ML 04-18 (24/01/2018)

J Cell Physiol. 2018 Jan 18. doi: 10.1002/jcp.26493. [Epub ahead of print]

Autocrine signals increase Ovine Mesenchymal Stem Cells migration through Aquaporin-1 and CXCR4 overexpression.

Pelagalli A[1,2], Nardelli A[2], Lucarelli E[3], Zannetti A[2], Brunetti A[1].
Author information

Abstract

Sheep is a relevant large animal model that is frequently used to test innovative tissue engineering (TE) approaches especially for bone reconstruction. Mesenchymal stem cells (MSCs) are used in TE applications because they represent key component of adult tissue repair. Importantly, MSCs from different species show similar characteristics, which facilitated their application in translational studies using animal models. Nowadays, many researches are focusing on the use of ovine mesenchymal stem cells (oMSCs) in orthopedic preclinical settings for regenerative medicine purposes. Therefore, there is a need to amplify our knowledge on the mechanisms underlying the behaviour of these cells. Recently, several studies have shown that MSC function is largely dependent on factors that MSCs release in the environment as well as in conditioned medium (CM). It has been demonstrated that MSCs through autocrine and paracrine signals are able to stimulate proliferation, migration and differentiation of different type of cells including themselves. In this study, we investigated the effects of the CM produced by oMSCs on oMSCs themselves and we explored the signal pathways involved. We observed that CM caused an enhancement of oMSC migration. Furthermore, we found that CM increased levels of two membrane proteins involved in cell migration, Aquaporin 1 (AQP1) and C-X-C chemokine receptor type 4 (CXCR4), and activated Akt and Erk intracellular signal pathways. In conclusion, taken together our results suggest the high potential of autologous CM as a promising tool to modulate behaviour of MSCs thus improving their use in therapeutically approaches.

J Bone Joint Surg Am. 2018 Jan 17;100(2):138-146. doi: 10.2106/JBJS.17.00132.

Minimally Manipulated Bone Marrow Concentrate Compared with Microfracture Treatment of Full-Thickness Chondral Defects: A One-Year Study in an Equine Model.

Chu CR[1,2], Fortier LA[3], Williams A[1], Payne KA[4], McCarrel TM[5], Bowers ME[6], Jaramillo D[2,7].

Author information

Abstract

BACKGROUND:

Microfracture is commonly performed for cartilage repair but usually results in fibrocartilage. Microfracture augmented by autologous bone marrow concentrate (BMC) was previously shown to yield structurally superior cartilage repairs in an equine model compared with microfracture alone. The

current study was performed to test the hypothesis that autologous BMC without concomitant microfracture improves cartilage repair compared with microfracture alone.

METHODS:

Autologous sternal bone marrow aspirate (BMA) was concentrated using a commercial system. Cells from BMC were evaluated for chondrogenic potential in vitro and in vivo. Bilateral full-thickness chondral defects (15-mm diameter) were created on the midlateral trochlear ridge in 8 horses. Paired defects were randomly assigned to treatment with BMC without concomitant microfracture, or to microfracture alone. The repairs were evaluated at 1 year by in vitro assessment, arthroscopy, morphological magnetic resonance imaging (MRI), quantitative T2-weighted and ultrashort echo time enhanced T2* (UTE-T2*) MRI mapping, and histological assessment.

RESULTS:

Culture-expanded but not freshly isolated cells from BMA and BMC underwent cartilage differentiation in vitro. In vivo, cartilage repairs in both groups were fibrous to fibrocartilaginous at 1 year of follow-up, with no differences observed between BMC and microfracture by arthroscopy, T2 and UTE-T2* MRI values, and histological assessment ($p > 0.05$). Morphological MRI showed subchondral bone changes not observed by arthroscopy and improved overall outcomes for the BMC repairs ($p = 0.03$). Differences in repair tissue UTE-T2* texture features were observed between the treatment groups ($p < 0.05$).

CONCLUSIONS:

When BMC was applied directly to critical-sized, full-thickness chondral defects in an equine model, the cartilage repair results were similar to those of microfracture. Our data suggest that, given the few mesenchymal stem cells in minimally manipulated BMC, other mechanisms such as paracrine, anti-inflammatory, or immunomodulatory effects may have been responsible for tissue regeneration in a previous study in which BMC was applied to microfractured repairs. While our conclusions are limited by small numbers, the better MRI outcomes for the BMC repairs may have been related to reduced surgical trauma to the subchondral bone.

CLINICAL RELEVANCE:

MRI provides important information on chondral defect subsurface repair organization and subchondral bone structure that is not well assessed by arthroscopy.

Bioconjug Chem. 2018 Jan 23. doi: 10.1021/acs.bioconjchem.7b00757. [Epub ahead of print]

Combination of Heparin Binding Peptide and Heparin Cell Surface Coatings for Mesenchymal Stem Cell Spheroid Assembly.

Lei J, Murphy WL[1,2], Temenoff JS[3].
Author information

Abstract

Microtissues containing multiple cell types have been used in both in vitro models and in vivo tissue repair applications. However, to improve throughput, there is a need to develop a platform that supports self-assembly of a large number of 3D microtissues containing multiple cell types in a dynamic suspension system. Thus, the objective of this study was to exploit the binding interaction between the negatively charged glycosaminoglycan, heparin, and a known heparin binding peptide to establish a method that promotes assembly of mesenchymal stem cell (MSC) spheroids into larger aggregates. We characterized heparin binding peptide (HEPpep) and heparin coatings on cell surfaces and determined the specificity of these coatings in promoting assembly of MSC spheroids in dynamic culture. Overall, combining spheroids with both coatings promoted up to 70 ± 11% of spheroids to assemble into multiaggregate structures, as compared to only 10 ± 4% assembly when cells having the heparin coating were cultured with cells coated with a scrambled peptide. These results suggest that this self-assembly method represents an exciting approach that may be applicable for a wide range of applications in which cell aggregation is desired.

Aging Cell. 2018 Jan 16. doi: 10.1111/acel.12722. [Epub ahead of print]

Senescence chips for ultrahigh-throughput isolation and removal of senescent cells.

Chen Y[1], Mao P[1], Snijders AM[2], Wang D[1].
Author information

Abstract

Cellular senescence plays an important role in organismal aging and age-related diseases. However, it is challenging to isolate low numbers of senescent cells from small volumes of biofluids for downstream analysis. Furthermore, there is no technology that could selectively remove senescent cells in a high-throughput manner. In this work, we developed a novel microfluidic chip platform, termed senescence chip, for ultrahigh-throughput isolation and removal of senescent cells. The core component of our senescence chip is a slanted and tunable 3D micropillar array with a variety of shutters in the vertical direction for rapid cell sieving, taking advantage of the characteristic cell size increase during cellular senescence. The 3D configuration achieves high throughput, high recovery rate, and device robustness with minimum clogging. We demonstrated proof-of-principle applications in isolation and enumeration of senescent mesenchymal stem cells (MSCs) from undiluted human whole blood, and senescent cells from mouse bone marrow after total body irradiation, with the single-cell resolution. After scale-up to a multilayer and multichannel structure, our senescence chip achieved ultrahigh-throughput removal of senescent cells from human whole blood with an efficiency of over 70% at a flow rate of 300 ml/hr. Sensitivity and specificity of our senescence chips could be augmented with implementation of multiscale size separation, and identification of background white blood cells using their cell surface markers such as CD45. With the advantages of high throughput, robustness, and simplicity, our senescence chips may find wide applications and contribute to diagnosis and therapeutic targeting of cellular senescence.

Biotechnol J. 2018 Jan 15. doi: 10.1002/biot.201700085. [Epub ahead of print]

Donor variability in growth kinetics of healthy hMSCs using manual processing: considerations for manufacture of cell therapies.

Detela G[1], Bain OW[1], Kim HW[2,3], Williams DJ[4], Mason C[1], Mathur A[5], Wall IB[1,2,6].
Author information

Abstract

Human mesenchymal stromal cells (hMSCs) are excellent candidates for cell therapy but their expansion to desired clinical quantities can be compromised by ex vivo processing, due to differences between donor material and process variation. The aim of this article was to characterize growth kinetics of healthy baseline "reference" hMSCs using typical manual processing. Bone-marrow derived hMSCs from ten donors were isolated based on plastic adherence, expanded and analyzed for their growth kinetics until passage 4. Results indicate that hMSC density decreased with overall time in culture ($p<0.001$) but no significant differences were observed between successive passages after passage 1. In addition, fold increase in cell number dropped between passage 1 and 2 for three batches, which correlated to lower performance in total fold increase and expansion potential of these batches, suggesting that proliferative ability of hMSCs can be predicted at an early stage. An indicative bounded operating window was determined between passage 1 and 3 (PDL<10), despite the high inter-donor variability present under standardized hMSC expansion conditions used. hMSC growth profile analysis will be of benefit to cell therapy manufacturing as a tool to predict culture performance and attainment of clinically-relevant yields, therefore stratifying the patient population based on early observation.

Curr Med Chem. 2018 Jan 10. doi: 10.2174/0929867325666180111101410. [Epub ahead of print]

Mesenchymal Stem Cell Therapy in Intracerebral Haemorrhagic Stroke.

Bedini G[1], Bersano A[1], Zanier ER[2], Pischiutta F[2], Parati EA[1].

Author information

Abstract

BACKGROUND:

Spontaneous intracerebral haemorrhage (ICH) is a relatively common fatal disease, with an overall global incidence estimated at 24.6 per 100,000 person-years. Given the high degree of morbidity and mortality associated with ICH, therapies that may have neuroprotective effects are of increasing interest to clinicians. In this last context, cell therapies offer the promise of improving the disease course which cannot be addressed adequately by existing treatments.

OBJECTIVE:

The aim of this review is to evaluate the protective effects and molecular mechanisms of mesenchymal stem cells (MSCs) on haemorrhagic brain following ICH. We also discuss possible emerging therapeutic approaches worth of further research.

METHODS AND RESULTS:

The available literature on the therapeutic potential of MSCs in ICH animal models clearly demonstrated that MSCs enhance the functional recovery and reduce the volume of the infarct size exerting anti-inflammatory and angiogenic properties. However, the quality of the original articles investigating the efficacy of stem cell therapies in ICH animal models is still poor and the lack of ICH clinical trial does not permit to reach any relevant conclusions.

CONCLUSION:

Further studies have to be implemented in order to achieve standardized methods of MSCs isolation, characterization and administration to improve ICH treatments with MSCs or MSC-derived products.

J Biomed Sci. 2018 Jan 19;25(1):5. doi: 10.1186/s12929-018-0407-7.

Mesenchymal stem cells show functional defect and decreased anti-cancer effect after exposure to chemotherapeutic drugs.

Somaiah C[1], Kumar A[1], Sharma R[1], Sharma A[1], Anand T[1], Bhattacharyya J[2], Das D[2], Deka Talukdar S[2], Jaganathan BG[3].

Author information

Abstract

BACKGROUND:

Mesenchymal stem cells (MSC) are used for several therapeutic applications to improve the functions of bone, cardiac, nervous tissue as well as to facilitate the repopulation of hematopoietic stem cells. MSC give rise to the non-hematopoietic stromal cells of the bone marrow and are important for the maintenance of normal hematopoiesis. Chemotherapeutic drugs used for treatment of leukemia extensively damage the stromal cells and alter their gene expression profiles.

METHODS:

We determined the changes in adipogenic, osteogenic differentiation, phenotypic and gene expression in MSC during treatment with chemotherapeutic drugs cytarabine, daunorubicin and vincristine. We also tested anti-cancer effects of drug treated MSC on leukemia cells.

RESULTS:

Treatment with the chemotherapeutic drugs resulted in functional defects in MSC, leading to reduced proliferation, osteogenic and adipogenic differentiation. The drug treated MSC also showed decreased expression of cell surface receptors, and the changes in proliferation, phenotype and differentiation defect was partially reversible after withdrawing the drugs from the cells. The drug treated MSC showed increased expression of cytokines, IL6, FGF2 and TNFA but reduced levels of differentiation markers SOX9 and ACTC1. Drug treated MSC also contributed to reduced anti-cancer effects in leukemia cells.

CONCLUSIONS:

Chemotherapeutic drug treatment altered the phenotype, osteogenic and adipogenic differentiation potential of MSC and modified the gene expression profile of the cells to render them more chemoprotective of the leukemic cells. Thus, additional therapeutic efforts to target the stromal cell population will help in preventing chemoresistance, disease relapse in leukemia and to maintain a healthy bone marrow stroma.