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Long-term and label-free monitoring for osteogenic differentiation of mesenchymal stem cells using force sensor and impedance measurement

Zhizhong Zhang[1], Tianyang Zheng[1], Rong Zhu[1]
Affiliations expand

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Abstract

Stem cells have attracted increasing research interest in the field of regenerative medicine due to their unique abilities to differentiate into multiple cell lineages. Label-free, real-time, and long-term monitoring for stem cell differentiation is requisite in studying directional differentiation and development mechanisms for tissue engineering applications, but a great challenge because of the rigorous demands for sensitivity, stability and biocompatibility of devices. In this article, a label-free and real-time monitoring approach using a zinc oxide (ZnO) nanorod field effect transistor (FET) is proposed to detect cell traction forces (CTFs) exerted by cells on underlying substrates. The ZnO nanorod FET with the approach of difference-frequency lock-in detection achieves high sensitivity, good stability, and excellent biocompatibility, by which real-time and long-term (over 20 days) monitoring of cellular mechanical changes in osteogenic differentiation of mesenchymal stem cells (MSCs) is successfully achieved. We also employ electrical impedance monitoring using microelectrode array chips and microscopic observation to investigate cell migration and nodular aggregation behaviors of MSCs in osteogenic differentiation. Various biochemical assays including alkaline phosphatase (ALP), osteopontin expression and alizarin red staining are utilized to verify osteogenic differentiation of MSCs. We propose a combination of cell traction force measurement, impedance measurement and microscopic observation to provide multimodal profiling of cell morphology, and cellular biomechanical and electrophysiological phenotypes, which can track cellular dynamics in

stem cell development and help to deeply understand the mechanism of osteogenic differentiation.

World J Stem Cells
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Senescent mesenchymal stem/stromal cells and restoring their cellular functions

Qing-Shu Meng[1], Jing Liu[1], Lu Wei[1], Hui-Min Fan[1], Xiao-Hui Zhou[1], Xiao-Ting Liang[1]
Affiliations expand

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Free PMC article

Abstract

Mesenchymal stem/stromal cells (MSCs) have various properties that make them promising candidates for stem cell-based therapies in clinical settings. These include self-renewal, multilineage differentiation, and immunoregulation. However, recent studies have confirmed that aging is a vital factor that limits their function and therapeutic properties as standardized clinical products. Understanding the features of senescence and exploration of cell rejuvenation methods are necessary to develop effective strategies that can overcome the shortage and instability of MSCs. This review will summarize the current knowledge on characteristics and functional changes of aged MSCs. Additionally, it will highlight cell rejuvenation strategies such as molecular regulation, non-coding RNA modifications, and microenvironment controls that may enhance the therapeutic potential of MSCs in clinical settings.

Biologicals
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Novel application of adipose-derived mesenchymal stem cells via producing antiangiogenic factor TSP-1 in lung metastatic melanoma animal model

Saeid Bagheri-Mohammadi[1], Rana Moradian-Tehrani[2], Mahdi Noureddini[3], Behrang Alani[2]
Affiliations expand

- PMID: 33032882

- DOI: 10.1016/j.biologicals.2020.09.004

Abstract

Human adipose tissue derived mesenchymal stem cells (hAD-MSCs) with suppressive immunogenicity, homing to injury, inflammatory, and cancer sites can be suitable for gene therapy. PiggyBac (PB) is a type of transposon vector applied in mammalian systems and could overcome some limitations of other transposon and viral vectors. In this study, the therapeutic potential hAD-MSCs expressing thrombospondin-1 (TSP-1) is assessed through tail vein injection in C57BL/6 models bearing melanoma mice. Twenty days after injection, antiangiogenic effects and number of activated T. cells are assessed by Immunohistochemistry (IHC) method. Apoptosis value is analyzed by tunnel assay. Mice survival and numbers of nodules in mice lungs also are assessed. By western blotting, value of TSP-1, Bax and Bcl2 expression are assessed. The result revealed that hAD-MSCs.TSP-1 can inhibit angiogenesis and induce apoptosis and activated T. cells in a significant manner in C57BL/6 mice models bearing melanoma. Survival also significantly increased and number of nodules decreased, value of Bax and TSP-1 expression increased and value of Bcl2 expression decreased. In conclusion, our result showed that hAD-MSC. TSP-1 can be applied as an effective delivery vehicle in lung metastatic melanoma therapy.

PLoS Comput Biol

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Machine learning to predict mesenchymal stem cell efficacy for cartilage repair

Yu Yang Fredik Liu[1], Yin Lu[2], Steve Oh[2], Gareth J Conduit[1]
Affiliations expand

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- DOI: 10.1371/journal.pcbi.1008275

Free article

Abstract

Inconsistent therapeutic efficacy of mesenchymal stem cells (MSCs) in regenerative medicine has been documented in many clinical trials. Precise prediction on the therapeutic outcome of a MSC therapy based on the patient's conditions would provide valuable references for clinicians to decide the treatment strategies. In this article, we performed a meta-analysis on MSC therapies for cartilage repair using machine learning. A small database was generated from published in vivo and clinical studies. The unique features of our neural network model in handling missing data and calculating prediction uncertainty enabled precise prediction of post-treatment cartilage repair scores with coefficient of determination of 0.637 ± 0.005. From this model, we identified defect area percentage, defect depth percentage, implantation cell number, body weight, tissue source, and the type of cartilage damage as critical properties that significant impact cartilage repair. A dosage of 17 - 25 million MSCs was found to achieve optimal cartilage repair. Further, critical thresholds at 6% and 64% of cartilage damage in area, and 22% and 56% in depth were predicted to significantly compromise on the efficacy of MSC therapy. This study, for the first time, demonstrated machine learning of patient-specific cartilage repair post MSC therapy. This approach can be applied to identify and investigate more critical properties involved in MSC-induced cartilage repair, and adapted for other clinical indications.

Int J Mol Sci

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Anti-Tumor Effects of Exosomes Derived from Drug-Incubated Permanently Growing Human MSC

Catharina Melzer[1], Juliane von der Ohe[1], Ralf Hass[1]
Affiliations expand

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Free article

Abstract

Similar to growth-limited human primary cultures of mesenchymal stroma/stem-like cells (MSC), the continuously proliferating human MSC544 cell line produced extracellular vesicles as characterized by expression of the tetraspanin molecules CD9, CD63, and CD81. Release of these particles was predominantly detectable during continuous cell growth of MSC544 in contrast to confluency-mediated transient growth arrest. For therapeutic use, these particles were isolated from proliferating MSC544 after taxol treatment and applied to different cancer cell cultures. A pronounced cytotoxicity of lung, ovarian, and breast cancer cells was observed primarily with taxol-loaded exosomes, similar to the effects displayed by application of taxol substance. While these findings suggested pronounced cancer cell targeting of MSC544 exosomes, a tumor therapeutic approach was performed using a mouse in vivo breast cancer model. Thus, intravenous injection of taxol-loaded MSC544 exosomes displayed superior tumor-reducing capabilities as compared to application of taxol exosomes by oral gavage. To broaden this therapeutic spectrum, epirubicin was applied to MSC544, and the derived exosomes likewise exhibited significant cytotoxic effects in different cancer cell cultures. These findings suggest an unlimited source for large-scale exosome production with reproducible quality to enable variable drug targeting of tumors or other diseases.

Stem Cells Int

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The Potential Use of Mesenchymal Stem Cells and Their Derived Exosomes as Immunomodulatory Agents for COVID-19 Patients

Faisal A Alzahrani[1], Islam M Saadeldin[2,3], Abrar Ahmad[1], Dipak Kumar[4], Esam I Azhar[5], Arif Jamal Siddiqui[6], Bassem Kurdi[7], Abdulrahim Sajini[8], Abdulmajeed F Alrefaei[9], Sadaf Jahan[10]
Affiliations expand

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Free PMC article

Abstract

A novel severe acute respiratory syndrome coronavirus (SARS-CoV-2) causing lethal acute respiratory disease emerged in December 2019. The World Health Organization named this disease "COVID-19" and declared it a pandemic on March 11, 2020. Many studies have shown that mesenchymal stem cells (MSCs) and their exosomes (MSCs-Exo), which are isolated from allogenic bone marrow stem cells, significantly lower the risk of alveolar inflammation and other pathological conditions associated with distinct lung injuries. For example, in acute respiratory distress syndrome (ARDS) and pneumonia patients, MSCs-Exo and MSCs provide similar healing properties and some clinical trials have used cell-based inhalation therapy which show great promise. MSCs and MSCs-Exo have shown potential in clinical trials as a therapeutic tool for severely affected COVID-19 patients when compared to other cell-based therapies, which may face challenges like the cells' sticking to the respiratory tract epithelia during administration. However, the use of MSCs or MSCs-Exo for treating COVID-19 should strictly adhere to the appropriate manufacturing practices, quality control measurements, preclinical safety and efficacy data, and the proper ethical regulations. This review highlights the available clinical trials that support the therapeutic potential of MSCs or MSCs-Exo in severely affected COVID-19 patients.