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Lung transplantation, *ex-vivo* reconditioning and regeneration: state of the art and perspectives.

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Author information

Abstract

Lung transplantation is the only therapeutic option for end-stage pulmonary failure. Nevertheless, the shortage of donor pool available for transplantation does not allow to satisfy the requests, thus the mortality on the waiting list remains high. One of the tools to overcome the donor pool shortage is the use of *ex-vivo* lung perfusion (EVLP) to preserve, evaluate and recondition selected lung grafts not otherwise suitable for transplantation. EVLP is nowadays a clinical reality and have several destinations of use. After a narrative review of the literature and looking at our experience we can assume that one of the chances to improve the outcome of lung transplantation and to overcome the donor pool shortage could be the tissue regeneration of the graft during EVLP and the immunomodulation of the recipient. Both these strategies are performed using mesenchymal stem cells (MSC). The results of the models of lung perfusion with MSC-based cell therapy open the way to a new innovative approach that further increases the potential for using of the lung perfusion platform.

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Current status and potential challenges of mesenchymal stem cell-based therapy for malignant gliomas.

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Abstract

Glioma, which accounts for more than 30% of primary central nervous system tumours, is characterised by symptoms such as headaches, epilepsy, and blurred vision. Glioblastoma multiforme is the most aggressive, malignant, and lethal brain tumour in adults. Even with progressive combination treatment with surgery, radiotherapy, and chemotherapy, the prognosis for glioma patients is still extremely poor. Compared with the poor outcome and slowly developing technologies for surgery and radiotherapy, the application of targeted chemotherapy with a new mechanism has become a research focus in this field.Moreover, targeted therapy is promising for most solid tumours. The tumour-tropic ability of stem cells, including neural stem cells and mesenchymal stem cells, provides an alternative therapeutic approach. Thus, mesenchymal stem cell-based therapy is based on a tumour-selective capacity and has been thought to be an effective anti-tumour option over the past decades. An increasing number of basic studies on mesenchymal stem cell-based therapy for gliomas has yielded complex outcomes.In this review, we summarise the biological characteristics of human mesenchymal stem cells, and the

current status and potential challenges of mesenchymal stem cell-based therapy in patients with malignant gliomas.

Send to

Biomaterials. 2018 Aug 9;182:259-268. doi: 10.1016/j.biomaterials.2018.08.024. [Epub ahead of print]

TRAIL-secreting human mesenchymal stem cells engineered by a non-viral vector and photochemical internalization for pancreatic cancer gene therapy.

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Author information

Abstract

Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) is a promising therapeutic protein to selectively induce cancer cell apoptosis. However, TRAIL exhibits low stability and short half-life due to its denaturation. Thus, delivering the TRAIL gene for stem cell-mediated gene therapy was conducted by using non-viral vectors (a less efficient but safer method). To overcome the limitation of non-viral vectors, photochemical internalization (PCI) was utilized for enhanced transfection efficiency of secreting TRAIL from human mesenchymal stem cells (hMSCs). To explore a more effective approach for cancer treatment, polyplexes were formed by using TRAIL plasmid (pTRAIL) and branched polyethyleneimine (bPEI). PCI is applied to improve polyplex entrapping in hMSCs and enhance the transfection efficiency of TRAIL into hMSCs for secretion in tumors via a homing effect. We demonstrate that PCI-mediated polyplex loading significantly enhanced TRAIL expression in stem cells and that homing ability magnified cancer targeting. The xenograft mouse model shows that polyplex loaded hMSCs (pTRAIL/bPEI@hMSCs) under laser irradiation results in a beneficial therapeutic antitumor effect compared to unloaded polyplexes and pTRAIL/bPEI@hMSCs. Taken together, the delivery of PCI-pTRAIL/bPEI@hMSCs offers exciting potential treatments in pancreatic cancer gene therapy via the enhanced the transfection efficiency of TRAIL by PCI system and the tumor homing properties of hMSCs.

JAMA Dermatol. 2018 Aug 22. doi: 10.1001/jamadermatol.2018.2516. [Epub ahead of print]

Pathogenetic Characteristics of Mesenchymal Stem Cells in Hidradenitis Suppurativa.

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Author information

Abstract

IMPORTANCE:

Hidradenitis suppurativa (HS) is a disease of the terminal hair follicle in apocrine gland-enriched skin areas, where immunobiology dysregulation of mesenchymal stem cells (MSCs) may have a key role.

OBJECTIVE:

To investigate the MSC profile in patients with HS and in healthy controls.

DESIGN, SETTING, AND PARTICIPANTS:

In this prospective case-control study, patients with HS were recruited from the Dermatological Clinic at the Department of Clinical and Molecular Sciences, Università Politecnica delle Marche, Ancona, Italy. Biopsy specimens were analyzed at the Histology Section of the Department of Clinical and Molecular Sciences. Participants included 11 patients with HS and 9 healthy controls, who were recruited into the study between January 20, 2015, and September 20, 2016, and underwent punch biopsy from axillary skin. None of the participants had received any antibiotics (systemic or topical therapy) within almost 12 weeks before the study.

MAIN OUTCOMES AND MEASURES:

The immunophenotypic profile of MSCs was characterized following the minimal criteria established by the International Society for Cellular Therapy for the identification of MSCs. Levels of 12 cytokines belonging to helper T-cell subtypes 1, 2, and 17 pathways were examined on the secretome of isolated cells by enzyme-linked immunoabsorbent assay.

RESULTS:

Skin MSCs were characterized in 11 patients with HS (8 women and 3 men; mean [SD] age, 35.8 [7.9] years) and 9 healthy controls (7 women and 2 men; mean [SD] age, 36.7 [6.9] years). The healthy controls were matched with patients with HS for body mass index. Mesenchymal stem cells isolated from patients with HS (HS-MSCs) and from healthy controls (C-MSCs) met the International Society for Cellular Therapy minimal criteria. Compared with C-MSCs, cytokine analyses of HS-MSCs revealed statistically significant overexpression of interleukin (IL) 6 (median [interquartile range {IQR}], 8765.00 [7659.00-9123.00] vs 2849.00 [2609.00-3001.00] pg/mL; P = .008), IL-10 (median [IQR], 29.46 [26.35-35.79] vs 21.36 [19.89-23.33] pg/mL; P = .004), IL-12 (median [IQR], 15.25 [13.27-16.25] vs 11.89 [10.73-12.33] pg/mL; P = .03), IL-17A (median [IQR], 15.24 [13.23-17.24] vs 11.24 [10.28-11.95] pg/mL; P = .008), tumor necrosis factor (median [IQR], 42.54 [42.20-43.94] vs 32.55 [31.78-33.28] pg/mL; P = .004), transforming growth factor β1 (median [IQR], 1728.00 [1535.00-1979.00] vs 500.80 [465.00-634.50] pg/mL; P = .004), and interferon γ (median [IQR], 11.49 [10.71-12.35] vs 9.45 [9.29-10.01] pg/mL; P = .005).

CONCLUSIONS AND RELEVANCE:

Mesenchymal stem cells isolated from the skin of patients with HS seem to be activated toward an inflammatory status. The imbalance between proinflammatory and anti-inflammatory activities of MSCs favors the hypothesis of their pathogenic involvement in HS.

Sci Rep. 2018 Aug 20;8(1):12439. doi: 10.1038/s41598-018-30772-4.

Evaluation of platelet lysate as a substitute for FBS in explant and enzymatic isolation methods of human umbilical cord MSCs.

Kandoi S[1], L PK[2], Patra B[1], Vidyasekar P[1], Sivanesan D[1], S V[2], K R[3], Verma RS[4].
Author information

Abstract

Mesenchymal stem cells (MSCs) have immense potential for cell-based therapy of acute and chronic pathological conditions. MSC transplantation for cell-based therapy requires a substantial number of cells in the range of 0.5-2.5 × 10^6 cells/kg body weight of an individual. A prolific source of MSCs followed by in vitro propagation is therefore an absolute prerequisite for clinical applications. Umbilical cord tissue (UCT) is an abundantly available prolific source of MSC that are fetal in nature and have higher potential for ex-vivo expansion. However, the ex-vivo expansion of MSCs using a xenogeneic supplement such as fetal bovine serum (FBS) carries the risk of transmission of zoonotic infections and immunological reactions. We used platelet lysate (PL) as a xeno-free, allogeneic replacement for FBS and compared the biological and functional characteristics of MSC processed and expanded with PL and FBS by explant and enzymatic method. UCT-MSCs expanded using PL displayed typical immunophenotype, plasticity, immunomodulatory property and chromosomal stability. PL supplementation also showed 2-fold increase in MSC yield from explant culture with improved immunomodulatory activity as compared to enzymatically dissociated cultures. In conclusion, PL from expired platelets is a viable alternative to FBS for generating clinically relevant numbers of MSC from explant cultures over enzymatic method.

Acta Biomater. 2018 Sep 1;77:142-154. doi: 10.1016/j.actbio.2018.07.004. Epub 2018 Jul 4.

Fractionated human adipose tissue as a native biomaterial for the generation of a bone organ by endochondral ossification.

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Author information

Abstract

Many steps are required to generate bone through endochondral ossification with adipose mesenchymal stromal cells (ASC), from cell isolation to in vitro monolayer expansion, seeding into scaffolds, cartilaginous differentiation and in vivo remodeling. Moreover, monolayer expansion and passaging of ASC strongly decreases their differentiation potential. Here, we propose that adipose tissue itself can be used as scaffold for ASC expansion and endochondral ossification. Human liposuctions were fractionated and cultured for 3 weeks with proliferative medium in suspension. The resulting constructs, named Adiscaf, were compared to constructs generated with a previously developed, control approach, i.e. collagen sponges seeded with monolayer-expanded ASC. After 4 weeks of chondrogenic differentiation, Adiscaf contained cartilage tissue, characterized by glycosaminoglycans and collagen type II. After 2 additional weeks of hypertrophic differentiation, Adiscaf showed upregulation of hypertrophic markers at the gene expression and protein levels. After 8 weeks of in vivo implantation, Adiscaf resulted in ectopic bone tissue formation, including bone marrow elements. Adiscaf showed superior in vitro differentiation and in vivo performance as compared to the control paradigm involving isolation and monolayer expansion of ASC. This new paradigm exploits the physiological niche of adipose tissue and strongly suggests a higher functionality of cells inside adipose tissue after in vitro expansion. This study demonstrates that adult human adipose tissue

used as a native construct can generate a bone organ by endochondral ossification. The concept could be exploited for the generation of osteogenic grafts for bone repair.

STATEMENT OF SIGNIFICANCE:

In this study we used adult human adipose tissue as scaffolding materials (called Adiscaf) to generate a bone organ by endochondral ossification. Adiscaf concept is based on the culture of adipose tissue cells inside their native microenvironment for the generation of osteogenic grafts for bone repair. This simplified approach overcomes several limitations linked to the current techniques in bone tissue engineering, such as isolation of cells and inadequate properties of the biomaterials used as scaffolds. In addition, the present paradigm proposes to exploit physiological niches in order to better maintain the functionality of cells during their in vitro expansion. This project not only has a scientific impact by evaluating the impact of native physiological niches on the functionality and chondrogenic differentiation of mesenchymal progenitors but also a clinical impact to generate osteogenic grafts and/or osteoinductive materials for bone regeneration and repair.

Cell J. 2019 Jan;20(4):592-598. doi: 10.22074/cellj.2019.5370. Epub 2018 Aug 1.

Safety, Feasibility of Intravenous and Intrathecal Injection of Autologous Bone Marrow Derived Mesenchymal Stromal Cells in Patients with Amyotrophic Lateral Sclerosis: An Open Label Phase I Clinical Trial.

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Abstract

OBJECTIVE:

Amyotrophic lateral sclerosis (ALS) is the most severe disorder within the spectrum of motor neuron diseases (MND) that has no effective treatment and a progressively fatal outcome. We have conducted two clinical trials to assess the safety and feasibility of intravenous (IV) and intrathecal (IT) injections of bone marrow derived mesenchymal stromal cells (BM-MSCs) in patients with ALS.

MATERIALS AND METHODS:

This is an interventional/experimental study. We enrolled 14 patients that met the following inclusion criteria: definitive diagnosis of sporadic ALS, ALS Functional Rating Scale (ALS-FRS) ≥24, and ≥40% predicted forced vital capacity (FVC). All patients underwent bone marrow (BM) aspiration to obtain an adequate sample for cell isolation and culture. Patients in group 1 (n=6) received an IV and patients in group 2 (n=8) received an IT injection of the cell suspension. All patients in both groups were followed at 24 hours and 2, 4, 6, and 12 months after the injection with ALS-FRS, FVC, laboratory tests, check list of side effects and brain/spinal cord magnetic resonance imaging (MRI). In each group, one patient was lost to follow up one month after cell injection and one patient from IV group died due to severe respiratory insufficiency and infection.

RESULTS:

During the follow up there were no reports of adverse events in terms of clinical and laboratory assessments. In MRI, there was not any new abnormal finding. The ALS-FRS score and FVC percentage significantly reduced in all patients from both groups.

CONCLUSION:

This study has shown that IV and IT transplantation of BM-derived stromal cells is safe and feasible (Registration numbers: NCT01759797 and NCT01771640).

Stem Cells Int. 2018 Jul 5;2018:7089484. doi: 10.1155/2018/7089484. eCollection 2018.

Human Bone Marrow Mesenchymal Stromal Cells Promote Bone Regeneration in a Xenogeneic Rabbit Model: A Preclinical Study.

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Author information

Abstract

Significant research efforts have been undertaken during the last decades to treat musculoskeletal disorders and improve patient's mobility and quality of life. The goal is the return of function as quickly and completely as possible. Cellular therapy has been increasingly employed in this setting. The design of this study was focused on cell-based alternatives. The present study aimed at investigating the bone regeneration capacity of xenogeneic human bone marrow-derived mesenchymal stromal cell (hMSC) implantation with tricalcium phosphate (TCP) granules in an immunocompetent rabbit model of critical-size bone defects at the femoral condyles. Two experimental groups, TCP and hMSC + TCP, were compared. Combination of TCP and hMSC did not affect cell viability or osteogenic differentiation. We also observed significantly higher bone regeneration in vivo in the hMSC + TCP group, which also displayed better TCP osteointegration. Also, evidence of hMSC contribution to a better TCP osteointegration was noticed. Finally, no inflammatory reaction was detected, besides the xenotransplantation of human cells into an immunocompetent recipient. In summary, hMSC combined with TCP granules is a potential combination for bone regeneration purposes that provides better preclinical results compared to TCP alone.

Curr Osteoporos Rep. 2018 Aug 20. doi: 10.1007/s11914-018-0471-7. [Epub ahead of print]

Interactions Between Disseminated Tumor Cells and Bone Marrow Stromal Cells Regulate Tumor Dormancy.

Widner DB[1], Park SH[1], Eber MR[1], Shiozawa Y[2].
Author information

Abstract

PURPOSE OF REVIEW:

To succinctly summarize recent findings concerning dormancy regulating interactions between bone marrow stromal cells and disseminated tumor cells.

RECENT FINDINGS:

Recent studies have highlighted roles of the bone marrow microenviroment, including osteoblasts, mesenchymal stem cells (MSCs), and endothelial cells, in inducing or maintaining cancer cell dormancy. Key pathways of interest include: osteoblast-induced transforming growth factor (TGF)-β2 signaling, transfer of MSC-derived exosomes containing dormancy inducing microRNA, cancer cell cannibalism of MSCs, and endothelial cell secretion of thrombospondin 1 (TSP1). The bone marrow is a common site of metastatic disease recurrence following a period of cancer cell dormancy. Understanding why disseminated tumor cells enter into dormancy and later resume cell proliferation and growth is vital to developing effective therapeutics against these cells. The bone marrow stroma and the various pathways through which it participates in crosstalk with cancer cells are essential to furthering understanding of how dormancy is regulated.