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Molecular Mechanisms Responsible for Therapeutic Potential of Mesenchymal Stem Cell-Derived Secretome.

Harrell CR[1], Fellabaum C[2], Jovicic N[3], Djonov V[4], Arsenijevic N[5], Volarevic V[6].
Author information

Abstract

Mesenchymal stem cell (MSC)-sourced secretome, defined as the set of MSC-derived bioactive factors (soluble proteins, nucleic acids, lipids and extracellular vesicles), showed therapeutic effects similar to those observed after transplantation of MSCs. MSC-derived secretome may bypass many side effects of MSC-based therapy, including unwanted differentiation of engrafted MSCs. In contrast to MSCs which had to be expanded in culture to reach optimal cell number for transplantation, MSC-sourced secretome is immediately available for treatment of acute conditions, including fulminant hepatitis, cerebral ischemia and myocardial infarction. Additionally, MSC-derived secretome could be massively produced from commercially available cell lines avoiding invasive cell collection procedure. In this review article we emphasized molecular and cellular mechanisms that were responsible for beneficial effects of MSC-derived secretomes in the treatment of degenerative and inflammatory diseases of hepatobiliary, respiratory, musculoskeletal, gastrointestinal, cardiovascular and nervous system. Results obtained in a large number of studies suggested that administration of MSC-derived secretomes represents a new, cell-free therapeutic approach for attenuation of inflammatory and degenerative diseases. Therapeutic effects of MSC-sourced secretomes relied on their capacity to deliver genetic material, growth and immunomodulatory factors to the target cells enabling activation of anti-apoptotic and pro-survival pathways that resulted in tissue repair and regeneration.

Biofabrication. 2019 May 16. doi: 10.1088/1758-5090/ab21f6. [Epub ahead of print]

Fabrication of size-controllable human mesenchymal stromal cell spheroids from micro-scaled cell sheets.

Byun HY[1], Lee YB[1], Kim EM[2], Shin H[3].
Author information

Abstract

Recently, stem cell spheroids have been actively studied for use in tissue regeneration. In this study, we report a method for the fabrication of size-controllable stem cell spheroids in different sizes from micro-scaled cell sheets (μCS) using thermosensitive hydrogels and investigated their effects on stem cell function. Mesenchymal stem cells isolated from different tissues such as human turbinate tissue, bone marrow, and adipose tissue were adhered selectively to each micro-pattern (squares with widths of 100 and 400 μm) on the surface of the hydrogel and formed μCS. The diameters of the spheroids were modulated by the size of the patterns (45±5 and 129±4 μm in diameter for the 100 and 400 μm micro-patterns, respectively) and the seeding density (129±4, 149±6, and 163±6 μm for 5.0, 10.0, and 15.0 × 10⁴

cells/cm², respectively, on 400-μm micro-pattern). In addition, the spheroids were successfully fabricated regardless of stem cell origin, and the diameter of the spheroids was also affected by cell spreading area on a cell culture dish. Stemness markers were highly expressed in the spheroids regardless of the spheroid size. Furthermore, an increase in E-cadherin and decrease in N-cadherin gene expression showed the stable formation of spheroids of different sizes. Gene expression levels of hypoxia inducible factors and secretion of vascular endothelial growth factor (VEGF) were increased (13.2±1.4, 325±83.4 and 534.3±121.5 pg/ng DNA in a monolayer, and 100- and 400-μm micro-patterned spheroids, respectively) proportional to the diameters of the spheroids. The size of spheroids were maintained even after injection, cryopreservation and 7 days of suspension culture with high viability (~90%). In conclusion, this novel technique to fabricate spheroids with controlled size could be widely applied in various applications that require a controlled size in regenerative medicine.

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In Vitro Evaluation of Proliferation and Migration Behaviour of Human Bone Marrow-Derived Mesenchymal Stem Cells in Presence of Platelet-Rich Plasma.

Nguyen ATM[1], Tran HLB[2], Pham TAV[3].

Author information

Abstract

OBJECTIVE:

To access the effects of platelet-rich plasma (PRP) on the behaviour of human bone marrow-derived mesenchymal stem cells (hBMSCs), including proliferation and migration.

METHODS:

PRP was diluted with DMEM/F12, resulting in concentrations of 1%, 2%, and 5%. The proliferation of hBMSCs was examined by 2 methods: cell-number counting with the haemocytometer method and the colony-forming unit-fibroblast (CFU-F) assay. Cell migration was evaluated using the scratch wound healing (SWH) assay; after that, the recorded digital images were analysed by the Image-Analysis J 1.51j8 software to compare the cell-free areas between groups after 0, 24, and 48 hours.

RESULTS:

hBMSCs cultured in DMEM/F12 at PRP concentrations of 1%, 2%, and 5% were all able to proliferate and migrate. In the 5% PRP group, hBMSCs proliferated greatly with a significantly higher cell number than reported for all other groups on days 5, 7, and 9. CFU-Fs were observed in all groups, except for the negative control group. The SWH assay demonstrated that hBMSCs cultured in 2% and 5% PRP almost filled the artificial wound scratch and significantly migrated more than those of all other groups at both 24 h and 48 h.

CONCLUSION:

This study indicated that, due to the significant enhancement of cell proliferation and migration, 5% PRP might be the optimal concentration that should be used to promote the potential of hBMSCs in wound healing.

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Study on the Dynamic Biological Characteristics of Human Bone Marrow Mesenchymal Stem Cell Senescence.

Chen X[1,2], Wang L[2,3], Hou J[2,3], Li J[2,3], Chen L[2,3], Xia J[2,3], Wang Z[2,3], Xiao M[2,3], Wang Y[2,3].

Author information

Abstract

OBJECTIVE:

To preliminary explore the senescent dynamic changes of the bone marrow mesenchymal stem cells (BMMSCs) by human ageing and its possible mechanism.

METHODS:

The bone marrows were harvested from healthy volunteers, and according to volunteers' age, these were divided into group A (≤25 years), group B (26-45 years), group C (46-65 years), and group D (>65 years). Totally, the bone marrows were extracted from the posterior superior iliac spine from volunteers under aseptic conditions. Diluted with isovolumic PBS, followed by centrifugation at $1 \times 10^5/cm^2$, cells were cultured in a 5% CO_2 incubator at 37°C. After three passages, surface marker identification of hBMMSCs was tested by flow cytometry (FCM), oil red O staining was used to observe the ability of osteogenic differentiation, alkaline phosphatase (ALP) staining and the levels of osteocalcin (OST) in the supernatants were used to observe the ability of adipogenic differentiation, senescence-associated *β*-galactosidase (SA-*β*-Gal) staining was used to detect the senescent BMSCs, the ability of BMSC proliferation was detected by cell counting kit-8 (CCK-8), the distribution of the cell cycle was analyzed by flow cytometry (FCM), and malondialdehyde (MDA) content, total glutathione peroxidase, total antioxidant capacity, and total superoxide dismutase (SOD) activity was analyzed using enzymatic assay.

RESULTS:

The BMSCs highly expressed CD73 and CD90, but lowly expressed CD34 and CD19/CD14. With age, osteogenic differentiation was markedly increased and audiogenic differentiation was significantly decreased. The number of SA-*β*-gal-positive cells was significantly increased, the proliferation ability of hBMMSCs declined, the BMSCs were held in the G1 phase, the MDA level of BMSCs was significantly increased, and total glutathione peroxidase, total antioxidant capacity, and SOD activity significantly declined.

CONCLUSIONS:

With age, the aging BMSCs were intensified; the mechanism may be related to oxidative damage mediated aging-related pathways.

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Mesenchymal Progenitors Derived from Different Locations in Long Bones Display Diverse Characteristics.

Lu W[1], Gao B[1], Fan J[1], Cheng P[1], Hu Y[1], Jie Q[2], Luo Z[1], Yang L[1].
Author information

Abstract

Mesenchymal progenitors within bone marrow have multiple differentiation potential and play an essential role in the maintenance of adult skeleton homeostasis. Mesenchymal progenitors located in bone regions other than the bone marrow also display bone-forming properties. However, owing to the

differences in each distinct microenvironment, the mesenchymal characteristics of skeletal progenitor cells within different regions of long bones may show some differences. In order to clearly elucidate these differences, we performed a comparative study on mesenchymal progenitors from different regions of long bones. Here, we isolated mesenchymal progenitors from the periosteum, endosteum, and bone marrow of rat long bones. The three groups exhibited similar cellular morphologies and expressed the typical surface markers associated with mesenchymal stem cells. Interestingly, after cell proliferation assays and bidirectional differentiation analysis, periosteal mesenchymal progenitors showed a higher proliferative ability and adipogenic differentiation potential. In contrast, endosteal mesenchymal progenitors were more prone to osteogenic differentiation. Using *in vitro* osteoclast culture systems, conditioned media from different mesenchymal progenitor cultures were used to induce osteoclastic differentiation. Osteoclast formation was found to be significantly promoted by the secretion of RANKL and IL-6 by endosteal progenitors. Overall, our results provide strong evidence for the importance of selecting the appropriate source of skeletal progenitors for applications in future skeleton regeneration therapies.

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MSC Therapy for Osteoarthritis: An Unfinished Story.

Barry F[1].
Author information

Abstract

Mesenchymal stromal cells (MSCs) have firmly occupied the attention of orthopedic clinicians and scientists for most of the last 25 years. Hundreds of laboratories worldwide have carried out research aimed at unraveling the biological characteristics of these cells and probing the manner in which they potentially contribute to cartilage and bone repair. Clinical trials registries indicate that they are also being tested in patient studies for a wide range of conditions such as osteoarthritis, rheumatoid arthritis, fracture repair, regeneration of articular cartilage, tendon repair, and for treatment of degenerative disc disease. Despite these efforts, the effectiveness of MSCs as a treatment modality for these conditions is still uncertain and market authorizations have been limited. In addition, critical and clear phenotypic parameters for defining MSCs are uncertain and a coherent biological framework surrounding the therapeutic mechanism of action is not yet available. Added to this, cell manufacturing protocols are complex and costly and present substantial challenges in terms of regulatory oversight and standardization. Despite these obstacles, MSCs still remain at the forefront of efforts in Regenerative Medicine, based on a conviction that this technology can provide an effective treatment paradigm for major diseases where there is still an unmet need.