Websites:
http://www.sciencepub.net
http://www.sciencepub.net/stem

Emails:
editor@sciencepub.net
sciencepub@gmail.com

Stem Cell

MARSLAND PRESS
Multidisciplinary Academic Journal Publisher

# Stem Cell Research Literatures (4)

Mark Herbert, PhD

39-06 Main Street, Flushing, Queens, New York 11354, USA, ma8080@gmail.com

**Abstract**: Stem cells are derived from embryonic and non-embryonic tissues. Most stem cell studies are for animal stem cells and plants have also stem cell. Stem cells were discovered in 1981 from early mouse embryos. Stem cells have the potential to develop into all different cell types in the living body. Stem cell is a body repair system. When a stem cell divides it can be still a stem cell or become adult cell, such as a brain cell. Stem cells are unspecialized cells and can renew themselves by cell division, and stem cells can also differentiate to adult cells with special functions. Stem cells replace the old cells and repair the damaged tissues. Embryonic stem cells can become all cell types of the body because they are pluripotent. Adult stem cells are thought to be limited to differentiating into different cell types of their tissue of origin. This article introduces recent research reports as references in the related studies.
[Dr. Mark Herbert. **Stem Cell Research Literatures (4).** Stem Cell. 2024;15(1):51-65] ISSN: 1945-4570 (print); ISSN: 1945-4732 (online). http://www.sciencepub.net/stem. 4. doi:10.7537/marsscj150124.04.

**Key words**: stem cell; life; research; literature

## Introduction

The stem cell is the origin of an organism's life that has the potential to develop into many different types of cells in life bodies. In many tissues stem cells serve as a sort of internal repair system, dividing essentially without limit to replenish other cells as long as the person or animal is still alive. When a stem cell divides, each new cell has the potential either to remain a stem cell or become another type of cell with a more specialized function, such as a red blood cell or a brain cell. This article introduces recent research reports as references in the related studies.

The following introduces recent reports as references in the related studies.

Alihemmati, Z., et al. (2017). "Computational simulation of static/cyclic cell stimulations to investigate mechanical modulation of an individual mesenchymal stem cell using confocal microscopy." Mater Sci Eng C Mater Biol Appl **70**(Pt 1): 494-504.

It has been found that cells react to mechanical stimuli, while the type and magnitude of these cells are different in various physiological and pathological conditions. These stimuli may affect cell behaviors via mechanotransduction mechanisms. The aim of this study is to evaluate mechanical responses of a mesenchymal stem cell (MSC) to a pressure loading using finite elements method (FEM) to clarify procedures of MSC mechanotransduction. The model is constructed based on an experimental set up in which statics and cyclic compressive loads are implemented on a model constructed from a confocal microscopy 3D image of a stem cell. Both of the applied compressive loads are considered in the physiological loading regimes. Moreover, a viscohyperelastic material model was assumed for the cell through which the finite elements simulation anticipates cell behavior based on strain and stress distributions in its components. As a result, high strain and stress values were captured from the viscohyperelastic model because of fluidic behavior of cytosol when compared with the obtained results through the hyperelastic models. It can be concluded that the generated strain produced by cyclic pressure is almost 8% higher than that caused by the static load and the von Mises stress distribution is significantly increased to about 150kPa through the cyclic loading. In total, the results does not only trace the efficacy of an individual 3D model of MSC using biomechanical experiments of cell modulation, but these results provide knowledge in interpretations from cell geometry. The current study was performed to determine a realistic aspect of cell behavior.

Chatzistamatiou, T. K., et al. (2014). "Optimizing isolation culture and freezing methods to preserve Wharton's jelly's mesenchymal stem cell (MSC) properties: an MSC banking protocol validation for the

Hellenic Cord Blood Bank." Transfusion **54**(12): 3108-3120.

BACKGROUND: Mesenchymal stem or stromal cells (MSCs) are a heterogeneous population that can be isolated from many tissues including umbilical cord Wharton's jelly (UC-WJ). Although initially limited in studies such as a hematopoietic stem cell transplantation adjuvant, an increasing number of clinical trials consider MSCs as a potential anti-inflammatory or a regenerative medicine agent. It has been proposed that creating a repository of MSCs would increase their availability for clinical applications. The aim of this study was to assess the optimal isolation and cryopreservation procedures to facilitate WJ MSC banking. STUDY DESIGN AND METHODS: Cells were isolated from UC-WJ using enzymatic digestion or plastic adhesion methods. Their isolation efficacy, growth kinetics, immunophenotype, and differentiation potential were studied, as well as the effects of freezing. Flow cytometry for common MSC markers was performed on all cases and differentiation was shown with histocytochemical staining. Finally, the isolation efficacy on cryopreserved WJ tissue fragments was tested. RESULTS: MSC isolation was successful using both isolation methods on fresh UC-WJ tissue. However, UC-WJ MSC isolation from frozen tissue fragments was impossible. Flow cytometry analysis revealed that only MSC markers were expressed on the surface of the isolated cells while differentiation assays showed that they were capable of trilinear differentiation. All the above characteristics were also preserved in isolated UC-WJ MSCs over the cryopreservation study period. CONCLUSION: These data showed that viable MSCs can only be isolated from fresh UC-WJ tissue, setting the foundation for clinical-grade banking.

Choi, H. Y., et al. (2018). "Generation of a human induced pluripotent stem cell line, KSCBi003-A, from human adipose tissue-derived mesenchymal stem cells using a chromosomal integration-free system." Stem Cell Res **31**: 1-4.

We generated a human induced pluripotent stem cell (hiPSC) line, KSCBi003-A, from adipose tissue-derived mesenchymal stem cells (Ad-MSCs) using a Sendai virus-based gene delivery system. We confirmed that the KSCBi003-A has a normal karyotype and short tandem repeat (STR)-based identities that match the parent cells. We also confirmed that the cell line expresses pluripotent stem cell markers such as Nanog, OCT4, SSEA-4, TRA-1-60, and TRA-1-81. We also analyzed that the KSCBi003-A has an ability to differentiate three germ layers (ectoderm, mesoderm, endoderm). This cell line is registered and available at the National Stem Cell Bank, Korea National Institute of Health.

Cobo, F., et al. (2008). "Electron microscopy reveals the presence of viruses in mouse embryonic fibroblasts but neither in human embryonic fibroblasts nor in human mesenchymal cells used for hESC maintenance: toward an implementation of microbiological quality assurance program in stem cell banks." Cloning Stem Cells **10**(1): 65-74.

Human embryonic stem cells (hESCs) are expected to open up new avenues in regenerative medicine by allowing the generation of transplantable cells to be used in future cell replacement therapies. Maintenance of hESCs in the presence of xenogenic compounds is likely to prevent their use in future therapeutic applications in humans. Recently, it has been claimed that human foreskin-derived human embryonic fibroblast (HEFs) and human adult marrow cells have the ability to support prolonged expansion of hESCs in culture similar to murine feeders. Here, to minimize the use of xenogenic components for hESC maintenance, we performed transmission electron microscopy-based microbiological studies in an attempt to implement a microbiological Quality Assurance Program in Stem Cell Banks by determining the potential presence of viral particles in MEFs compared with human HEFs and bone marrow-derived mesenchymal cells. We observed in three out of nine MEF samples (33.3%) viruses belonging to the Retroviridae family. Within the Retroviridae family, these viruses have a C morphology, which indicates they belong to the subfamily Orthoretroviridae. In contrast, no viral particles could be observed in either the HEF samples (n = 5) or the human BM-derived mesenchymal cells (n = 9) analyzed. Based on these experimental microbiological data, we recommend the implementation of microbiological Quality Assurance Programs by means of transmission electron microscopy as a routine technique to assess the potential presence of viral particles in any feeder cell used in stem cell banks and support the use of human cells rather than murine cells as

feeders to maintain hESC cultures in an undifferentiated state.

Cooper, K. and C. Viswanathan (2011). "Establishment of a mesenchymal stem cell bank." Stem Cells Int **2011**: 905621.

Adult stem cells have generated great amount of interest amongst the scientific community for their potential therapeutic applications for unmet medical needs. We have demonstrated the plasticity of mesenchymal stem cells isolated from the umbilical cord matrix. Their immunological profile makes it even more interesting. We have demonstrated that the umbilical cord is an inexhaustible source of mesenchymal stem cells. Being a very rich source, instead of discarding this tissue, we worked on banking these cells for regenerative medicine application for future use. The present paper gives a detailed account of our experience in the establishment of a mesenchymal stem cell bank at our facility.

Cras, A., et al. (2015). "Update on mesenchymal stem cell-based therapy in lupus and scleroderma." Arthritis Res Ther **17**: 301.

Current systemic therapies are rarely curative for patients with severe life-threatening forms of autoimmune diseases (ADs). During the past 15 years, autologous hematopoietic stem cell transplantation has been demonstrated to cure some patients with severe AD refractory to all other available therapies. As a consequence, ADs such as lupus and scleroderma have become an emerging indication for cell therapy. Multipotent mesenchymal stem cells (MSCs), isolated from bone marrow and other sites, display specific immunomodulation and anti-inflammatory properties and appear as ideal tools to treat such diseases. The present update aims at summarizing recent knowledge acquired in the field of MSC-based therapies for lupus and scleroderma.

de la Puente, P., et al. (2013). "Differentiation within autologous fibrin scaffolds of porcine dermal cells with the mesenchymal stem cell phenotype." Exp Cell Res **319**(3): 144-152.

Porcine mesenchymal stem cells (pMSCs) are an attractive source of cells for tissue engineering because their properties are similar to those of human stem cells. pMSCs can be found in different tissues but their dermal origin has not been studied in depth. Additionally, MSCs differentiation in monolayer cultures requires subcultured cells, and these cells are at risk of dedifferentiation when implanting them into living tissue. Following this, we attempted to characterize the MSCs phenotype of porcine dermal cells and to evaluate their cellular proliferation and differentiation in autologous fibrin scaffolds (AFSs). Dermal biopsies and blood samples were obtained from 12 pigs. Dermal cells were characterized by flow cytometry. Frozen autologous plasma was used to prepare AFSs. pMSC differentiation was studied in standard structures (monolayers and pellets) and in AFSs. The pMSCs expressed the CD90 and CD29 markers of the mesenchymal lineage. AFSs afforded adipogenic, osteogenic and chondrogenic differentiation. The porcine dermis can be proposed to be a good source of MSCs with adequate proliferative capacity and a suitable expression of markers. The pMSCs also showed optimal proliferation and differentiation in AFSs, such that these might serve as a promising autologous and implantable material for use in tissue engineering.

De Luca, L., et al. (2016). "MiRNAs and piRNAs from bone marrow mesenchymal stem cell extracellular vesicles induce cell survival and inhibit cell differentiation of cord blood hematopoietic stem cells: a new insight in transplantation." Oncotarget **7**(6): 6676-6692.

Hematopoietic stem cells (HSC), including umbilical cord blood CD34+ stem cells (UCB-CD34+), are used for the treatment of several diseases. Although different studies suggest that bone marrow mesenchymal stem cells (BM-MSC) support hematopoiesis, the exact mechanism remains unclear. Recently, extracellular vesicles (EVs) have been described as a novel avenue of cell communication, which may mediate BM-MSC effect on HSC. In this work, we studied the interaction between UCB-CD34+ cells and BM-MSC derived EVs. First, by sequencing EV derived miRNAs and piRNAs we found that EVs contain RNAs able to influence UCB-CD34+ cell fate. Accordingly, a gene expression profile of UCB-CD34+ cells treated with EVs, identified about 100 down-regulated genes among those targeted by EV-derived miRNAs and piRNAs (e.g. miR-27b/MPL, miR-21/ANXA1, miR-181/EGR2), indicating that EV content was able to modify gene expression profile of receiving cells. Moreover, we demonstrated that UCB-CD34+

cells, exposed to EVs, significantly changed different biological functions, becoming more viable and less differentiated. UCB-CD34+ gene expression profile also identified 103 up-regulated genes, most of them codifying for chemokines, cytokines and their receptors, involved in chemotaxis of different BM cells, an essential function of hematopoietic reconstitution. Finally, the exposure of UCB-CD34+ cells to EVs caused an increased expression CXCR4, paralleled by an in vivo augmented migration from peripheral blood to BM niche in NSG mice. This study demonstrates the existence of a powerful cross talk between BM-MSC and UCB-CD34+ cells, mediated by EVs, providing new insight in the biology of cord blood transplantation.

Fouladiha, H., et al. (2018). "Applications of a metabolic network model of mesenchymal stem cells for controlling cell proliferation and differentiation." Cytotechnology **70**(1): 331-338.

Mesenchymal stem cells (MSCs) can be isolated from several tissues of adults. In addition, MSCs have the potential of differentiation into several cell types. Therefore, MSCs are very useful in stem cell therapy and regenerative medicine. MSCs have also been used as gene or protein carriers. As a result, maintaining MSCs in a desirable metabolic state has been the subject of several studies. Here, we used a genome scale metabolic network model of bone marrow derived MSCs for exploring the metabolism of these cells. We analyzed metabolic fluxes of the model in order to find ways of increasing stem cell proliferation and differentiation. Consequently, the experimental results were in consistency with computational results. Therefore, analyzing metabolic models was proven to be a promising field in biomedical researches of stem cells.

Garcia-Castro, J., et al. (2008). "Mesenchymal stem cells and their use as cell replacement therapy and disease modelling tool." J Cell Mol Med **12**(6B): 2552-2565.

Mesenchymal stem cells (MSCs) from adult somatic tissues may differentiate in vitro and in vivo into multiple mesodermal tissues including bone, cartilage, adipose tissue, tendon, ligament or even muscle. MSCs preferentially home to damaged tissues where they exert their therapeutic potential. A striking feature of the MSCs is their low inherent immunogenicity as they induce little, if any, proliferation of allogeneic lymphocytes and antigen-presenting cells. Instead, MSCs appear to be immunosuppressive in vitro. Their multilineage differentiation potential coupled to their immuno-privileged properties is being exploited worldwide for both autologous and allogeneic cell replacement strategies. Here, we introduce the readers to the biology of MSCs and the mechanisms underlying immune tolerance. We then outline potential cell replacement strategies and clinical applications based on the MSCs immunological properties. Ongoing clinical trials for graft-versus-host-disease, haematopoietic recovery after co-transplantation of MSCs along with haematopoietic stem cells and tissue repair are discussed. Finally, we review the emerging area based on the use of MSCs as a target cell subset for either spontaneous or induced neoplastic transformation and, for modelling non-haematological mesenchymal cancers such as sarcomas.

Ghaemi, R. V., et al. (2016). "Fluid-Structure Interactions Analysis of Shear-Induced Modulation of a Mesenchymal Stem Cell: An Image-Based Study." Artif Organs **40**(3): 278-287.

Although effects of biochemical modulation of stem cells have been widely investigated, only recent advances have been made in the identification of mechanical conditioning on cell signaling pathways. Experimental investigations quantifying the micromechanical environment of mesenchymal stem cells (MSCs) are challenging while computational approaches can predict their behavior due to in vitro stimulations. This study introduces a 3D cell-specific finite element model simulating large deformations of MSCs. Here emphasizing cell mechanical modulation which represents the most challenging multiphysics phenomena in sub-cellular level, we focused on an approach attempting to elicit unique responses of a cell under fluid flow. Fluorescent staining of MSCs was performed in order to visualize the MSC morphology and develop a geometrically accurate model of it based on a confocal 3D image. We developed a 3D model of a cell fixed in a microchannel under fluid flow and then solved the numerical model by fluid-structure interactions method. By imposing flow characteristics representative of vigorous in vitro conditions, the model predicts that the employed external

flow induces significant localized effective stress in the nucleo-cytoplasmic interface and average cell deformation of about 40%. Moreover, it can be concluded that a lower strain level is made in the cell by the oscillatory flow as compared with steady flow, while same ranges of effective stress are recorded inside the cell in both conditions. The deeper understanding provided by this study is beneficial for better design of single cell in vitro studies.

Haghighipour, N., et al. (2012). "Differential effects of cyclic uniaxial stretch on human mesenchymal stem cell into skeletal muscle cell." Cell Biol Int **36**(7): 669-675.

Both fetal and adult skeletal muscle cells are continually being subjected to biomechanical forces. Biomechanical stimulation during cell growth affects proliferation, differentiation and maturation of skeletal muscle cells. Bone marrow-derived hMSCs [human MSCs (mesenchymal stem cells)] can differentiate into a variety of cell types, including skeletal muscle cells that are potentially a source for muscle regeneration. Our investigations involved a 10% cyclic uniaxial strain at 1 Hz being applied to hMSCs grown on collagen-coated silicon membranes with or without IGF-I (insulin-like growth factor-I) for 24 h. Results obtained from morphological studies confirmed the rearrangement of cells after loading. Comparison of MyoD and MyoG mRNA levels between test groups showed that mechanical loading alone can initiate myogenic differentiation. Furthermore, comparison of Myf5, MyoD, MyoG and Myf6 mRNA levels between test groups showed that a combination of mechanical loading and growth factor results in the highest expression of myogenic genes. These results indicate that cyclic strain may be useful in myogenic differentiation of stem cells, and can accelerate the differentiation of hMSCs into MSCs in the presence of growth factor.

Hajizadeh-Saffar, E., et al. (2015). "Inducible VEGF expression by human embryonic stem cell-derived mesenchymal stromal cells reduces the minimal islet mass required to reverse diabetes." Sci Rep **5**: 9322.

UNLABELLED: Islet transplantation has been hampered by loss of function due to poor revascularization. We hypothesize that co-transplantation of islets with human embryonic stem cell-derived mesenchymal stromal cells that conditionally overexpress VEGF (hESC-MSC:VEGF) may augment islet revascularization and reduce the minimal islet mass required to reverse diabetes in mice. HESC-MSCs were transduced by recombinant lentiviruses that allowed conditional (Dox-regulated) overexpression of VEGF. HESC-MSC: VEGF were characterized by tube formation assay. After co-transplantation of hESC-MSC:VEGF with murine islets in collagen-fibrin hydrogel in the omental pouch of diabetic nude mice, we measured blood glucose, body weight, glucose tolerance and serum C-peptide. As control, islets were transplanted alone or with non-transduced hESC-MSCs. Next, we compared functional parameters of 400 islets alone versus 200 islets co-transplanted with hESC-MSC:VEGF. As control, 200 islets were transplanted alone. Metabolic function of islets transplanted with hESC-MSC:VEGF significantly improved, accompanied by superior graft revascularization, compared with control groups. Transplantation of 200 islets with hESC-MSC:VEGF showed superior function over 400 islets alone. We conclude that co-transplantation of islets with VEGF-expressing hESC-MSCs allowed for at least a 50% reduction in minimal islet mass required to reverse diabetes in mice. This approach may contribute to alleviate the need for multiple donor organs per patient.

He, Y., et al. (2017). "Umbilical cord-derived mesenchymal stem cell transplantation for treating elderly vascular dementia." Cell Tissue Bank **18**(1): 53-59.

This study aimed to determine the efficacy and safety of human umbilical cord-derived mesenchymal stem cell (HUC-MSC) transplantation for treating elderly vascular dementia (VaD). Ten VaD patients (average age, 73.88 years old) were treated. HUC-MSCs were isolated, cultured, stem cell-marked, and qualified and administered as a 3-course intravenous infusion to these patients. The Mini-Mental State Exam (MMSE) and the Activities of Daily Living Index (Barthel Index scoring system) were used to assess the cognitive function and daily living activity improvements in these patients before transplantation (T0), 3 months after transplantation (T1), and 6 months after transplantation (T2). The MMSE and Barthel Index scores were 15.80 +/- 5.49 and 42.00 +/- 9.33 points at T0, respectively, and were significantly different when compared with

those at T1 (19.20 +/- 6.39 and 49.20 +/- 10.86 points, respectively, P < 0.05), whereas there was no difference when compared with those at T2 (14.00 +/- 6.55 and 40.70 +/- 10.37 points, respectively, P > 0.05). HUC-MSC transplantation was safe and feasible for VaD and improved early cognitive functions and daily living activities in VaD patients to a certain extent, thus improving patients' quality of life.

Hung, H. S., et al. (2014). "In vitro study of a novel nanogold-collagen composite to enhance the mesenchymal stem cell behavior for vascular regeneration." PLoS One **9**(8): e104019.

Novel nanocomposites based on type I collagen (Col) containing a small amount (17.4, 43.5, and 174 ppm) of gold nanoparticles (AuNPs, approximately 5 nm) were prepared in this study. The pure Col and Col-AuNP composites (Col-Au) were characterized by the UV-Vis spectroscopy (UV-Vis), surface-enhanced raman spectroscopy (SERS) and atomic force microscopy (AFM). The interaction between Col and AuNPs was confirmed by infrared (IR) spectra. The effect of AuNPs on the biocompatibility of Col, evaluated by the proliferation and reactive oxygen species (ROS) production of mesenchymal stem cells (MSCs) as well as the activation of monocytes and platelets, was investigated. Results showed that Col-Au had better biocompatibility than Col. Upon stimulation by vascular endothelial growth factor (VEGF) and stromal derived factor-1alpha (SDF-1alpha), MSCs expressed the highest levels of alphavbeta3 integrin/CXCR4, focal adhesion kinase (FAK), matrix metalloproteinase-2 (MMP-2), and Akt/endothelial nitric oxide synthase (eNOS) proteins when grown on the Col-Au (43.5 ppm) nanocomposite. Taken together, Col-Au nanocomposites may promote the proliferation and migration of MSCs and stimulate the endothelial cell differentiation. These results suggest that Col-Au may be used to construct tissue engineering scaffolds for vascular regeneration.

Jakobsen, K. K., et al. (2017). "Mesenchymal stem cell therapy for laryngotracheal stenosis: A systematic review of preclinical studies." PLoS One **12**(9): e0185283.

BACKGROUND: Laryngotracheal stenosis (LTS) can be either congenital or acquired. Laryngeal stenosis is most often encountered after prolonged intubation. The mechanism for stenosis following intubation is believed to be hypertrophic scarring. Mesenchymal stem cells (MSCs) therapy has shown promising results in regenerative medicine. We aimed to systematically review the literature on MSC therapy for stenosis of the conductive airways. METHODS: PubMed, EMBASE, Google Scholar and the Cochrane Library were systematically searched from January 1980-January 2017 with the purpose of identifying all studies addressing the effect of MSC therapy on the airway. We assessed effect on inflammation, fibrosis, and MSC as a component in tissue engineering for treating defects in the airway. RESULTS: We identified eleven studies (n = 256 animals) from eight countries evaluating the effect of MSCs as a regenerative therapy in the upper airways. The studies indicate that MSC therapy may lead to a more constructive inflammatory response as well as support tissue regeneration. CONCLUSION: There may be a favorable effect of MSCs in inhibiting inflammation and as a component in tissue engineering. Given the heterogeneous nature of the included animal studies, any clear conclusion regarding the effect of tracheal stenosis in human subjects cannot be drawn. The included preclinical studies are however encouraging for further research.

Jensen, D. H., et al. (2014). "Mesenchymal stem cell therapy for salivary gland dysfunction and xerostomia: a systematic review of preclinical studies." Oral Surg Oral Med Oral Pathol Oral Radiol **117**(3): 335-342 e331.

The most severe forms of xerostomia and salivary gland dysfunction, as well as a severely reduced quality of life, are seen in Sjogren syndrome (SS) and after radiotherapy for head and neck cancer. For both conditions, no effective regenerative therapies yet exist. Thus, the aim of this article was to assess, through systematic review, the potential benefit of mesenchymal stem cell (MSC) therapy in radiation-induced and SS-related salivary gland dysfunction and xerostomia. We searched PubMed/MEDLINE, Embase, Web of Science, the Cochrane Database of Systematic Reviews, the World Health Organization Clinical Trials Registry Platform, and Google Scholar. We identified 6 separate study comparisons eligible for inclusion. Owing to the limited number of studies, we

conclude that more randomized, adequately powered clinical trials are needed to validate the potential beneficial effect of MSCs on salivary gland dysfunction and xerostomia. Nonetheless, the preliminary studies identified in the present review were encouraging for further research.

Kajbafzadeh, A. M., et al. (2017). "Evaluating the role of autologous mesenchymal stem cell seeded on decellularized pericardium in the treatment of myocardial infarction: an animal study." Cell Tissue Bank **18**(4): 527-538.

Inappropriate left ventricular remodeling following myocardial infarction (MI) can result in subsequent severe dysfunction. In this study, we tested the hypothesis that decellularized pericardium (DP) or seeded pericardial patch with autologous adipose-derived mesenchymal stem cells (ADMSCs) could be safely used in a MI scar and could improve heart function. Twelve rabbits were randomly divided into three equal groups. Four weeks after MI induction by ligation of the left anterior descending artery in 12 rabbits, animals of G1 (n = 4) received DP patch with labeled ADMSCs. DP patch was implanted in animals of G2 (n = 4). Rabbits of G3 (n = 4) remained without any intervention after MI induction (control group). Serial examinations including echocardiography, electrocardiography (ECG), scanning electron microscopy, histology and immunohistochemistry (IHC) were performed to evaluate the efficacy of the implanted scaffolds on recovery of the infracted myocardium. The results demonstrated that left ventricular contractile function and myocardial pathological changes were significantly improved in rabbits implanted with either DP or ADMSC-seeded pericardium. However, the seeded pericardium was more effective in scar repairing 2 months after the operation, IHC staining with Desmin and CD34 and positive immunofluorescence staining verified the differentiation of ADMSCs to functional cardiomyocytes. This approach may involve the application of autologous ADMSCs seeded on pericardial patch in an attempt to regenerate a contractible myocardium in an animal model of MI.

Kucera, T., et al. (2017). "Elution kinetics of vancomycin and gentamicin from carriers and their effects on mesenchymal stem cell proliferation: an in vitro study." BMC Musculoskelet Disord **18**(1): 381.

BACKGROUND: Musculoskeletal infections remain a major complication in orthopedic surgery. The local delivery of antibiotics provides the high levels required to treat an infection without systemic toxicity. However, the local toxicity of antibiotic carriers to the mesenchymal stem cells, as a result of both the peak concentrations and the type of carrier, may be significant. METHODS: To address this concern, the elution kinetics of vancomycin and gentamicin from several commercially available antibiotic carriers and several carriers impregnated by a surgeon (10 ml of each sterile carrier were manually mixed with a 500 mg vancomycin and an 80 mg gentamicin solution, and the duration of impregnation was 30 min) were assessed. Moreover, the effects of these antibiotic carriers on stem cell proliferation were investigated. The following two types of stem cells were used: bone marrow and dental pulp stem cells. RESULTS: The high eluted initial concentrations from antibiotic impregnated cancellous allogeneic bone grafts (which may be increased with the addition of fibrin glue) did not adversely affect stem cell proliferation. Moreover, an increased dental pulp stem cell proliferation rate in the presence of antibiotics was identified. In contrast to allogeneic bone grafts, a significant amount of antibiotics remained in the cement. Despite the favorable elution kinetics, the calcium carriers, bovine collagen carrier and freeze-dried bone exhibited decreased stem cell proliferation activity even in lower antibiotic concentrations compared with an allogeneic graft. CONCLUSIONS: This study demonstrated the benefits of antibiotic impregnated cancellous allogeneic bone grafts versus other carriers.

Luznik, Z., et al. (2016). "Effect of Cryopreserved Amniotic Membrane Orientation on the Expression of Limbal Mesenchymal and Epithelial Stem Cell Markers in Prolonged Limbal Explant Cultures." PLoS One **11**(10): e0164408.

PURPOSE: To evaluate the effect of prolonged limbal explants cultured without any scaffolds or on amniotic membrane (AM) on the viability, proliferation and differentiation potential of putative phenotypically defined cultured limbal mesenchymal (LMSC) and epithelial stem cells (LESC). METHODS: Limbal explants

were cultivated on cryopreserved intact AM or plastic plates using medium supplemented with only human serum. AM was positioned with either the epithelial or stromal side up. The outgrowing cells were immunophenotyped for the co-expression of mesenchymal stem cell markers (CD73/CD90/CD105 positive and CD45 negative), proliferation and putative progenitor markers (CXCR4, CD117), epithelial markers and antigen presenting cell markers (CD80, CD83, CD86) by flow cytometry. Immunohistochemistry on limbal cultures cultivated on AM was carried out with antibodies against pan-cytokeratin, p63, Ki67. RESULTS: Morphological and immunostaining analyses revealed two distinct stem cell population types, which could be identified over prolonged culturing time periods. Expression of LMSC markers and CXCR4 was significantly higher ($p < 0.05$) in cultures cultivated without AM. However, no statistically significant difference was observed in CD117 expression. The cells cultivated on AM retained an epithelial cell structure, which was further confirmed by histology examination. Histology revealed limbal epithelial growth and p63, Ki67 positive cells on both sides of AM. CONCLUSION: Limbal cells cultivated on AM exhibited a lower expression profile of LMSC and CXCR4 markers as limbal cells cultivated on plastic culture plates. However, CD117 expression was similar. Histology confirmed limbal epithelial cell growth on both sides of AM, with no morphological differences, or positivity of cells for p63 and Ki67.

Lysak, D., et al. (2016). "Validation of shortened 2-day sterility testing of mesenchymal stem cell-based therapeutic preparation on an automated culture system." Cell Tissue Bank **17**(1): 1-9.

Cell therapy products represent a new trend of treatment in the field of immunotherapy and regenerative medicine. Their biological nature and multistep preparation procedure require the application of complex release criteria and quality control. Microbial contamination of cell therapy products is a potential source of morbidity in recipients. The automated blood culture systems are widely used for the detection of microorganisms in cell therapy products. However the standard 2-week cultivation period is too long for some cell-based treatments and alternative methods have to be devised. We tried to verify whether a shortened cultivation of the supernatant from the mesenchymal stem cell (MSC) culture obtained 2 days before the cell harvest could sufficiently detect microbial growth and allow the release of MSC for clinical application. We compared the standard Ph. Eur. cultivation method and the automated blood culture system BACTEC (Becton Dickinson). The time to detection (TTD) and the detection limit were analyzed for three bacterial and two fungal strains. The Staphylococcus aureus and Pseudomonas aeruginosa were recognized within 24 h with both methods (detection limit ~10 CFU). The time required for the detection of Bacillus subtilis was shorter with the automated method (TTD 10.3 vs. 60 h for 10-100 CFU). The BACTEC system reached significantly shorter times to the detection of Candida albicans and Aspergillus brasiliensis growth compared to the classical method (15.5 vs. 48 and 31.5 vs. 48 h, respectively; 10-100 CFU). The positivity was demonstrated within 48 h in all bottles, regardless of the size of the inoculum. This study validated the automated cultivation system as a method able to detect all tested microorganisms within a 48-h period with a detection limit of ~10 CFU. Only in case of B. subtilis, the lowest inoculum (~10 CFU) was not recognized. The 2-day cultivation technique is then capable of confirming the microbiological safety of MSC and allows their timely release for clinical application.

Montemurro, T., et al. (2016). "Angiogenic and anti-inflammatory properties of mesenchymal stem cells from cord blood: soluble factors and extracellular vesicles for cell regeneration." Eur J Cell Biol **95**(6-7): 228-238.

In a recent work, our group showed the existence of two distinct mesenchymal stem cell (MSC) subsets within human umbilical cord blood. One less proliferative and short-living (SL-CBMSC), the other with higher growth rate and long-living (LL-CBMSC), and therefore better suited for regenerative medicine applications. We examined whether LL-CBMSC possess peculiar paracrine properties able to affect angiogenesis or inflammatory processes. It was shown for the first time that pro-angiogenic, proliferation-stimulating and tissue repairing factors were released at high level not only as soluble cytokines, but also as mRNA precursors embedded in membrane vesicles. The

combination of this primary (proteic factors interacting with surface receptors) and delayed (mRNA transferred and translated via vesicle fusion and cargo release) interaction in endothelial target cells resulted in strong blood vessel induction with the development of capillary-like structures. In addition, LL-CBMSC dynamically modulated their release of pro-angiogenic and anti-inflammatory factors in an in vitro model of damage. In conclusion, LL-CBMSC synthesize and secrete multiple factors that may be attuned in response to the status of the target cell, a crucial requisite when paracrine mechanisms are needed at onset of tissue regeneration.

Montes, R., et al. (2009). "Feeder-free maintenance of hESCs in mesenchymal stem cell-conditioned media: distinct requirements for TGF-beta and IGF-II." Cell Res **19**(6): 698-709.

A paracrine regulation was recently proposed in human embryonic stem cells (hESCs) grown in mouse embryonic fibroblast (MEF)-conditioned media (MEF-CM), where hESCs spontaneously differentiate into autologous fibroblast-like cells to maintain culture homeostasis by producing TGF-beta and insulin-like growth factor-II (IGF-II) in response to basic fibroblast growth factor (bFGF). Although the importance of TGF-beta family members in the maintenance of pluripotency of hESCs is widely established, very little is known about the role of IGF-II. In order to ease hESC culture conditions and to reduce xenogenic components, we sought (i) to determine whether hESCs can be maintained stable and pluripotent using CM from human foreskin fibroblasts (HFFs) and human mesenchymal stem cells (hMSCs) rather than MEF-CM, and (ii) to analyze whether the cooperation of bFGF with TGF-beta and IGF-II to maintain hESCs in MEF-CM may be extrapolated to hESCs maintained in allogeneic mesenchymal stem cell (MSC)-CM and HFF-CM. We found that MSCs and HFFs express all FGF receptors (FGFR1-4) and specifically produce TGF-beta in response to bFGF. However, HFFs but not MSCs secrete IGF-II. Despite the absence of IGF-II in MSC-CM, hESC pluripotency and culture homeostasis were successfully maintained in MSC-CM for over 37 passages. Human ESCs derived on MSCs and hESCs maintained in MSC-CM retained hESC morphology, euploidy, expression of surface markers and transcription factors linked to pluripotency and displayed in vitro and in vivo multilineage developmental potential, suggesting that IGF-II may be dispensable for hESC pluripotency. In fact, IGF-II blocking had no effect on the homeostasis of hESC cultures maintained either on HFF-CM or on MSC-CM. These data indicate that hESCs are successfully maintained feeder-free with IGF-II-lacking MSC-CM, and that the previously proposed paracrine mechanism by which bFGF cooperates with TGF-beta and IGF-II in the maintenance of hESCs in MEF-CM may not be fully extrapolated to hESCs maintained in CM from human MSCs.

Nicodemou, A. and L. Danisovic (2017). "Mesenchymal stromal/stem cell separation methods: concise review." Cell Tissue Bank **18**(4): 443-460.

Mesenchymal stem (stromal) cells (MSCs) possess unique biological characteristics such as plasticity, long term self-renewal, secretion of various bioactive molecules and ability of active migration to the diseased tissues that make them unique tool for regenerative medicine, nowadays. Until now MSCs were successfully derived from many tissue sources including bone marrow, umbilical cord, adipose tissue, dental pulp etc. The crucial step prior to their in vitro expansion, banking or potential clinical application is their separation. This review article aims to briefly describe the main MSCs separations techniques currently available, their basic principles, as well as their advantages and limits. In addition the attention is paid to the markers presently applicable for immunoaffinity-based separation of MSCs from different tissues and organs.

Normanton, M., et al. (2014). "Interleukin 7 plays a role in T lymphocyte apoptosis inhibition driven by mesenchymal stem cell without favoring proliferation and cytokines secretion." PLoS One **9**(9): e106673.

Since 2004, when a case report describing the use of human mesenchymal stem cells (hMSCs) infusion as a therapy for GVHD after bone marrow transplantation, a new perspective in MSC function emerged. Since then hMSCs immunomodulatory potential became the target of several studies. Although great progress has been made in our understanding of hMSCs, their effect on T cell remains obscure. Our study has confirmed the already described effect of hMSCs on lymphocytes proliferation and survival. We also show that the impairment of lymphocyte

proliferation and apoptosis is contact-independent and occurs in a prostaglandin-independent manner. A potential correlation between IL-7 and hMSCs effect is suggested, as we observed an increase in IL-7 receptors (CD127) on lymphocyte membrane in MSC presence. Additionally, blocking IL-7 in hMSCs-lymphocytes co-cultures increased lymphocytes apoptosis and we also have demonstrated that hMSCs are able to produce this interleukin. Moreover, we found that during Th1/Th17 differentiation in vitro, hMSCs presence leads to Th1/Th17 cells with reduced capacity of INF-y and IL-17 secretion respectively, regardless of having several pro-inflammatory cytokines in culture. We did not confirm an increment of Treg in these cultures, but a reduced percentage of INF-y/IL-17 secreting cells was observed, suggesting that the ratio between anti and pro-inflammatory cells changed. This changed ratio is very important to GvHD therapy and links hMSCs to an anti-inflammatory role. Taken together, our findings provide important preliminary results on the lymphocyte pathway modulated by MSCs and may contribute for developing novel treatments and therapeutic targets for GvHD and others autoimmune diseases.

Quaranta, P., et al. (2016). "Tweaking Mesenchymal Stem/Progenitor Cell Immunomodulatory Properties with Viral Vectors Delivering Cytokines." Stem Cells Dev **25**(18): 1321-1341.

Mesenchymal Stem Cells (MSCs) can be found in various body sites. Their main role is to differentiate into cartilage, bone, muscle, and fat cells to allow tissue maintenance and repair. During inflammation, MSCs exhibit important immunomodulatory properties that are not constitutive, but require activation, upon which they may exert immunosuppressive functions. MSCs are defined as "sensors of inflammation" since they modulate their ability of interfering with the immune system both in vitro and in vivo upon interaction with different factors. MSCs may influence immune responses through different mechanisms, such as direct cell-to-cell contact, release of soluble factors, and through the induction of anergy and apoptosis. Human MSCs are defined as plastic-adherent cells expressing specific surface molecules. Lack of MHC class II antigens makes them appealing as allogeneic tools for the therapy of both autoimmune diseases and cancer. MSC therapeutic potential could be highly enhanced by the expression of exogenous cytokines provided by transduction with viral vectors. In this review, we attempt to summarize the results of a great number of in vitro and in vivo studies aimed at improving the ability of MSCs as immunomodulators in the therapy of autoimmune, degenerative diseases and cancer. We will also compare results obtained with different vectors to deliver heterologous genes to these cells.

Sabetkish, S., et al. (2018). "The role of nonautologous and autologous adipose-derived mesenchymal stem cell in acute pyelonephritis." Cell Tissue Bank **19**(3): 301-309.

We compared the therapeutic effects of autologous and nonautologous adipose-derived mesenchymal stem cell (ADMSC), in ameliorating the renal function in a rabbit model of acute pyelonephritis. The difference of perirenal and neck subcutaneous ADMSCs were also evaluated. Twenty female rabbits were apportioned to 5 groups. In group I (n = 4), the rabbits were injected direct inoculation of Escherichia coli (E. coli) into the right kidney. In group II (n = 4), autologous ADMSCs obtained from nape adipose tissue were injected into the subcapsular space 1 week after E. coli injection, while nonautologous ADMSCs of the same origin (from male rabbits) were applied in group III (n = 4). In group IV (n = 4), autologous perirenal ADMSCs were applied with the same method, while perirenal nonautologous ADMSCs from male rabbits were used in group V (n = 4). Technetium-99m-DMSA renal scan was performed 1, 2 and 4 months post-injection in all groups. Kidneys were excised for the evaluation of histopathological changes in the same time points. PCR examination for detection of Y-chromosome (in group III and V) and fluorescent evaluation (in group II and IV) were also performed to determine the fate of injected cells. Injection of autologous ADMSCs resulted in more satisfactory outcomes in reduction of interstitial fibrosis, tubular, and glomerular atrophy as compared to nonautologous groups. However, histopathological ameliorations were significantly better in group IV in which autologous perirenal ADMSC was applied. Remarkably, two months after the injection, Technetium-99m-DMSA renal scan showed that right kidney reached to near normal cortical function (48 and 45%) in group IV

and V, respectively as compared to groups II (41%) and III (37%). Autologous ADMSCs may have better results in cell therapy as compared to nonautologous cells. However, more satisfactory outcomes may be obtained when the cell source is selected from the surrounding adipose tissue.

Shofuda, T., et al. (2013). "Human Decidua-Derived Mesenchymal Cells Are a Promising Source for the Generation and Cell Banking of Human Induced Pluripotent Stem Cells." Cell Med **4**(3): 125-147.

Placental tissue is a biomaterial with remarkable potential for use in regenerative medicine. It has a three-layer structure derived from the fetus (amnion and chorion) and the mother (decidua), and it contains huge numbers of cells. Moreover, placental tissue can be collected without any physical danger to the donor and can be matched with a variety of HLA types. The decidua-derived mesenchymal cells (DMCs) are highly proliferative fibroblast-like cells that express a similar pattern of CD antigens as bone marrow-derived mesenchymal cells (BM-MSCs). Here we demonstrated that induced pluripotent stem (iPS) cells could be efficiently generated from DMCs by retroviral transfer of reprogramming factor genes. DMC-hiPS cells showed equivalent characteristics to human embryonic stem cells (hESCs) in colony morphology, global gene expression profile (including human pluripotent stem cell markers), DNA methylation status of the OCT3/4 and NANOG promoters, and ability to differentiate into components of the three germ layers in vitro and in vivo. The RNA expression of XIST and the methylation status of its promoter region suggested that DMC-iPSCs, when maintained undifferentiated and pluripotent, had three distinct states: (1) complete X-chromosome reactivation, (2) one inactive X-chromosome, or (3) an epigenetic aberration. Because DMCs are derived from the maternal portion of the placenta, they can be collected with the full consent of the adult donor and have considerable ethical advantages for cell banking and the subsequent generation of human iPS cells for regenerative applications.

Szekiova, E., et al. (2018). "The neuroprotective effect of rat adipose tissue-derived mesenchymal stem cell-conditioned medium on cortical neurons using an in vitro model of SCI inflammation." Neurol Res **40**(4): 258-267.

Objectives In this study, a new approach was used with an in vitro model in which neural cells were exposed to conditioned media from the injured spinal cord (SCI-CM) mimicking a local inflammatory microenvironment . Subsequently, the neuroprotective effect of rat adipose tissue-derived msesenchymal stem cell-conditioned media (ATMSC-CM) was investigated through a cell-free based therapy, which was used to treat cortical neurons and astrocytes under inflammation. Methods Primary cell cultures isolated from postnatal day (P6) Wistar rat brain cortex were exposed to SCI-CM derived from the central lesion, rostral and caudal segments of injured spinal cord. After 48 h incubation, the SCI-CM was replaced and primary cultures were cultivated either in DMEM media alone or in ATMSC-CM for 72 h. The impact of ATMSC-CM on the viability of neurons and astrocytes was assessed using a CyQUANT(R) Direct Cell Proliferation Assay Kit as well as immunocytochemistry analysis. Results Immunocytochemical analysis revealed significant decrease in the number of MAP2 positive neurons exposed to SCI-CM compared to Control. Protection by ATMSC-CM was associated with increased survival of neurons compared to primary culture cultivated in DMEM media alone. The ATMSC-CM effect on astrocytes was more variable and without any significant impact. Conclusion The results demonstrate that SCI-CM mimicking inflammation can reduce cortical neuron survival, and subsequent exposure to ATMSC-CM can stabilize the neuronal population most likely via released neuroprotective and trophic factors. In addition, astrogliosis was not affected by ATMSC-CM.

Tan, S. L., et al. (2011). "Human amnion as a novel cell delivery vehicle for chondrogenic mesenchymal stem cells." Cell Tissue Bank **12**(1): 59-70.

This study investigates the feasibility of processed human amnion (HAM) as a substrate for chondrogenic differentiation of mesenchymal stem cells (MSCs). HAM preparations processed by air drying (AD) and freeze drying (FD) underwent histological examination and MSC seeding in chondrogenic medium for 15 days. Monolayer cultures were used as control for chondrogenic differentiation and HAMs without cell seeding

were used as negative control. Qualitative observations were made using scanning electron microscopy analysis and quantitative analyses were based on the sulfated glycosaminoglycans (GAG) assays performed on day 1 and day 15. Histological examination of HAM substrates before seeding revealed a smooth surface in AD substrates, while the FD substrates exhibited a porous surface. Cell attachment to AD and FD substrates on day 15 was qualitatively comparable. GAG were significantly highly expressed in cells seeded on FD HAM substrates. This study indicates that processed HAM is a potentially valuable material as a cell-carrier for MSC differentiation.

Wei, W., et al. (2016). "[Biological characteristics of mesenchymal stem cell and hematopoietic stem cell in the co-culture system]." Sheng Li Xue Bao **68**(5): 691-698.

The aim of the present study was to obtain the qualified hematopoietic stem/progenitor cells (HSC/HPC) and human umbilical cord-mesenchymal stem cells (MSC) in vitro in the co-culture system. Cord blood mononuclear cells were separated from umbilical cord blood by Ficoll lymphocyte separation medium, and then CD34(+) HSC was collected by MACS immunomagnetic beads. The selected CD34(+) HSC/HPC and MSC were transferred into culture flask. IMDM culture medium with 15% AB-type cord plasma supplemented with interleukin-3 (IL-3), IL-6, thrombopoietin (TPO), stem cell factor (SCF) and FMS-like tyrosine kinase 3 ligand (Flt-3L) factors were used as the co-culture system for the amplification of HSC/HPC and MSC. The cellular growth status and proliferation on day 6 and 10 after co-culture were observed by using inverted microscope. The percentage of positive expression of CD34 in HSC/HPC, as well as the percentages of positive expressions of CD105, CD90, CD73, CD45, CD34 and HLA-DR in the 4(th) generation MSC, was tested by flow cytometry. Semisolid colony culture was used to test the HSC/HPC colony forming ability. The osteogenic, chondrogenesis and adipogenic ability of the 4(th) generation MSC were assessed. The karyotype analysis of MSC was conducted by colchicines. The results demonstrated that the HSC/HPC of co-culture group showed higher ability of amplification, CFU-GM and higher CD34(+) percentage compared with the control group. The co-cultured MSC maintained the ability to differentiate into bone cells, fat cells and chondrocytes. And the karyotype stability of MSC remained normal. These results reveal that the appropriate co-culture system for MSC and HSC is developed, and via this co-culture system we could gain both two kinds of these cells. The MSCs under the co-culture system maintain the biological characteristics. The CFU-GM ability, cell counting and the flow cytometry results of HSC/HPC under the co-culture system are conform to the criterion, showing that the biological functions of HSC/HPC are maintained.

Wingstrand, V. L., et al. (2016). "Mesenchymal Stem Cell Therapy for the Treatment of Vocal Fold Scarring: A Systematic Review of Preclinical Studies." PLoS One **11**(9): e0162349.

OBJECTIVES: Therapy with mesenchymal stem cells exhibits potential for the development of novel interventions for many diseases and injuries. The use of mesenchymal stem cells in regenerative therapy for vocal fold scarring exhibited promising results to reduce stiffness and enhance the biomechanical properties of injured vocal folds. This study evaluated the biomechanical effects of mesenchymal stem cell therapy for the treatment of vocal fold scarring. DATA SOURCES: PubMed, Embase, the Cochrane Library and Google Scholar were searched. METHODS: Controlled studies that assessed the biomechanical effects of mesenchymal stem cell therapy for the treatment of vocal fold scarring were included. Primary outcomes were viscoelastic properties and mucosal wave amplitude. RESULTS: Seven preclinical animal studies (n = 152 single vocal folds) were eligible for inclusion. Evaluation of viscoelastic parameters revealed a decreased dynamic viscosity (eta') and elastic modulus (G'), i.e., decreased resistance and stiffness, in scarred vocal folds treated with mesenchymal stem cells compared to non-treated scarred vocal folds. Mucosal wave amplitude was increased in scarred vocal folds treated with mesenchymal stem cells vs. non-treated scarred vocal folds. CONCLUSION: The results from these studies suggest an increased regenerative effect of therapy with mesenchymal stem cells for scarred vocal folds and are encouraging for further clinical studies.

Yamada, K., et al. (2015). "Mesenchymal-epithelial cell interactions and proteoglycan matrix composition in the presumptive stem cell niche of the rabbit corneal limbus." Mol Vis **21**: 1328-1339.

PURPOSE: To investigate whether mesenchymal-epithelial cell interactions, similar to those described in the limbal stem cell niche in transplant-expired human eye bank corneas, exist in freshly enucleated rabbit eyes and to identify matrix molecules in the anterior limbal stroma that might have the potential to help maintain the stem cell niche. METHODS: Fresh limbal corneal tissue from adult Japanese white rabbits was obtained and examined in semithin resin sections with light microscopy, in ultrathin sections with transmission electron microscopy, and in three-dimensional (3D) reconstructions from data sets of up to 1,000 serial images from serial block face scanning electron microscopy. Immunofluorescence microscopy with five monoclonal antibodies was used to detect specific sulfation motifs on chondroitin sulfate glycosaminoglycans, previously identified in association with progenitor cells and their matrix in cartilage tissue. RESULTS: In the rabbit limbal cornea, while no palisades of Vogt were present, the basal epithelial cells stained differentially with Toluidine blue, and extended lobed protrusions proximally into the stoma, which were associated with interruptions of the basal lamina. Elongate processes of the mesenchymal cells in the superficial vascularized stroma formed direct contact with the basal lamina and basal epithelial cells. From a panel of antibodies that recognize native, sulfated chondroitin sulfate structures, one (6-C-3) gave a positive signal restricted to the region of the mesenchymal-epithelial cell associations. CONCLUSIONS: This study showed interactions between basal epithelial cells and subjacent mesenchymal cells in the rabbit corneal limbus, similar to those that have been observed in the human stem cell niche. A native sulfation epitope in chondroitin sulfate glycosaminoglycans exhibits a distribution specific to the connective tissue matrix of this putative stem/progenitor cell niche.

Zhao, D., et al. (2018). "Hypoxia with Wharton's jelly mesenchymal stem cell coculture maintains stemness of umbilical cord blood-derived CD34(+) cells." Stem Cell Res Ther **9**(1): 158.

BACKGROUND: The physiological approach suggests that an environment associating mesenchymal stromal cells with low O2 concentration would be most favorable for the maintenance of hematopoietic stem/progenitor cells (HSPCs). To test this hypothesis, we performed a coculture of cord blood CD34(+) cells with Wharton's jelly mesenchymal stem cells (WJ-MSCs) under different O2 concentration to simulate the growth of HSPCs in vivo, and assessed the impacts on stemness maintenance and proliferation of cord blood HSPCs in vitro. METHODS: CD34(+) cells derived from cord blood were isolated and cocultured under 1%, 3%, or 20% O2 concentrations with irradiated WJ-MSCs without adding exogenous cytokines for 7 days. The cultured cells were harvested and analyzed for phenotype and functionality, including total nuclear cells (TNC), CD34(+)Lin(-) cells, colony forming unit (CFU) for committed progenitors, and long-term culture initiating cells (LTC-ICs) for HSPCs. The cytokine levels in the medium were detected with Luminex liquid chips, and the mRNA expression of hypoxia inducible factor (HIF) genes and stem cell signal pathway (Notch, Hedgehog, and Wnt/beta-catenin) downstream genes in cord blood HSPCs were confirmed by quantitative real-time polymerase chain reaction (qRT-PCR). RESULTS: Our results showed that the number of TNC cells, CD34(+)Lin(-) cells, and CFU were higher or similar with 20% O2 (normoxia) in coculture and compared with 1% O2 (hypoxia). Interestingly, a 1% O2 concentration ensured better percentages of CD34(+)Lin(-) cells and LTC-IC cells. The hypoxia tension (1% O2) significantly increased vascular endothelial growth factor (VEGF) secretion and decreased interleukin (IL)-6, IL-7, stem cell factor (SCF), and thrombopoietin (TPO) secretion of WJ-MSCs, and selectively activated the Notch, Wnt/beta-catenin, and Hedgehog signaling pathway of cord blood HSPCs by HIF-related factors, which may play an important role in stemness preservation and for sustaining HSPC quiescence. CONCLUSIONS: Our data demonstrate that cord blood HSPCs maintain stemness better under hypoxia than normoxia with WJ-MSC coculture, partially due to the increased secretion of VEGF, decreased secretion of IL-6 by WJ-MSCs, and selective activation of stem cell signal pathways in HSPCs. This suggests that the oxygenation may not only be a physiological regulatory factor but also a cell engineering tool in HSPC

research, and this may have important translational and clinical implications.

The above contents are the collected information from Internet and public resources to offer to the people for the convenient reading and information disseminating and sharing.

**References**


[1]. Baidu. http://www.baidu.com. 2019.
[2]. Cancer Biology. http://www.cancerbio.net. 2019.
[3]. Google. http://www.google.com. 2019.
[4]. Journal of American Science. http://www.jofamericanscience.org. 2019.
[5]. Life Science Journal. http://www.lifesciencesite.com. 2019.
[6]. Ma H, Chen G. Stem cell. The Journal of American Science 2005;1(2):90-92. doi:10.7537/marsjas010205.14. http://www.jofamericanscience.org/journals/am-sci/0102/14-mahongbao.pdf.
[7]. Ma H, Cherng S. Eternal Life and Stem Cell. Nature and Science. 2007;5(1):81-96. doi:10.7537/marsnsj050107.10. http://www.sciencepub.net/nature/0501/10-0247-mahongbao-eternal-ns.pdf.
[8]. Ma H, Cherng S. Nature of Life. Life Science Journal 2005;2(1):7-15. doi:10.7537/marslsj020105.03. http://www.lifesciencesite.com/lsj/life0201/life-0201-03.pdf.
[9]. Ma H, Yang Y. Turritopsis nutricula. Nature and Science 2010;8(2):15-20. doi:10.7537/marsnsj080210.03. http://www.sciencepub.net/nature/ns0802/03_1279_hongbao_turritopsis_ns0802_15_20.pdf.
[10]. Ma H. The Nature of Time and Space. Nature and science 2003;1(1):1-11. doi:10.7537/marsnsj010103.01. http://www.sciencepub.net/nature/0101/01-ma.pdf.
[11]. Marsland Press. http://www.sciencepub.net. 2019; http://www.sciencepub.org. 2019.
[12]. National Center for Biotechnology Information, U.S. National Library of Medicine. http://www.ncbi.nlm.nih.gov/pubmed. 2019.
[13]. Nature and Science. http://www.sciencepub.net/nature. 2019.
[14]. Stem Cell. http://www.sciencepub.net/stem. 2019.
[15]. Wikipedia. The free encyclopedia. http://en.wikipedia.org. 2019.
[16]. Alihemmati, Z., et al. (2017). "Computational simulation of static/cyclic cell stimulations to investigate mechanical modulation of an individual mesenchymal stem cell using confocal microscopy." Mater Sci Eng C Mater Biol Appl **70**(Pt 1): 494-504.
[17]. Chatzistamatiou, T. K., et al. (2014). "Optimizing isolation culture and freezing methods to preserve Wharton's jelly's mesenchymal stem cell (MSC) properties: an MSC banking protocol validation for the Hellenic Cord Blood Bank." Transfusion **54**(12): 3108-3120.
[18]. Choi, H. Y., et al. (2018). "Generation of a human induced pluripotent stem cell line, KSCBi003-A, from human adipose tissue-derived mesenchymal stem cells using a chromosomal integration-free system." Stem Cell Res **31**: 1-4.
[19]. Cobo, F., et al. (2008). "Electron microscopy reveals the presence of viruses in mouse embryonic fibroblasts but neither in human embryonic fibroblasts nor in human mesenchymal cells used for hESC maintenance: toward an implementation of microbiological quality assurance program in stem cell banks." Cloning Stem Cells **10**(1): 65-74.
[20]. Cooper, K. and C. Viswanathan (2011). "Establishment of a mesenchymal stem cell bank." Stem Cells Int **2011**: 905621.
[21]. Cras, A., et al. (2015). "Update on mesenchymal stem cell-based therapy in lupus and scleroderma." Arthritis Res Ther **17**: 301.
[22]. de la Puente, P., et al. (2013). "Differentiation within autologous fibrin scaffolds of porcine dermal cells with the mesenchymal stem cell phenotype." Exp Cell Res **319**(3): 144-152.
[23]. De Luca, L., et al. (2016). "MiRNAs and piRNAs from bone marrow mesenchymal stem cell extracellular vesicles induce cell survival and inhibit cell differentiation of cord blood hematopoietic stem cells: a new insight in transplantation." Oncotarget **7**(6): 6676-6692.
[24]. Fouladiha, H., et al. (2018). "Applications of a metabolic network model of mesenchymal stem cells for controlling cell proliferation and differentiation." Cytotechnology **70**(1): 331-338.
[25]. Garcia-Castro, J., et al. (2008). "Mesenchymal stem cells and their use as cell replacement therapy and disease modelling tool." J Cell Mol Med **12**(6B): 2552-2565.
[26]. Ghaemi, R. V., et al. (2016). "Fluid-Structure Interactions Analysis of Shear-Induced Modulation of a Mesenchymal Stem Cell: An Image-Based Study." Artif Organs **40**(3): 278-287.
[27]. Haghighipour, N., et al. (2012). "Differential effects of cyclic uniaxial stretch on human

mesenchymal stem cell into skeletal muscle cell." Cell Biol Int **36**(7): 669-675.
[28]. Hajizadeh-Saffar, E., et al. (2015). "Inducible VEGF expression by human embryonic stem cell-derived mesenchymal stromal cells reduces the minimal islet mass required to reverse diabetes." Sci Rep **5**: 9322.
[29]. He, Y., et al. (2017). "Umbilical cord-derived mesenchymal stem cell transplantation for treating elderly vascular dementia." Cell Tissue Bank **18**(1): 53-59.
[30]. Hung, H. S., et al. (2014). "In vitro study of a novel nanogold-collagen composite to enhance the mesenchymal stem cell behavior for vascular regeneration." PLoS One **9**(8): e104019.
[31]. Jakobsen, K. K., et al. (2017). "Mesenchymal stem cell therapy for laryngotracheal stenosis: A systematic review of preclinical studies." PLoS One **12**(9): e0185283.
[32]. Jensen, D. H., et al. (2014). "Mesenchymal stem cell therapy for salivary gland dysfunction and xerostomia: a systematic review of preclinical studies." Oral Surg Oral Med Oral Pathol Oral Radiol **117**(3): 335-342 e331.
[33]. Kajbafzadeh, A. M., et al. (2017). "Evaluating the role of autologous mesenchymal stem cell seeded on decellularized pericardium in the treatment of myocardial infarction: an animal study." Cell Tissue Bank **18**(4): 527-538.
[34]. Kucera, T., et al. (2017). "Elution kinetics of vancomycin and gentamicin from carriers and their effects on mesenchymal stem cell proliferation: an in vitro study." BMC Musculoskelet Disord **18**(1): 381.
[35]. Luznik, Z., et al. (2016). "Effect of Cryopreserved Amniotic Membrane Orientation on the Expression of Limbal Mesenchymal and Epithelial Stem Cell Markers in Prolonged Limbal Explant Cultures." PLoS One **11**(10): e0164408.
[36]. Lysak, D., et al. (2016). "Validation of shortened 2-day sterility testing of mesenchymal stem cell-based therapeutic preparation on an automated culture system." Cell Tissue Bank **17**(1): 1-9.
[37]. Montemurro, T., et al. (2016). "Angiogenic and anti-inflammatory properties of mesenchymal stem cells from cord blood: soluble factors and extracellular vesicles for cell regeneration." Eur J Cell Biol **95**(6-7): 228-238.
[38]. Montes, R., et al. (2009). "Feeder-free maintenance of hESCs in mesenchymal stem cell-conditioned media: distinct requirements for TGF-beta and IGF-II." Cell Res **19**(6): 698-709.
[39]. Nicodemou, A. and L. Danisovic (2017). "Mesenchymal stromal/stem cell separation methods: concise review." Cell Tissue Bank **18**(4): 443-460.
[40]. Normanton, M., et al. (2014). "Interleukin 7 plays a role in T lymphocyte apoptosis inhibition driven by mesenchymal stem cell without favoring proliferation and cytokines secretion." PLoS One **9**(9): e106673.
[41]. Quaranta, P., et al. (2016). "Tweaking Mesenchymal Stem/Progenitor Cell Immunomodulatory Properties with Viral Vectors Delivering Cytokines." Stem Cells Dev **25**(18): 1321-1341.
[42]. Sabetkish, S., et al. (2018). "The role of nonautologous and autologous adipose-derived mesenchymal stem cell in acute pyelonephritis." Cell Tissue Bank **19**(3): 301-309.
[43]. Shofuda, T., et al. (2013). "Human Decidua-Derived Mesenchymal Cells Are a Promising Source for the Generation and Cell Banking of Human Induced Pluripotent Stem Cells." Cell Med **4**(3): 125-147.
[44]. Szekiova, E., et al. (2018). "The neuroprotective effect of rat adipose tissue-derived mesenchymal stem cell-conditioned medium on cortical neurons using an in vitro model of SCI inflammation." Neurol Res **40**(4): 258-267.
[45]. Tan, S. L., et al. (2011). "Human amnion as a novel cell delivery vehicle for chondrogenic mesenchymal stem cells." Cell Tissue Bank **12**(1): 59-70.
[46]. Wei, W., et al. (2016). "[Biological characteristics of mesenchymal stem cell and hematopoietic stem cell in the co-culture system]." Sheng Li Xue Bao **68**(5): 691-698.
[47]. Wingstrand, V. L., et al. (2016). "Mesenchymal Stem Cell Therapy for the Treatment of Vocal Fold Scarring: A Systematic Review of Preclinical Studies." PLoS One **11**(9): e0162349.
[48]. Yamada, K., et al. (2015). "Mesenchymal-epithelial cell interactions and proteoglycan matrix composition in the presumptive stem cell niche of the rabbit corneal limbus." Mol Vis **21**: 1328-1339.
[49]. Zhao, D., et al. (2018). "Hypoxia with Wharton's jelly mesenchymal stem cell coculture maintains stemness of umbilical cord blood-derived CD34(+) cells." Stem Cell Res Ther **9**(1): 158.

2/12/2024