Clin Transl Oncol. 2018 May 23. doi: 10.1007/s12094-018-1894-4. [Epub ahead of print]

Characterization of tumor-derived mesenchymal stem cells potentially differentiating into cancer-associated fibroblasts in lung cancer.

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Author information

Abstract

PURPOSE:

The goal of this study was to understand if mesenchymal stem cells isolated from lung tumor tissue (T-MSCs) may differentiate into cancer associated fibroblasts (CAFs), that promote neoplastic progression, angiogenesis and metastasis in the epithelial solid tumors, mimicking the tumor microenvironmental influence.

METHODS:

MSCs were been obtained from healthy (Control, C-MSCs) and tumor (T-MSCs) tissue of one patient who underwent a lobectomy for a lung adenocarcinoma pT1bN0. Isolated cells were characterized for the presence of molecular markers (identified by routine diagnostic characterization in differentiated tumoral cells), stemness properties, and CAF-related markers expression. Subsequently, cells were co-cultured with a lung adenocarcinoma cell line (A549 cells) to evaluate the effects on proliferation, oncogene expression and IL6 secretion.

RESULTS:

C- and T-MSCs did not present EGFR mutations unlike tumor tissue and showed a stem-like immunophenotype, characterized by the ability to differentiate towards osteo-, chondro- and adipogenic lineages. The expression of markers referred to CAFs (α-SMA, HI-1α, MMP11, VEGF, CXCL12, TGF-β1, TGF-βRII, IL6, TNFα) was significantly higher in T-MSCs than in C-MSCs. The co-cultures with A549 cells led to the over-expression of selected oncogenes and to the increase of IL6 secretion in T-MSCs but not in C-MSCs.

CONCLUSIONS:

MSCs isolated from tumor tissue displayed distinct properties compared to MSCs isolated from healthy tissue, suggesting T-MSCs differentiation towards a CAF-related phenotype under the influence of the tumoral microenvironment.

Int Orthop. 2018 May 24. doi: 10.1007/s00264-018-4000-1. [Epub ahead of print]

History of concentrated or expanded mesenchymal stem cells for hip osteonecrosis: is there a target number for osteonecrosis repair?

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Author information

Abstract

PURPOSE:

Despite multiple possible treatments, the risk of collapse remains the main problem of osteonecrosis. Heart failure (HF). In an effort to address the reverse this issue, curative strategies with regenerative medicine are increasingly being considered. The aim of this technology is to halt or reverse progression of the disease to collapse.

MATERIAL AND METHODS:

The pioneering report by Hernigou published in 2002 was the first pilot study suggesting that injection of bone marrow stem cells was a safe approach able to improve osteonecrosis in patients with early stages. Since then, an impressive number of studies and trials employing unselected BM-derived cells (1000 the last 2 years) showed that delivery of those cells to the site of osteonecrosis during core decompression was somehow able to ameliorate the patient with osteonecrosis. In order to translate the promise of this cell therapy into better clinical benefit, many questions need to be addressed. In this review, we therefore analyzed current clinical experience of the literature and our experience of 4000 cases to address these questions and particularly the number of cells that should be injected.

RESULTS:

After almost 20 years of clinical research in this field, we are still far from having drawn conclusions on the number of cells we should inject in regenerating hip osteonecrosis. Findings are difficult to interpret due to heterogeneity of causes of osteonecrosis, as well as differences in the cells count, sample quality, and stages of osteonecrosis. The authors address specific issues, as cell quality, cell numbers, volume of osteonecrosis, concentration of cells, and ex vivo expansion. Bone marrow mesenchymal stem cells are supposed to be "functionally competent," but are collected from the bon, marrow of patients with diseases and risk factors of osteonecrosis. The recipient organ (bone osteonecrosis) is a tissue where several alterations have already occurred. These questions are addressed in this review.

CONCLUSION:

In this review, we analyzed current clinical experience regarding cell therapy and address issues that should be a guide for future cell-based therapeutic application in osteonecrosis.

Sci Rep. 2018 May 25;8(1):8162. doi: 10.1038/s41598-018-26546-7.

Effects of Decade Long Freezing Storage on Adipose Derived Stem Cells Functionality.

Shaik S[1], Wu X[2], Gimble J[2,3], Devireddy R[4].

Author information

Abstract

Over the last decade and half, the optimization of cryopreservation for adipose tissue derived stromal/stem cells (ASCs) especially in determining the optimal combination of cryoprotectant type, cooling rate, and thawing rate have been extensively studied. In this study, we examined the functionality of ASCs that have been frozen-stored for more than 10 years denoted as long-term freezing, frozen within the last 3 to 7 years denoted as short-term freezing and compared their response with fresh ASCs. The mean post-thaw viability for long-term frozen group was 78% whereas for short-term frozen group 79% with no significant differences between the two groups. The flow cytometry evaluation of stromal surface markers, CD29, CD90, CD105, CD44, and CD73 indicated the expression (above 95%) in passages P1-P4 in all of the frozen-thawed ASC groups and fresh ASCs whereas the hematopoietic markers CD31, CD34, CD45, and CD146 were expressed extremely low (below 2%) within both the frozen-thawed and fresh cell groups. Quantitative real time polymerase chain reaction (qPCR) analysis revealed some differences between the osteogenic gene expression of long-term frozen group in comparison to fresh ASCs. Intriguingly, one group of cells from the short-term frozen group exhibited remarkably higher expression of osteogenic genes in comparison to fresh ASCs. The adipogenic differentiation potential remained virtually unchanged between all of the frozen-thawed groups and the fresh ASCs. Long-term cryopreservation of ASCs, in general, has a somewhat negative impact on the osteogenic potential of ASCs, especially as it relates to the decrease in osteopontin gene expression but not significantly so with respect to RUNX2 and osteonectin gene expressions. However, the adipogenic potential, post thaw viability, and immunophenotype characteristics remain relatively intact between all the groups.

J Cell Physiol. 2018 May 24. doi: 10.1002/jcp.26785. [Epub ahead of print]

Spheroids from adipose-derived stem cells exhibit an miRNA profile of highly undifferentiated cells.

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Author information

Abstract

Two-dimensional (2D) cell cultures have been extensively used to investigate stem cell biology, but new insights show that the 2D model may not properly represent the potential of the tissue of origin. Conversely, three-dimensional cultures exhibit protein expression patterns and intercellular junctions that are more representative of their in vivo condition. Multiclonal cells that grow in suspension are defined as "spheroids," and we have previously demonstrated that spheroids from adipose-derived stem cells (S-ASCs) displayed enhanced regenerative capability. With the current study, we further characterized S-ASCs to further understand the molecular mechanisms underlying their stemness properties. Recent studies have shown that microRNAs (miRNAs) are involved in many cellular mechanisms, including stemness maintenance and proliferation, and adipose stem cell differentiation. Most studies have been conducted to identify a specific miRNA profile on adherent adipose stem cells,

although little is still known about S-ASCs. In this study, we investigate for the first time the miRNA expression pattern in S-ASCs compared to that of ASCs, demonstrating that cell lines cultured in suspension show a typical miRNA expression profile that is closer to the one reported in induced pluripotent stem cells. Moreover, we have analyzed miRNAs that are specifically involved in two distinct moments of each differentiation, namely early and late stages of osteogenic, adipogenic, and chondrogenic lineages during long-term in vitro culture. The data reported in the current study suggest that S-ASCs have superior stemness features than the ASCs and they represent the true upstream stem cell fraction present in adipose tissue, relegating their adherent counterparts.

Bull Exp Biol Med. 2018 May;165(1):101-104. doi: 10.1007/s10517-018-4108-8. Epub 2018 May 24.

Use of Mesenchymal Stem Cells for Possible Repair of Doxorubicin-Damaged Organs and Tissues in Experimental Monkeys.

Agrba VZ[1], Karal-Ogly DD[2], Gvozdik TE[2], Kaplanyan PA[2], Demenkova NP[2], Gvaramiya IA[2], Mukhametzyanova EI[2], Shamsutdinova OA[2], Chuguev YP[2], Kal'sina SS[2], Konoplyannikov AG[2], Araviashvili DE[2], Klots IN[2], Lapin BA[2].
Author information

Abstract

Three injections of doxorubicin to rhesus macaques cause severe intoxication, characterized by anemia, cachexia, and degeneration of the viscera. The life span of monkeys injected with the drug and receiving after 24 h mesenchymal stem cell transplantation varied from 96 to 120 days in comparison with 50-74 days in animals receiving stem cells before doxorubicin. Controls received doxorubicin and saline; the lifespan of one monkey was 24 days, of the other - 1 year and 8 months. The increase in activity of proinflammatory cytokine IL-6 was paralleled by an increase in the level of C-reactive protein

Bull Exp Biol Med. 2018 May;165(1):115-120. doi: 10.1007/s10517-018-4111-0. Epub 2018 May 24.

Functional Parameters of Physiological Systems of Laboratory Primates after Administration of Doxorubicin and Transplantation of Mesenchymal Stem Cells.

Agrba VZ[1], Agrba VZ[2], Karal-Ogly DD[2], Kal'sina SS[2], Konoplyannikov AG[2], Gvozdik TE[2], Gvaramiya IA[2], Klots IN[2], Mukhametzyanova EI[2], Chuguev YP[2], Shamsutdinova OA[2], Araviashvili DE[2], Porkhanov VA[2], Lapin BA[2].
Author information

Abstract

We studied physiological parameters of rhesus monkeys after administration of anthracycline antibiotic doxorubicin. Intravenous administration of the drug caused intoxication manifested in in an abrupt body weight loss, baldness, vomiting, and exicosis. Intoxication in monkeys determined by the damaging effects of doxorubicin on organs and tissues is also characterized by significant changes in the blood: leukopenia, thrombocytopenia, neutropenia, monocytopenia, lymphocytosis, and a sharp drop of CD20+ B cell content. The total protein and albumin content in the blood significantly decreased. A sharp increase in C-reactive protein was also accompanied by an increase in activity of

proinflammatory cytokine IL-6. Transplantation of mesenchymal stem cells in some cases can significantly alleviate doxorubicin-induced damage to organs and maintain normal clinical status of monkeys after two injections of the drug. Late transplantation of stem cells does not have a protective effect and does not protect the animals from the damaging effects of doxorubicin. We found that the protective effect of mesenchymal stem cells depends on the dose of the drug, total number of cells, and the time of their transplantation. It should be noted that human and monkey mesenchymal stem cells produce similar regenerative effects, at least in the doxorubicin toxicity model.

Stem Cell Rev. 2018 May 26. doi: 10.1007/s12015-018-9822-0. [Epub ahead of print]

Validation of reference and identity-defining genes in human mesenchymal stem cells cultured under unrelated fetal bovine serum batches for basic science and clinical application.

Banfi F[1], Colombini A[2], Perucca Orfei C[2], Parazzi V[1], Ragni E[3].
Author information

Abstract

The molecular profile of human mesenchymal stem cells (MSCs) have emerged as a key factor in defining their identity. Nevertheless, the effect of fetal bovine serum (FBS) batches or origin on MSC molecular signature has been neglected. In this frame, chemical fingerprint of FBS batches from unrelated countries showed strong correlation between chemical composition and country of origin. Thus, the aim of this study was to evaluate in stem cells isolated from bone marrow (BMMSCs) and umbilical cord-blood (CBMSCs) the effects of independently collected FBS batches on both twelve commonly used reference genes (RGs) and a selected panel of thirty-eight genes crucial for MSC definition in both research and clinical settings. Gene expression stability was estimated comparing the outcomes of two applets: geNorm and NormFinder. The bioinformatics analysis emphasized that, in a panorama of general balance, few RG candidates (YWHAZ/UBC for BMMSCs, RPLP0/EF1A for CBMSCs and EF1A/TBP for both MSCs scored together) showed superior stability. In addition, a wider study on genes involved in differentiation/proliferation/stemness processes, often used to define MSC potency, showed that these genes exhibited no major transcriptional modulation after treatment with different FBS, and allowed the identification of genes strongly discriminating between BM- and CBMSC populations. Therefore, in conclusion, FBS origin does not dramatically impact the general molecular profile of MSCs, although we could identify validated candidates able to allow more reliable comparison of data regarding MSC identity and potency and obtained by research laboratories and clinical manufacturers using different sera.

Stem Cell Rev. 2018 May 24. doi: 10.1007/s12015-018-9824-y. [Epub ahead of print]

Mesenchymal Stem Cells: Miraculous Healers or Dormant Killers?

Ghaderi A[1], Abtahi S[2].
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Abstract

Mesenchymal Stem Cells (MSCs) are a heterogeneous population of fibroblast-like cells which maintain self-renewability and pluripotency to differentiate into mesodermal cell lineages. The use of MSCs in clinical settings began with high enthusiasm and the number of MSC-based clinical trials has been rising ever since. However; the very unique characteristics of MSCs that made them suitable to for therapeutic use, might give rise to unwanted outcomes, including tumor formation and progression. In this paper, we present a model of carcinogenesis initiated by MSCs, which chains together the tissue organization field theory, the stem cell theory, and the inflammation-cancer chain. We believe that some tissue resident stem cells could be leaked cells from bone marrow MSC pool to various injured tissue, which consequently transform and integrate in the host tissue. If the injury persists or chronic inflammation develops, as a consequence of recurring exposure to growth factors, cytokines, etc. the newly formed tissue from MSCs, which still has conserved their mesenchymal and stemness features, go through rapid population expansion, and nullify their tumor suppressor genes, and hence give rise to neoplastic cell (carcinomas, sarcomas, and carcino-sarcomas). Considering the probability of this hypothesis being true, the clinical and therapeutic use of MSCs should be with caution, and the recipients' long term follow-up seems to be insightful.

Cell Stem Cell. 2018 Jun 1;22(6):824-833. doi: 10.1016/j.stem.2018.05.004.

Mesenchymal Stromal Cells: Clinical Challenges and Therapeutic Opportunities.

Galipeau J[1], Sensébé L[2].
Author information
Abstract

Mesenchymal stromal cells (MSCs) have been the subject of clinical trials for more than a generation, and the outcomes of advanced clinical trials have fallen short of expectations raised by encouraging pre-clinical animal data in a wide array of disease models. In this Perspective, important biological and pharmacological disparities in pre-clinical research and human translational studies are highlighted, and analyses of clinical trial failures and recent successes provide a rational pathway to MSC regulatory approval and deployment for disorders with unmet medical needs.

Expert Rev Hematol. 2018 Jun 1. doi: 10.1080/17474086.2018.1483717. [Epub ahead of print]

Incorporating placental tissue in cord blood banking for stem cell transplantation.

Teofili L[1], Silini AR[2], Bianchi M[3], Valentini CG[3], Parolini O[2,4].
Author information
Abstract

Human term placenta is comprised of various tissues from which different cell populations can be obtained, including hematopoietic stem cells and mesenchymal stem/stromal cells (MSCs). Areas

covered: This review will discuss the possibility to incorporate placental tissue cells in cord blood banking. It will discuss general features of human placenta, with a brief review of the immune cells at the fetal-maternal interface and the different cell populations isolated from placenta, with a particular focus on MSCs. It will address the question as to why placenta-derived MSCs should be banked with their hematopoietic counterparts. It will discuss clinical trials which are studying safety and efficacy of placenta tissue-derived MSCs in selected diseases, and preclinical studies which have proven their therapeutic properties in other diseases. It will discuss banking of umbilical cord blood and raise several issues for improvement, and the applications of cord blood cells in non-malignant disorders. Expert Commentary: Umbilical cord blood banking saves lives worldwide. The concomitant banking of non-hematopoietic cells from placenta, which could be applied therapeutically in the future, alone or in combination to their hematopoietic counterparts, could exploit current banking processes while laying the foundation for clinical trials exploring placenta-derived cell therapies in regenerative medicine.

Oncol Lett. 2018 Jun;15(6):9142-9150. doi: 10.3892/ol.2018.8463. Epub 2018 Apr 11.

Tumor-derived mesenchymal-stem-cell-secreted IL-6 enhances resistance to cisplatin via the STAT3 pathway in breast cancer.

Xu H[1], Zhou Y[1], Li W[1], Zhang B[2], Zhang H[1], Zhao S[1], Zheng P[1], Wu H[1], Yang J[1].
Author information

Abstract

Cisplatin is used for the treatment of a range of solid malignant tumors; however, with prolonged treatment durations, the sensitivity of tumor cells to the drug decreases owing to an unclear mechanism of drug resistance. The present study aimed to investigate whether breast-cancer-tissue-derived mesenchymal stem cells (BC-MSCs) are involved in mediating the effects of cisplatin on breast cancer cells, and which component of the BC-MSC conditioned medium (BC-MSC-CM) exhibited an anti-apoptotic effect. Cytokines/chemokines in BC-MSC-CM were quantified using a Luminex immunoassay, and reverse transcription-quantitative polymerase chain reaction analysis detected interleukin-6 (IL-6) levels in MCF-7 cells following different treatments. MTT and flow cytometry analysis measured cell vitality and apoptosis, respectively, and activation of signal transduced and activator of transcription 3 (STAT3) was evaluated by western blotting. BC-MSCs reversed the pro-apoptotic effect of cisplatin and enhanced the proliferation of MCF-7 cells more potently than bone-marrow-derived MSCs. Further study revealed that BC-MSCs secreted IL-6 to protect MCF-7 cells from apoptosis and promote their survival. Neutralizing IL-6 with a specific antibody partially inhibited the IL-6/STAT3 signaling pathway and reversed the promoter role of BC-MSCs in MCF-7 cells. Taken together, the findings of the present study indicated that BC-MSCs decreased the level of cisplatin-induced apoptosis in MCF-7 cells by activating the IL-6/STAT3 pathway in cancer cells. BC-MSCs, as important cells in the tumor microenvironment, have a key role in the treatment of breast cancer.

Chin J Dent Res. 2018;21(2):101-111. doi: 10.3290/j.cjdr.a40436.

Transcriptomics and Functional Analysis of Graphene-Guided Osteogenic Differentiation of Mesenchymal Stem Cells.

Lv LW, Liu YS, Zhang P, Gu M, Bai XS, Xiong CY, Zhou YS.

Abstract

OBJECTIVE:

To explore graphene's effects on the gene expression profile of mesenchymal stem cells, and to reveal the mechanisms of graphene-guided osteogenic differentiation.

METHODS:

Human adipose-derived mesenchymal stem cells (hASCs) were cultured on single-layer graphene-coated titanium disks or titanium disks in proliferation medium (control) or osteoinduction medium for 7 days before RNA extraction. After library construction and RNA sequencing, identification of differentially expressed genes was performed through Limma package of R platform, with a cut-off value of log fold change (logFC) > = |1|. Pathway and Gene ontology (GO) analyses were conducted on DAVID Bioinformatics Resources 6.8 (NIAID/NIH). Network analyses were performed by the Ingenuity Pathways Analysis (IPA).

RESULTS:

Signalling pathway analysis revealed the top five pathways - cytokine-cytokine receptor interaction, neuroactive-ligand receptor interaction, calcium signalling pathway, PI3K-Akt signalling pathway and cell adhesion molecules. GO analyses demonstrated significant changes on cell adhesion, calcium signalling, and epigenetic regulation. IPA network analyses demonstrated that inflammation-related pathways were influenced by graphene, while the downstream factors of histone H3 and H4 were also altered especially under the existence of osteoinduction medium.

CONCLUSION:

Graphene promotes osteogenic differentiation of hASCs mainly by influencing cell adhesion, cytokine-cytokine receptor interactions, inflammatory responses, and potentially influences histone H3 and H4 through epigenetic regulation.

Cytotherapy. 2018 May 25. pii: S1465-3249(18)30514-0. doi: 10.1016/j.jcyt.2018.05.003. [Epub ahead of print]

Centralised versus decentralised manufacturing and the delivery of healthcare products: A United Kingdom exemplar.

Harrison RP[1], Rafiq QA[2], Medcalf N[3].

Author information

Abstract

BACKGROUND:

The cell and gene therapy (CGT) field is at a critical juncture. Clinical successes have underpinned the requirement for developing manufacturing capacity suited to patient-specific therapies that can satisfy the eventual demand post-launch. Decentralised or 'redistributed' manufacturing divides manufacturing capacity across geographic regions, promising local, responsive manufacturing, customised to the end user, and is an attractive solution to overcome challenges facing the CGT manufacturing chain.

METHODS:

A study was undertaken building on previous, so far unpublished, semi-structured interviews with key opinion leaders in advanced therapy research, manufacturing and clinical practice. The qualitative findings were applied to construct a cost of goods model that permitted the cost impact of regional siting to be combined with variable and fixed costs of manufacture of a mesenchymal stromal cell product.

RESULTS:

Using the United Kingdom as an exemplar, cost disparities between regions were examined. Per patient dose costs of ~£1,800 per 75,000,000 cells were observed. Financial savings from situating the facility outside of London allow 25-41 additional staff or 24-35 extra manufacturing vessels to be employed. Decentralised quality control to mitigate site-to-site variation was examined. Partial decentralisation of quality control was observed to be financially possible and an attractive option for facilitating release 'at risk'.

DISCUSSION:

There are important challenges that obstruct the easy adoption of decentralised manufacturing that have the potential to undermine the market success of otherwise promising products. By using the United Kingdom as an exemplar, the modelled data provide a framework to inform similar regional policy considerations across other global territories.