ML 06-20 (06/02/2020)

EClinicalMedicine. 2020 Jan 17;19:100249. doi: 10.1016/j.eclinm.2019.100249. eCollection 2020 Feb.

Cell therapy with intravascular administration of mesenchymal stromal cells continues to appear safe: An updated systematic review and meta-analysis.

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Author information

Abstract

BACKGROUND:

Characterization of the mesenchymal stromal cell (MSC) safety profile is important as this novel therapy continues to be evaluated in clinical trials for various inflammatory conditions. Due to an increase in published randomized controlled trials (RCTs) from 2012-2019, we performed an updated systematic review to further characterize the MSC safety profile.

METHODS:

MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials and Web of Science (to May 2018) were searched. RCTs that compared intravascular delivery of MSCs to controls in adult populations were included. Pre-specified adverse events were grouped according to: (1) immediate, (2) infection, (3) thrombotic/embolic, and (4) longer-term events (mortality, malignancy). Adverse events were pooled and meta-analyzed by fitting inverse-variance binary random effects models. Primary and secondary clinical efficacy endpoints were summarized descriptively.

FINDINGS:

7473 citations were reviewed and 55 studies met inclusion criteria (*n* = 2696 patients). MSCs as compared to controls were associated with an increased risk of fever (Relative Risk (RR) = 2·48, 95% Confidence Interval (CI) = 1·27-4·86; I^2 = 0%), but not non-fever acute infusional toxicity, infection, thrombotic/embolic events, death, or malignancy (RR = 1·16, 0·99, 1·14, 0·78, 0·93; 95% CI = 0·70-1·91, 0·81-1·21, 0·67-1·95, 0·65-0·94, 0·60-1·45; I^2 = 0%, 0%, 0%, 0%, 0%). No included trials were ended prematurely due to safety concerns.

INTERPRETATIONS:

MSC therapy continues to exhibit a favourable safety profile. Future trials should continue to strengthen study rigor, reporting of MSC characterization, and adverse events.

Regen Ther. 2020 Jan 16;14:95-102. doi: 10.1016/j.reth.2019.10.004. eCollection 2020 Jun.

A pair of cell preservation solutions for therapy with human adipose tissue-derived mesenchymal stromal cells.

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Abstract

INTRODUCTION:

Stem cells for therapy are often suspended in a preservation solution, such as normal saline or lactated Ringer's solution, for a short time before intravenous infusion. However, these solutions are not necessarily ideal for maintaining cell viability and preventing the sedimentation of cells during storage and infusion. In this study, we attempted to optimize the compositions of preservation solutions, which could affect the efficacy and safety of stem cell therapy.

METHODS:

We determined the characteristics of a preservation solution that would optimize cell viability and the percentage of cells in the supernatant using human adipose-derived mesenchymal stromal cells (hADSCs). We compared solutions that differed by electrolytes (e.g., normal saline and Ringer's solution) and the concentrations of dextran 40 and trehalose. The effects of the solutions on hADSCs were evaluated by assessing cell surface markers, colony-forming capacity, differentiation potential, and cell concentrations in the infusion line.

RESULTS:

Optimized preservation solutions consisted of lactated Ringer's solution with 3% trehalose without or with 5% dextran 40 (LR-3T and LR-3T-5D, respectively). The cell viabilities after 24 h of storage at 5 °C in LR-3T and LR-3T-5D were 94.9% ± 2.4% and 97.6% ± 2.4%, respectively. The percentage of cells in the supernatant after 1 h of storage at room temperature in LR-3T-5D was 83.5% ± 7.6%. These solutions preserved the percentage of cell surface marker-positive cells, the colony-forming capacity, and the adipogenic and osteogenic differentiation ability in hADSCs for at least 24 h after preservation at 5 °C and 25 °C.

DISCUSSION:

We determined the optimal composition of preservation solutions for hADSCs and confirmed the effects of these solutions on cell viability and the stability of cell characteristics *in vitro*. Our results suggest that LR-3T and LR-3T-5D can help maintain the quality of stem cells for therapy during preservation and infusion. However, further *in vivo* research is needed on the efficacy and safety of the solutions in different therapeutic cell lines before clinical use.

Regen Ther. 2020 Jan 14;14:59-71. doi: 10.1016/j.reth.2019.12.008. eCollection 2020 Jun.

Co-cultured spheroids of human periodontal ligament mesenchymal stem cells and vascular endothelial cells enhance periodontal tissue regeneration.

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Abstract

INTRODUCTION:

Human periodontal ligament mesenchymal stem cells (hPDLMSCs) have been known that they play important roles in homeostasis and regeneration of periodontal tissues. Additionally, spheroids are superior to monolayer-cultured cells. We investigated the characteristics and potential of periodontal tissue regeneration in co-cultured spheroids of hPDLMSCs and human umbilical vein endothelial cells (HUVECs) *in vitro* and *in vivo*.

METHODS:

Co-cultured spheroids were prepared with cell ratios of hPDLMSCs: HUVECs = 1:1, 1:2, and 2:1, using microwell chips. Real-time polymerase chain reaction (PCR) analysis, Enzyme-Linked Immuno Sorbent Assay (ELISA), and nodule formation assay were performed to examine the properties of co-cultured spheroids. Periodontal tissue defects were prepared in the maxillary first molars of rats and subjected to transplantation assay.

RESULTS:

The expression levels of stemness markers, vascular endothelial growth factor (*VEGF*), osteogenesis-related genes were up-regulated in co-cultured spheroids, compared with monolayer and spheroid-cultured hPDLMSCs. The nodule formation was also increased in co-cultured spheroids, compared with monolayer and spheroid cultures of hPDLMSCs. Treatment with co-cultured spheroids enhanced new cementum formation after 4 or 8 weeks of transplantation, although there was no significant difference in the new bone formation between co-cultured spheroids and hPDLMSC spheroids.

CONCLUSIONS:

We found that co-cultured spheroids enhance the periodontal tissue regeneration. Co-cultured spheroids of hPDLMSCs and HUVECs may be a useful therapy that can induce periodontal tissue regeneration.

Acta Biomater. 2020 Jan 24. pii: S1742-7061(20)30042-8. doi: 10.1016/j.actbio.2020.01.027. [Epub ahead of print]

Engineering the mode of morphogenetic signal presentation to promote branching from salivary gland spheroids in 3D hydrogels.

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Abstract

Previously we developed a fibrin hydrogel (FH) decorated with laminin-111 peptides (L_{1p}-FH) and supports three-dimensional (3D) gland microstructures containing polarized acinar cells. Here we expand on these results and show that co-culture of rat parotid Par-C10 cells with mesenchymal stem cells produces migrating branches of gland cells into the $L1_p$-FH and we identify FGF-7 as the principal morphogenetic signal responsible for branching. On the other hand, another FGF family member and gland morphogen, FGF-10 increased proliferation but did not promote migration and therefore, limited

the number and length of branched structures grown into the gel. By controlling the mode of growth factor presentation and delivery, we can control the length and cellularity of branches as well as formation of new nodes/clusters within the hydrogel. Such spatial delivery of two or more morphogens may facilitate engineering of anatomically complex tissues/mini organs such as salivary glands that can be used to address developmental questions or as platforms for drug discovery. Statement of Significance Hyposalivation leads to the development of a host of oral diseases. Current treatments only provide temporary relief. Tissue engineering may provide promising permanent solutions. Yet current models are limited to salivary spheroids with no branching networks. Branching structures are vital to an effective functioning gland as they increase the surface area/glandular volume ratio of the tissue, allowing a higher output from the small-sized gland. We describe a strategy that controls branch network formation in salivary glands that is a key in advancing the field of salivary gland tissue engineering.

Cell Signal. 2020 Jan 24;69:109549. doi: 10.1016/j.cellsig.2020.109549. [Epub ahead of print]

Human omental adipose-derived mesenchymal stem cells enhance autophagy in ovarian carcinoma cells through the STAT3 signalling pathway.

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Abstract

BACKGROUND:

Our previous study showed that human omental adipose-derived stem cells (ADSCs) promote ovarian cancer growth and metastasis. In this study, the role of autophagy in the ovarian cancer-promoting effects of omental ADSCs was further determined.

METHODS:

The growth and invasion of ovarian cancer cells were detected by CCK-8 and Transwell assays, respectively. The autophagy of ovarian cancer cells transfected with MRFP-GFP-LC3 adenoviral vectors was evaluated by confocal microscopy and western blot assay. Transfection of STAT3 siRNA was used to inhibit the expression of STAT3.

RESULTS:

Our results show that autophagy plays a vital role in ovarian cancer and is promoted by ADSCs. Specifically, we show that proliferation and invasion are correlated with autophagy induction by ADSCs in two ovarian cancer cell lines under hypoxic conditions. Mechanistically, ADSCs activate the STAT3 signalling pathway, thereby promoting autophagy. Knockdown of STAT3 expression using siRNA decreased hypoxia-induced autophagy and decreased the proliferation and metastasis of ovarian cancer cells.

CONCLUSION:

Taken together, our data indicate that STAT3-mediated autophagy induced by ADSCs promotes ovarian cancer growth and metastasis.

J Cell Physiol. 2020 Jan 29. doi: 10.1002/jcp.29574. [Epub ahead of print]

Adipose-derived stem cells and cancer cells fuse to generate cancer stem cell-like cells with increased tumorigenicity.

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Abstract

Adipose-derived stem cells (ADSCs) are a type of mesenchymal stem cells isolated from adipose tissue and have the ability to differentiate into adipogenic, osteogenic, and chondrogenic lineages. Despite their great therapeutic potentials, previous studies showed that ADSCs could enhance the proliferation and metastatic potential of breast cancer cells (BCCs). In this study, we found that ADSCs fused with BCCs spontaneously, while breast cancer stem cell (CSC) markers $CD44^{+}$ $CD24^{-/low}$ $EpCAM^{+}$ were enriched in this fusion population. We further assessed the fusion hybrid by multicolor DNA FISH and mouse xenograft assays. Only single nucleus was observed in the fusion hybrid, confirming that it was a synkaryon. In vivo mouse xenograft assay indicated that the tumorigenic potential of the fusion hybrid was significantly higher than that of the parent tumorigenic triple-negative BCC line MDA-MB-231. We had compared the fusion efficiency between two BCC lines, the CD44-rich MDA-MB-231 and the CD44-poor MCF-7, with ADSCs. Interestingly, we found that the fusion efficiency was much higher between MDA-MB-231 and ADSCs, suggesting that a potential mechanism of cell fusion may lie in the dissimilarity between these two cell lines. The cell fusion efficiency was hampered by knocking down the CD44. Altogether, our findings suggest that CD44-mediated cell fusion could be a potential mechanism for generating CSCs.

J Cell Physiol. 2020 Jan 28. doi: 10.1002/jcp.29572. [Epub ahead of print]

Molecular mechanism underlying the difference in proliferation between placenta-derived and umbilical cord-derived mesenchymal stem cells.

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Abstract

The placenta and umbilical cord are pre-eminent candidate sources of mesenchymal stem cells (MSCs). However, placenta-derived MSCs (P-MSCs) showed greater proliferation capacity than umbilical cord-derived MSCs (UC-MSCs) in our study. We investigated the drivers of this proliferation

difference and elucidated the mechanisms of proliferation regulation. Proteomic profiling and Gene Ontology (GO) functional enrichment were conducted to identify candidate proteins that may influence proliferation. Using lentiviral or small interfering RNA infection, we established overexpression and knockdown models and observed changes in cell proliferation to examine whether a relationship exists between the candidate proteins and proliferation capacity. Real-time quantitative polymerase chain reaction, western blot analysis, and immunofluorescence assays were conducted to elucidate the mechanisms underlying proliferation. Six candidate proteins were selected based on the results of proteomic profiling and GO functional enrichment. Through further validation, yes-associated protein 1 (YAP1) and β-catenin were confirmed to affect MSCs proliferation rates. YAP1 and β-catenin showed increased nuclear colocalization during cell expansion. YAP1 overexpression significantly enhanced proliferation capacity and upregulated the expression of both β-catenin and the transcriptional targets of Wnt signaling, CCND1, and c-MYC, whereas silencing β-catenin attenuated this influence. We found that YAP1 directly interacts with β-catenin in the nucleus to form a transcriptional YAP/β-catenin/TCF4 complex. Our study revealed that YAP1 and β-catenin caused the different proliferation capacities of P-MSCs and UC-MSCs. Mechanism analysis showed that YAP1 stabilized the nuclear β-catenin protein, and also triggered the Wnt/β-catenin pathway, promoting proliferation.