020-00238-1

Free PMC article

Abstract

Background: Human mesenchymal stem cells (hMSCs) are intensely researched for applications in cell therapeutics due to their unique properties, however, intrinsic therapeutic properties of hMSCs could be enhanced by genetic modification. Viral transduction is efficient, but suffers from safety issues. Conversely, nonviral gene delivery, while safer compared to viral, suffers from inefficiency and cytotoxicity, especially in hMSCs. To address the shortcomings of nonviral gene delivery to hMSCs, our lab has previously demonstrated that pharmacological 'priming' of hMSCs with the glucocorticoid dexamethasone can significantly increase transfection in hMSCs by modulating transfection-induced cytotoxicity. This work seeks to establish a library of transfection priming compounds for hMSCs by screening 707 FDA-approved drugs, belonging to

diverse drug classes, from the NIH Clinical Collection at four concentrations for their ability to modulate nonviral gene delivery to adipose-derived hMSCs from two human donors.

Results: Microscope images of cells transfected with a fluorescent transgene were analyzed in order to identify compounds that significantly affected hMSC transfection without significant toxicity. Compound classes that increased transfection across both donors included glucocorticoids, antibiotics, and antihypertensives. Notably, clobetasol propionate, a glucocorticoid, increased transgene production 18-fold over unprimed transfection. Furthermore, compound classes that decreased transfection across both donors included flavonoids, antibiotics, and antihypertensives, with the flavonoid epigallocatechin gallate decreasing transgene production - 41-fold compared to unprimed transfection.

Conclusions: Our screen of the NCC is the first high-throughput and drug-repurposing approach to identify nonviral gene delivery priming compounds in two donors of hMSCs. Priming compounds and classes identified in this screen suggest that modulation of proliferation, mitochondrial function, and apoptosis is vital for enhancing nonviral gene delivery to hMSCs.

J Drug Target

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Engineering Mesenchymal Stem Cells: A Novel Therapeutic Approach in Breast Cancer

Razieh Heidari[1], Neda Gholamian Dehkordi[2], Roohollah Mohseni[3], Mohsen Safaei[1]
Affiliations expand

- PMID: 32463709

- DOI: 10.1080/1061186X.2020.1775842

Abstract

Breast cancer is one of the most prevalent and deadliest cancers among women in the world because of its aggressive behavior and inadequate response to conventional therapies. Cellular and gene therapies based on mesenchymal stem cells (MSCs) represent promising treatment strategies for multiple diseases, such as cancers. MSCs are

multipotent adult stem cells with important features for cell therapy, such as tissue homing to injured sites, their differentiation potential, their capacity of secreting plenty of trophic factors, and low immunogenicity. The quite easy isolation of these cells from various types of tissues are associated with no ethical concern when dealing with fetal or embryonic stem cells. The MSCs exhibit both pro and anti-oncogenic properties. However, genetic engineering of MSCs and nanoparticles is being employed as a means to solve some of these problems and improve the antitumor properties of these cells. The tumor-homing ability of MSCs and their exosomes to tumor niches have made them as a promising vector for targeted delivery of therapeutic agents to tumors site. The present study investigated MSCs specifications, pro- and anti-oncogenic properties of MSCs in breast cancer, and reviewed targeted breast cancer therapy via engineered MSCs, likely as potent cellular vehicles.

Cancer Gene Ther

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AKT and JUN Are Differentially Activated in Mesenchymal Stem Cells After Infection With Human and Canine Oncolytic Adenoviruses

Miguel Ángel Rodríguez-Milla[1], Alvaro Morales-Molina[1], Ana Judith Perisé-Barrios[1,2], Teresa Cejalvo[1], Javier García-Castro[3]
Affiliations expand

- PMID: 32457488

- DOI: 10.1038/s41417-020-0184-9

Abstract

There is increasing evidence about the use of oncolytic adenoviruses (Ads) as promising immunotherapy agents. We have previously demonstrated the clinical efficiency of mesenchymal stem cells (MSCs) infected with oncolytic Ads as an antitumoral immunotherapy (called Celyvir) in human and canine patients, using ICOVIR-5 or ICOCAV17 as human and canine oncolytic Ads, respectively. Considering the better clinical outcomes of canine patients, in this study we searched for differences in cellular responses of human and canine MSCs to Ad infection that may help understand the mechanisms

leading to higher antitumor immune response. We found that infection of human and canine MSCs with ICOVIR-5 or ICOCAV17 did not activate the NF-κB pathway or the interferon regulatory factors IRF3 and IRF7. However, we observed differences in the profile of cytokines secretion, as infection of canine MSCs with ICOCAV17 resulted in lower secretion of several cytokines. Moreover, we showed that infection of human MSCs with ICOVIR-5 increased the phosphorylation of a number of proteins, including AKT and c-JUN. Finally, we demonstrated that differences in regulation of AKT and c-JUN in human and canine MSCs by ICOVIR-5 or ICOCAV17 are intrinsic to each virus. Our findings suggest that ICOCAV17 induces a more limited host response in canine MSCs, which may be related to a better clinical outcome. This result opens the possibility to develop new human oncolytic Ads with these specific properties. In addition, this improvement could be imitated by selecting specific human MSC on the basis of a limited host response after Ad infection.

PLoS One

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Examination of Ex-Vivo Viability of Human Adipose Tissue Slice Culture

Nikolas Schopow[1,2], Sonja Kallendrusch[1], Siming Gong[1,2], Felicitas Rapp[1,3], Justus Körfer[1,4], Martin Gericke[1], Nick Spindler[2], Christoph Josten[2], Stefan Langer[2], Ingo Bechmann[1]
Affiliations expand

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Free article

Abstract

Obesity is associated with significantly higher mortality rates, and excess adipose tissue is involved in respective pathologies. Here we established a human adipose tissue slice cultures (HATSC) model ex vivo. HATSC match the in vivo cell composition of human adipose tissue with, among others, mature adipocytes, mesenchymal stem cells as well as stroma tissue and immune cells. This is a new method, optimized for live imaging, to study adipose tissue and cell-based mechanisms of obesity in particular. HATSC survival was tested by means of conventional and immunofluorescence histological techniques,

functional analyses and live imaging. Surgery-derived tissue was cut with a tissue chopper in 500 µm sections and transferred onto membranes building an air-liquid interface. HATSC were cultured in six-well plates filled with Dulbecco's Modified Eagle's Medium (DMEM), insulin, transferrin, and selenium, both with and without serum. After 0, 1, 7 and 14 days in vitro, slices were fixated and analyzed by morphology and Perilipin A for tissue viability. Immunofluorescent staining against IBA1, CD68 and Ki67 was performed to determine macrophage survival and proliferation. These experiments showed preservation of adipose tissue as well as survival and proliferation of monocytes and stroma tissue for at least 14 days in vitro even in the absence of serum. The physiological capabilities of adipocytes were functionally tested by insulin stimulation and measurement of Phospho-Akt on day 7 and 14 in vitro. Viability was further confirmed by live imaging using Calcein-AM (viable cells) and propidium iodide (apoptosis/necrosis). In conclusion, HATSC have been successfully established by preserving the monovacuolar form of adipocytes and surrounding macrophages and connective tissue. This model allows further analysis of mature human adipose tissue biology ex vivo.

Biol Trace Elem Res

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Insights Into the Role of Magnesium Ions in Affecting Osteogenic Differentiation of Mesenchymal Stem Cells

Tiantian Qi[1,2], Jian Weng[1,2], Fei Yu[1,2], Weifei Zhang[1,2], Guoqing Li[1,2], Haotian Qin[1,2], Zhen Tan[1,2], Hui Zeng[3,4]
Affiliations expand

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- DOI: 10.1007/s12011-020-02183-y

Abstract

Bone marrow mesenchymal stem cells (MSCs) are multipotent stem cells with the ability to differentiate into bone-producing cells, which is essential for bone formation. Magnesium biomedical materials, such as biodegradable matters with osteoinductive properties, play a vital role in the osteogenic differentiation of MSCs. International and Chinese studies have

shown that magnesium ions, which are produced by biodegradation, mainly achieve this effect by regulating the expression of genes and proteins associated with osteogenesis, activating multiple signal pathways, elevating autophagic activities, and adjusting the pH in the microenvironment. It is of great significance to study the regulatory mechanisms and identify the optimal conditions that how magnesium ions promote osteogenic differentiation of MSCs. In this study, we summarized the regulatory mechanisms noted above.

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reviewed targeted breast cancer therapy via engineered MSCs, likely as potent cellular vehicles.