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Stem Cell

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Stem Cell Research Literatures (3)

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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.
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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.

Abbas, O. L., et al. (2018). "Comparative Analysis of Mesenchymal Stem Cells from Bone Marrow, Adipose Tissue, and Dental Pulp as Sources of Cell Therapy for Zone of Stasis Burns." J Invest Surg: 1-14.

> INTRODUCTION: The implantation of mesenchymal stem cells (MSCs) has been shown to exert benefits for the survival of the zone-of-stasis. However, the clinical experience indicates the importance of selecting the right source and type of stem cells. Therefore, we planned the current study to perform a quantitative comparison of MSCs isolated from three different sources to provide information useful in selection of the optimal source and to see whether critical mechanisms are conserved between different populations. METHODS: The protective effects of MSCs derived from bone marrow, adipose tissue and dental pulp were compared in a rat model of thermal trauma. The stasis zones were evaluated 72 h after the burn using histochemistry, immunohistochemistry and biochemistry. RESULTS: Gross evaluation of burn wounds revealed that the differences between the mean percentages of the calculated necrotic areas weren't statistically significant. Semi-quantitative grading of the histopathological findings revealed that there were no significant differences between damage scores. Immunohistochemical assessment of apoptotic and necrotic cell deaths revealed that the differences between the mean numbers of apoptotic and necrotic cells weren't statistically significant. Myeloperoxidase activity was found to be significantly lower in the adipose tissue group. Biochemical and immunohistochemical assessment of tissue malondialdehyde revealed that the differences between the groups weren't statistically significant. Finally, the number of neo-vessels in the dental pulp group was found to be significantly higher. CONCLUSION: Our findings suggest that bone marrow, adipose tissue and dental pulp may serve as a universal donor MSC source for the prevention of burn wound progression.

Akazawa, Y., et al. (2015). "Recruitment of mesenchymal stem cells by stromal cell-derived factor 1alpha in pulp cells from deciduous teeth." Int J Mol Med **36**(2): 442-448.

Dental pulp cells (DPCs), including dental pulp (DP) stem cells, play a role in dentine repair under certain conditions caused by bacterial infections associated with caries, tooth fracture and injury. Mesenchymal stem cells (MSCs) have also been shown to be involved in this process of repair. However, the mechanisms through which MSCs are recruited to the DP have not yet been elucidated. Therefore, the aim of the present in vitro study was to investigate whether stromal cell-derived factor 1alpha (SDF1)-C-X-C chemokine receptor type 4 (CXCR4) signaling is involved in tissue repair in the DP of deciduous teeth. A single-cell clone from DPCs (SDP11) and UE7T-13 cells were used as pulp cells and MSCs, respectively. The MG-63 and HuO9 cells, two osteosarcoma cell lines, were used as positive control cells. Reverse transcription polymerase chain reaction (RT-PCR) revealed that all cell lines (SDP11, UE7T-13 MG-63 and HuO9) were positive for both SDF1 and CXCR4 mRNA expression. Moreover, immunocytochemical analysis indicated that SDF1 and CXCR4 proteins were expressed in the SDP11 and UE7T-13 cells. SDF1 was also detected in the cell lysates (CLs) and conditioned medium (CM) collected from the SDP11 and UE7T-13 cells, and AMD3100, a specific antagonist of CXCR4, inhibited the migration of the UE7T-13 cells; this migration was induced by treatment with CM, which was collected from the SDP11 cells. In addition, real-time PCR showed that the expression of SDF1 in the SDP11 cells was inhibited by treatment with 20 ng/ml fibroblast growth factor (FGF)-2, and exposure to AZD4547, an inhibitor of the FGF receptor, blocked this inhibition. Collectively, these data suggest that SDF1 produced by DP plays an important role in homeostasis, repair and regeneration via the recruitment of MSCs.

Ansari, S., et al. (2017). "Hydrogel elasticity and microarchitecture regulate dental-derived mesenchymal stem cell-host immune system cross-talk." Acta Biomater **60**: 181-189.

The host immune system (T-lymphocytes and their pro-inflammatory cytokines) has been shown to compromise bone regeneration ability of mesenchymal stem cells (MSCs). We have recently shown that hydrogel, used as an encapsulating biomaterial affects the cross-talk among host immune cells and MSCs. However, the role of hydrogel elasticity and porosity in regulation of cross-talk between dental-derived MSCs and immune cells is unclear. In this study, we demonstrate that the modulus of elasticity and porosity of the scaffold influence T-lymphocyte-dental MSC interplay by regulating the penetration of inflammatory T cells and their cytokines. Moreover, we demonstrated that alginate hydrogels with different elasticity and microporous structure can regulate the viability and determine the fate of the encapsulated MSCs through modulation of NF-kB pathway. Our in vivo data show that alginate hydrogels with smaller pores and higher elasticity could prevent pro-inflammatory cytokine-induced MSC apoptosis by down-regulating the Caspase-3- and 8- associated proapoptotic cascades, leading to higher amounts of ectopic bone regeneration. Additionally, dental-derived MSCs encapsulated in hydrogel with higher elasticity exhibited lower expression levels of NF-kB p65 and Cox-2 in vivo. Taken together, our findings demonstrate that the mechanical characteristics and microarchitecture of the microenvironment encapsulating MSCs, in addition to presence of T-lymphocytes and their pro-inflammatory cytokines, affect the fate of encapsulated dental-derived MSCs. STATEMENT OF SIGNIFICANCE: In this study, we demonstrate that alginate hydrogel regulates the viability and the fate of the encapsulated dental-derived MSCs through modulation of NF-kB pathway. Alginate hydrogels with smaller pores and higher elasticity prevent pro-inflammatory cytokine-induced MSC apoptosis by down-regulating the Caspase-3- and 8- associated proapoptotic cascade, leading to higher amounts of ectopic bone regeneration. MSCs encapsulated in hydrogel with higher elasticity exhibited lower expression levels of NF-kB p65 and Cox-2 in vivo. These findings confirm that the fate of encapsulated MSCs are affected by the stiffness and microarchitecture of the encapsulating hydrogel biomaterial, as well as presence of T-lymphocytes/pro-inflammatory cytokines providing evidence concerning material science, stem cell biology, the molecular mechanism of dental-derived MSC-associated therapies, and the potential clinical therapeutic impact of MSCs.

Bose, B., et al. (2018). "Breast Cancer Stem Cell Therapeutics, Multiple Strategies Versus Using Engineered Mesenchymal Stem Cells With Notch

Inhibitory Properties: Possibilities and Perspectives." J Cell Biochem **119**(1): 141-149.

Relapse cases of cancers are more vigorous and difficult to control due to the preponderance of cancer stem cells (CSCs). Such CSCs that had been otherwise dormant during the first incidence of cancer gradually appear as radiochemoresistant cancer cells. Hence, cancer therapeutics aimed at CSCs would be an effective strategy for mitigating the cancers during relapse. Alternatively, CSC therapy can also be proposed as an adjuvant therapy, along-with the conventional therapies. As regenerative stem cells (RSCs) are known for their trophic effects, anti-tumorogenicity, and better migration toward an injury site, this review aims to address the use of adult stem cells such as dental pulp derived; cord blood derived pure populations of regenerative stem cells for targeting CSCs. Indeed, pro-tumorogenicity of RSCs is of concern and hence has also been dealt with in relation to breast CSC therapeutics. Furthermore, as notch signaling pathways are upregulated in breast cancers, and anti-notch antibody based and sh-RNA based therapies are already in the market, this review focuses the possibilities of engineering RSCs to express notch inhibitory proteins for breast CSC therapeutics. Also, we have drawn a comparison among various possibilities of breast CSC therapeutics, about, notch1 inhibition. J. Cell. Biochem. 119: 141-149, 2018. (c) 2017 Wiley Periodicals, Inc.

Carbone, A., et al. (2016). "Adipose-derived mesenchymal stromal (stem) cells differentiate to osteoblast and chondroblast lineages upon incubation with conditioned media from dental pulp stem cell-derived osteoblasts and auricle cartilage chondrocytes." J Biol Regul Homeost Agents **30**(1): 111-122.

The potential of adipose-derived mesenchymal stromal (stem) cells (ADSCs) to differentiate into either osteoblasts or chondrocytes is controversial. In this study we investigated the multicapacity potential of ADSCs to differentiate towards adipocyte, osteoblast, and chondrocyte lineages when cells are seeded onto plastic in comparison with incubation with conditioned media (CM) obtained from differentiated cell types.ADSCs, obtained from liposuctions, were characterized for mesenchymal and hematopoietic markers by cytofluorimetry. Their differentiation capacity towards adipocytes, osteoblasts, and chondrocytes was investigated by histochemistry methods (Oil-Red-O staining, Safranin O and Alizarin Red staining, respectively). Dental pulp stem cells (DPSCs) and dedifferentiated auricle derived-chondrocytes were differentiated towards osteoblastic and chondrocytic lineages respectively, and the CM obtained from these cultures was used to induce differentiation of ADSCs. ADSCs were positive for mesenchymal markers (CD29, CD105, CD73, CD44), but not for hematopoietic lineage markers (CD14, CD34, CD45) and this behavior was conserved from the isolation up to the fifth passage. While ADSCs were readily differentiated in adipocytes, they were not towards chondrocytes and osteoblastic lineages, a behavior different from that of bone marrow-derived MSCs that differentiated into the three lineages at two weeks post-induction. Only ADSCs treated with CM from cultured chondrocytes and DPSCs, produced glycosaminoglycans and mineralized matrix. These results indicate that ADSCs need growth/morphogenic factor supplementation from the tissue environment to be appropriately differentiated to mesodermic lineages.

Dehghani Nazhvani, A., et al. (2015). "Identification of Mesenchymal Stem Cell Marker STRO-1 in Oral Reactive Lesions by Immunofluorescence Method." J Dent (Shiraz) **16**(3 Suppl): 246-250.

STATEMENT OF THE PROBLEM: Stem cells are considered as new implement for tissue regeneration. Several niches in adult human body are colonized by multipotent stem cells but access to these potential reservoirs is often limited. Although human dental pulp stem cells isolated from healthy teeth have been extensively characterized, it is still unknown whether stem cells also exist in reactive lesions of oral cavity such as pyogenic granuloma and peripheral ossifying fibroma which are deliberated as inflammatory proliferation of different cell families. PURPOSE: The aim of this study was to explore for clues to see whether pyogenic granuloma or peripheral ossifying fibroma contain dental mesenchymal stem cell (DMSC). MATERIALS AND METHOD: Four pyogenic granuloma and four peripheral ossifying fibroma specimens were collected by excisional biopsy and preserved in PBS-EDTA at -86 degrees C. Then we cut them in 5microm diameter using Cryostat. Having been rinsed with PBS, the samples were stained with a primary mouse anti-human

STRO-1 monoclonal IgM antibody. Afterward, a secondary goat anti-mouse IgM-FITC antibody was applied to detect STRO-1+ cells as probable stem cells by immunofluorescence technique. RESULTS: Immunofluorescence microscopy revealed presence of STRO-1+ cells in these lesions, particularly localized on perivascular zone. The negative control group was not glowing. CONCLUSION: Based on these results, it was found that reactive lesions of pyogenic granuloma and peripheral ossifying fibroma have STRO-1 positive cells, which raises the possibility that these cells may be DMSCs.

Di Scipio, F., et al. (2014). "Injured cardiomyocytes promote dental pulp mesenchymal stem cell homing." Biochim Biophys Acta **1840**(7): 2152-2161.

BACKGROUND: The heart is unable to regenerate its tissues after severe injuries. Stem cell therapy appears to be one of the most promising approaches, though preclinical results are hitherto contradictory and clinical trials scanty and/or limited to phase-I. The limited knowledge about stem cell early homing in infarcted cardiac tissues can concur to this scenario. METHODS: The stem cell migration was assessed in in-vitro and ex-vivo models of heart ischemia, employing a rat dental pulp stem cell line (MUR-1) that shares the same ontogenic progenitors with portions of the heart, expresses markers typical of cardiac/vascular-like progenitors and is able to differentiate into cardiomyocytes in-vitro. RESULTS: Here, we demonstrated that the MUR-1 can reach the injured cells/tissue and make contacts with the damaged cardiomyocytes, likely through Connexin 43, N-cadherin and von Willebrand Factor mediated cell-cell interactions, both in in-vitro and ex-vivo models. Furthermore, we found that SDF-1, FGF-2 and HGF, but not VEGF are involved as chemotactic factors in MUR-1 migration, notifying a similarity with neural crest cell behavior during the organogenesis of both the splanchnocranium and the heart. CONCLUSIONS: Herein we found a similarity between what happens during the heart organogenesis and the early migration and homing of MUR-1 cells in ischemic models. GENERAL SIGNIFICANCE: The comprehension of molecular aspects underlying the early phases of stem cell migration and interaction with damaged organ contributes to the future achievement of the coveted stem cell-mediated organ regeneration and function preservation in-vivo.

El Omar, R., et al. (2014). "Umbilical cord mesenchymal stem cells: the new gold standard for mesenchymal stem cell-based therapies?" Tissue Eng Part B Rev **20**(5): 523-544.

Due to their self-renewal capacity, multilineage differentiation potential, paracrine effects, and immunosuppressive properties, mesenchymal stromal cells (MSCs) are an attractive and promising tool for regenerative medicine. MSCs can be isolated from various tissues but despite their common immunophenotypic characteristics and functional properties, source-dependent differences in MSCs properties have recently emerged and lead to different clinical applications. Considered for a long time as a medical waste, umbilical cord appears these days as a promising source of MSCs. Several reports have shown that umbilical cord-derived MSCs are more primitive, proliferative, and immunosuppressive than their adult counterparts. In this review, we aim at synthesizing the differences between umbilical cord MSCs and MSCs from other sources (bone marrow, adipose tissue, periodontal ligament, dental pulp,...) with regard to their proliferation capacity, proteic and transcriptomic profiles, and their secretome involved in their regenerative, homing, and immunomodulatory capacities. Although umbilical cord MSCs are until now not particularly used as an MSC source in clinical practice, accumulating evidence shows that they may have a therapeutic advantage to treat several diseases, especially autoimmune and neurodegenerative diseases.

Gagari, E., et al. (2006). "Expression of stem cell factor and its receptor, c-kit, in human oral mesenchymal cells." Eur J Oral Sci **114**(5): 409-415.

Stem cell factor (SCF) is the pleiotropic ligand for the tyrosine kinase receptor, c-kit. Ligand and receptor are usually expressed in different cell types, and binding of SCF to c-kit promotes cell proliferation, differentiation, and recruitment of progenitor cells in various biologic systems. However, the localization of these two molecules in cells of the oral cavity has not been systematically examined. We investigated the expression of SCF and c-kit in human dental pulp (HDP) cells as well as in human gingival fibroblasts (HGF). Both alternatively spliced isoforms of SCF were

detected (through reverse transcription-polymerase chain reaction) in RNA obtained from the two cell types. Western analysis established that both cell types express SCF and/or c-kit, whereas flow cytometry demonstrated distinct cell populations expressing only the ligand (SCF), only the receptor (c-kit), or co-expressing the two. HDP cultures showed higher soluble SCF (sSCF) production associated with faster cell growth, as compared with HGF cultures. In both cell types, however, sSCF levels appeared to increase as a result of in vitro aging and/or differentiation.

Ginani, F., et al. (2015). "Effect of low-level laser therapy on mesenchymal stem cell proliferation: a systematic review." Lasers Med Sci **30**(8): 2189-2194.

Low-level laser therapy (LLLT) has been used in several in vitro experiments in order to stimulate cell proliferation. Cells such as fibroblasts, keratinocytes, lymphocytes, and osteoblasts have shown increased proliferation when submitted to laser irradiation, although little is known about the effects of LLLT on stem cells. This study aims to assess, through a systematic literature review, the effects of LLLT on the in vitro proliferation of mesenchymal stem cells. Using six different terms, we conducted an electronic search in PubMed/Medline database for articles published in the last twelve years. From 463 references obtained, only 19 papers met the search criteria and were included in this review. The analysis of the papers showed a concentration of experiments using LLLT on stem cells derived from bone marrow, dental pulp, periodontal ligament, and adipose tissue. Several protocols were used to irradiate the cells, with variations on wavelength, power density, radiation time, and state of light polarization. Most studies demonstrated an increase in the proliferation rate of the irradiated cells. It can be concluded that the laser therapy positively influences the in vitro proliferation of stem cells studied, being necessary to carry out further experiments on other cell types and to uniform the methodological designs.

Gonzalez-King, H., et al. (2017). "Hypoxia Inducible Factor-1alpha Potentiates Jagged 1-Mediated Angiogenesis by Mesenchymal Stem Cell-Derived Exosomes." Stem Cells **35**(7): 1747-1759.

Insufficient vessel growth associated with ischemia remains an unresolved issue in vascular medicine. Mesenchymal stem cells (MSCs) have been shown to promote angiogenesis via a mechanism that is potentiated by hypoxia. Overexpression of hypoxia inducible factor (HIF)-1alpha in MSCs improves their therapeutic potential by inducing angiogenesis in transplanted tissues. Here, we studied the contribution of exosomes released by HIF-1alpha-overexpressing donor MSCs (HIF-MSC) to angiogenesis by endothelial cells. Exosome secretion was enhanced in HIF-MSC. Omics analysis of miRNAs and proteins incorporated into exosomes pointed to the Notch pathway as a candidate mediator of exosome communication. Interestingly, we found that Jagged1 was the sole Notch ligand packaged into MSC exosomes and was more abundant in HIF-MSC than in MSC controls. The addition of Jagged1-containing exosomes from MSC and HIF-MSC cultures to endothelial cells triggered transcriptional changes in Notch target genes and induced angiogenesis in an in vitro model of capillary-like tube formation, and both processes were stimulated by HIF-1alpha. Finally, subcutaneous injection of Jagged 1-containing exosomes from MSC and HIF-MSC cultures in the Matrigel plug assay induced angiogenesis in vivo, which was more robust when they were derived from HIF-MSC cultures. All Jagged1-mediated effects could be blocked by prior incubation of exosomes with an anti-Jagged 1 antibody. All together, the results indicate that exosomes derived from MSCs stably overexpressing HIF-1alpha have an increased angiogenic capacity in part via an increase in the packaging of Jagged1, which could have potential applications for the treatment of ischemia-related disease. Stem Cells 2017;35:1747-1759.

Hatlapatka, T., et al. (2011). "Optimization of culture conditions for the expansion of umbilical cord-derived mesenchymal stem or stromal cell-like cells using xeno-free culture conditions." Tissue Eng Part C Methods **17**(4): 485-493.

First isolated from bone marrow, mesenchymal stem or stromal cells (MSC) were shown to be present in several postnatal and extraembryonic tissues as well as in a large variety of fetal tissues (e.g., fatty tissue, dental pulp, placenta, umbilical cord blood, and tissue). In this study, an optimized protocol for the expansion of MSC-like cells from whole umbilical cord tissue under xeno-

free culture conditions is proposed. Different fetal calf sera and human serum (HS) were compared with regard to cell proliferation and MSC marker stability in long-term expansion experiments, and HS was shown to support optimal growth conditions. Additionally, the optimal concentration of HS during the cultivation was determined. With regard to cell proliferative potential, apoptosis, colony-forming unit fibroblast frequency, and cell senescence, our findings suggest that an efficient expansion of the cells is carried out best in media supplemented with 10% HS. Under our given xeno-free culture conditions, MSC-like cells were found to display in vitro immunoprivileged and immunomodulatory properties, which were assessed by co-culture and transwell culture experiments with carboxyfluorescein diacetate succinimidyl ester-labeled peripheral blood mononuclear cells. These findings may be of great value for the establishment of biotechnological protocols for the delivery of sufficient cell numbers of high quality for regenerative medicine purposes.

Jewett, A., et al. (2010). "Strategies to rescue mesenchymal stem cells (MSCs) and dental pulp stem cells (DPSCs) from NK cell mediated cytotoxicity." PLoS One **5**(3): e9874.

BACKGROUND: The aim of this paper is to study the function of allogeneic and autologous NK cells against Dental Pulp Stem Cells (DPSCs) and Mesenchymal Stem Cells (MSCs) and to determine the function of NK cells in a three way interaction with monocytes and stem cells. METHODOLOGY/PRINCIPAL FINDINGS: We demonstrate here that freshly isolated untreated or IL-2 treated NK cells are potent inducers of cell death in DPSCs and MSCs, and that anti-CD16 antibody which induces functional split anergy and apoptosis in NK cells inhibits NK cell mediated lysis of DPSCs and MSCs. Monocytes co-cultured with either DPSCs or MSCs decrease lysis of stem cells by untreated or IL-2 treated NK cells. Monocytes also prevent NK cell apoptosis thereby raising the overall survival and function of NK cells, DPSCs or MSCs. Both total population of monocytes and those depleted of CD16(+) subsets were able to prevent NK cell mediated lysis of MSCs and DPSCs, and to trigger an increased secretion of IFN-gamma by IL-2 treated NK cells. Protection of stem cells from NK cell mediated lysis was also seen when monocytes were sorted out from stem cells before they were added to NK cells. However, this effect was not specific to monocytes since the addition of T and B cells to stem cells also protected stem cells from NK cell mediated lysis. NK cells were found to lyse monocytes, as well as T and B cells. CONCLUSION/SIGNIFICANCE: By increasing the release of IFN-gamma and decreasing the cytotoxic function of NK cells monocytes are able to shield stem cells from killing by the NK cells, resulting in an increased protection and differentiation of stem cells. More importantly studies reported in this paper indicate that anti-CD16 antibody can be used to prevent NK cell induced rejection of stem cells.

Karaoz, E., et al. (2011). "Human dental pulp stem cells demonstrate better neural and epithelial stem cell properties than bone marrow-derived mesenchymal stem cells." Histochem Cell Biol **136**(4): 455-473.

Dental pulp stem cells (hDP-SCs) were primarily derived from pulp tissues of primary incisors, exfoliated deciduous and permanent third molar teeth. To understand the characteristics of hDP-SCs from impacted third molar, proliferation capacities, gene expression profiles, phenotypic, ultrastructural, and differentiation characteristics were analyzed in comparison with human bone marrow-derived mesenchymal stem cells (hBM-MSCs), extensively. hDP-SCs showed more developed and metabolically active cells. Contrary to hBM-MSCs, hDP-SCs strongly expressed both cytokeratin (CK)-18 and -19, which could involve in odontoblast differentiation and dentine repair. The intrinsic neuro-glia characteristics of hDP-MSCs were demonstrated by the expression of several specific transcripts and proteins of neural stem cell and neurons. These cells not only differentiate into adipogenic, osteogenic, and chondrogenic lineage, but also share some special characteristics of expressing some neural stem cell and epithelial markers. Under defined conditions, hDP-SCs are able to differentiate into both neural and vascular endothelial cells in vitro. Dental pulp might provide an alternative source for human MSCs. hDP-SCs with a promising differentiation capacity could be easily isolated, and possible clinical use could be developed for neurodegenerative and oral diseases in the future.

Kawazoe, Y., et al. (2008). "Activation of the FGF signaling pathway and subsequent induction of mesenchymal stem cell differentiation by inorganic polyphosphate." Int J Biol Sci **4**(1): 37-47.

Inorganic polyphosphate [poly(P)] is a biopolymer existing in almost all cells and tissues, although its biological functions in higher eukaryotes have not been completely elucidated. We previously demonstrated that poly(P) enhances the function of fibroblast growth factors (FGFs) by stabilizing them and strengthening the affinity between FGFs and their cell surface receptors. Since FGFs play crucial roles in bone regeneration, we further investigated the effect of poly(P) on the cell differentiation of human stem cells via FGF signaling systems. Human dental pulp cells (HDPCs) isolated from human dental pulp show the characteristics of multipotent mesenchymal stem cells (MSCs). HDPCs secreted FGFs and the proliferation of HDPCs was shown to be enhanced by treatment with poly(P). Cell surface receptor-bound FGF-2 was stably maintained for more than 40 hours in the presence of poly(P). The phosphorylation of ERK1/2 was also enhanced by poly(P). The effect of poly(P) on the osteogenic differentiation of HDPCs and human MSCs (hMSCs) were also investigated. After 5 days of treatment with poly(P), type-I collagen expression of both cell types was enhanced. The C-terminal peptide of type-I collagen was also released at higher levels in poly(P)-treated HDPCs. Microarray analysis showed that expression of matrix metalloproteinase-1 (MMP1), osteopontin (OPN), osteocalcin (OC) and osteoprotegerin was induced in both cell types by poly(P). Furthermore, induced expression of MMP1, OPN and OC genes in both cells was confirmed by real-time PCR. Calcification of both cell types was clearly observed by alizarin red staining following treatment with poly(P). The results suggest that the activation of the FGF signaling pathway by poly(P) induces both proliferation and mineralization of stem cells.

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.

Lapthanasupkul, P., et al. (2012). "Ring1a/b polycomb proteins regulate the mesenchymal stem cell niche in continuously growing incisors." Dev Biol **367**(2): 140-153.

Rodent incisors are capable of growing continuously and the renewal of dental epithelium giving rise to enamel-forming ameloblasts and dental mesenchyme giving rise to dentin-forming odontoblasts and pulp cells is achieved by stem cells residing at their proximal ends. Although the dental epithelial stem cell niche (cervical loop) is well characterized, little is known about the dental mesenchymal stem cell niche. Ring1a/b are the core Polycomb repressive complex1 (PRC1) components that have recently also been found in a protein complex with BcoR (Bcl-6 interacting corepressor) and Fbxl10.

During mouse incisor development, we found that genes encoding members of the PRC1 complex are strongly expressed in the incisor apical mesenchyme in an area that contains the cells with the highest proliferation rate in the tooth pulp, consistent with a location for transit amplifying cells. Analysis of Ring1a(-/-);Ring1b(cko/cko) mice showed that loss of Ring1a/b postnatally results in defective cervical loops and disturbances of enamel and dentin formation in continuously growing incisors. To further characterize the defect found in Ring1a(-/-);Ring1b(cko/cko) mice, we demonstrated that cell proliferation is dramatically reduced in the apical mesenchyme and cervical loop epithelium of Ring1a(-/-);Ring1b(cko/cko) incisors in comparison to Ring1a(-/-);Ring1b(fl/fl)cre- incisors. Fgf signaling and downstream targets that have been previously shown to be important in the maintenance of the dental epithelial stem cell compartment in the cervical loop are downregulated in Ring1a(-/-);Ring1b(cko/cko) incisors. In addition, expression of other genes of the PRC1 complex is also altered. We also identified an essential postnatal requirement for Ring1 proteins in molar root formation. These results show that the PRC1 complex regulates the transit amplifying cell compartment of the dental mesenchymal stem cell niche and cell differentiation in developing mouse incisors and is required for molar root formation.

Lei, M., et al. (2014). "Mesenchymal stem cell characteristics of dental pulp and periodontal ligament stem cells after in vivo transplantation." Biomaterials **35**(24): 6332-6343.

Mesenchymal stem cells (MSCs) isolated from human postnatal dental pulp and periodontal ligament (PDL) tissues can give rise to multilineage differentiation in vitro and generate related dental tissues in vivo. However, the cell properties of human dental pulp stem cells (DPSCs) and PDL stem cells (PDLSCs) after in vivo implantation remain largely unidentified. In this study, cells were re-isolated from in vivo-generated dental pulp-like and PDL-like tissues (termed re-DPCs and re-PDLCs, respectively) as a result of ectopic transplantation of human DPSC and PDLSC sheets. The cell characteristics in terms of colony-forming ability, cell surface antigens and multi-differentiation potentials were all evaluated before and after implantation. It was found that re-DPCs and re-PDLCs were of human and mesenchymal origin and positive for MSC markers such as STRO-1, CD146, CD29, CD90 and CD105; and, to some extent, re-DPCs could maintain their colony forming abilities. Moreover, both cell types were able to form mineral deposits and differentiate into adipocytes and chondrocytes; however, quantitative analysis and related gene expression determination showed that the osteo-/chondro-differentiation capabilities of re-DPCs and re-PDLCs were significantly reduced compared to those of DPSCs and PDLSCs, respectively ($P < 0.05$); re-PDLCs showed a greater reduction potential than re-DPCs. We conclude that DPSCs and PDLSCs may maintain their MSC characteristics after in vivo implantation and, compared to PDLSCs, DPSCs appear much more stable under in vivo conditions. These findings provide additional cellular and molecular evidence that supports expanding the use of dental tissue-derived stem cells in cell therapy and tissue engineering.

Marei, M. K. and R. M. El Backly (2018). "Dental Mesenchymal Stem Cell-Based Translational Regenerative Dentistry: From Artificial to Biological Replacement." Front Bioeng Biotechnol **6**: 49.

Dentistry is a continuously changing field that has witnessed much advancement in the past century. Prosthodontics is that branch of dentistry that deals with replacing missing teeth using either fixed or removable appliances in an attempt to simulate natural tooth function. Although such "replacement therapies" appear to be easy and economic they fall short of ever coming close to their natural counterparts. Complications that arise often lead to failures and frequent repairs of such devices which seldom allow true physiological function of dental and oral-maxillofacial tissues. Such factors can critically affect the quality of life of an individual. The market for dental implants is continuously growing with huge economic revenues. Unfortunately, such treatments are again associated with frequent problems such as peri-implantitis resulting in an eventual loss or replacement of implants. This is particularly influential for patients having co-morbid diseases such as diabetes or osteoporosis and in association with smoking and other conditions that undoubtedly affect the final treatment outcome. The advent of tissue engineering and regenerative medicine therapies along with the enormous strides

taken in their associated interdisciplinary fields such as stem cell therapy, biomaterial development, and others may open arenas to enhancing tissue regeneration via designing and construction of patient-specific biological and/or biomimetic substitutes. This review will overview current strategies in regenerative dentistry while overviewing key roles of dental mesenchymal stem cells particularly those of the dental pulp, until paving the way to precision/translational regenerative medicine therapies for future clinical use.

Mrozik, K. M., et al. (2010). "Proteomic characterization of mesenchymal stem cell-like populations derived from ovine periodontal ligament, dental pulp, and bone marrow: analysis of differentially expressed proteins." Stem Cells Dev **19**(10): 1485-1499.

Postnatal mesenchymal stem/stromal-like cells (MSCs) including periodontal ligament stem cells (PDLSCs), dental pulp stem cells (DPSCs), and bone marrow stromal cells (BMSCs) are capable of self-renewal and differentiation into multiple mesenchymal cell lineages. Despite their similar expression of MSC-associated and osteoblastic markers, MSCs retain the capacity to generate structures resembling the microenvironments from which they are derived in vivo and represent a promising therapy for the regeneration of complex tissues in the clinical setting. With this in mind, systematic approaches are required to identify the differential protein expression patterns responsible for lineage commitment and mediating the formation of these complex structures. This is the first study to compare the differential proteomic expression profiles of ex vivo-expanded ovine PDLSCs, DPSCs, and BMSCs derived from an individual donor. The two-dimensional electrophoresis was performed and regulated proteins were identified by liquid chromatography--electrospray-ionization tandem mass spectrometry (MS and MS/MS), database searching, and de novo sequencing. In total, 58 proteins were differentially expressed between at least 2 MSC populations in both sheep, 12 of which were up-regulated in one MSC population relative to the other two. In addition, the regulation of selected proteins was also conserved between equivalent human MSC populations. We anticipate that differential protein expression profiling will provide a basis for elucidating the protein expression patterns and molecular cues that are crucial in specifying the characteristic growth and developmental capacity of dental and non-dental tissue-derived MSC populations. These expression patterns can serve as important tools for the regeneration of particular tissues in future stem cell-based tissue engineering studies using animal models.

Murakami, M., et al. (2015). "Trophic Effects and Regenerative Potential of Mobilized Mesenchymal Stem Cells From Bone Marrow and Adipose Tissue as Alternative Cell Sources for Pulp/Dentin Regeneration." Cell Transplant **24**(9): 1753-1765.

Dental pulp stem cell (DPSC) subsets mobilized by granulocyte-colony-stimulating factor (G-CSF) are safe and efficacious for complete pulp regeneration. The supply of autologous pulp tissue, however, is very limited in the aged. Therefore, alternative sources of mesenchymal stem/progenitor cells (MSCs) are needed for the cell therapy. In this study, DPSCs, bone marrow (BM), and adipose tissue (AD)-derived stem cells of the same individual dog were isolated using G-CSF-induced mobilization (MDPSCs, MBMSCs, and MADSCs). The positive rates of CXCR4 and G-CSFR in MDPSCs were similar to MADSCs and were significantly higher than those in MBMSCs. Trophic effects of MDPSCs on angiogenesis, neurite extension, migration, and antiapoptosis were higher than those of MBMSCs and MADSCs. Pulp-like loose connective tissues were regenerated in all three MSC transplantations. Significantly higher volume of regenerated pulp and higher density of vascularization and innervation were observed in response to MDPSCs compared to MBMSC and MADSC transplantation. Collagenous matrix containing dentin sialophosphoprotein (DSPP)-positive odontoblast-like cells was the highest in MBMSCs and significantly higher in MADSCs compared to MDPSCs. MBMSCs and MADSCs, therefore, have potential for pulp regeneration, although the volume of regenerated pulp tissue, angiogenesis, and reinnervation, were less. Thus, in conclusion, an alternative cell source for dental pulp/dentin regeneration are stem cells from BM and AD tissue.

Nancarrow-Lei, R., et al. (2017). "A Systemic Review of Adult Mesenchymal Stem Cell Sources and their

Multilineage Differentiation Potential Relevant to Musculoskeletal Tissue Repair and Regeneration." Curr Stem Cell Res Ther **12**(8): 601-610.

BACKGROUND: Adult mesenchymal stem cells (MSCs) were first isolated from bone marrow by Friedenstein in 1976. These cells were clonogenic, non-haematopoietic, and able to replicate extensively in vitro. The fields of regenerative medicine and tissue engineering have grown dramatically since their inception. In the decades since, MSCs have been identified from mesoderm-, endoderm- and ectoderm-derived tissues. In light of our ageing population, the need for effective cell-based therapies for tissue repair and regeneration is ever-expanding. OBJECTIVES: The purpose of this systematic review was to summarise evidence from the most recent studies outlining different sources of adult MSCs and their suitability in musculoskeletal applications. METHODS: Online published articles were searched for using the PubMed/MEDLINE and Ovid databases, and relevant articles fulfilling the pre-defined eligibility criteria were analysed. RESULTS: To date, MSCs have been isolated from a number of adult tissues, including trabecular bone, adipose tissue, bone marrow, synovium, dermis, periodontal ligament, dental pulp, bursa and the umbilical cord. Bone marrow MSCs are currently considered the gold standard, with which newly discovered sources are compared on the basis of their renewal capabilities and multipotency. Furthermore, MSCs have been successful in the regeneration of osteonecrosis, osteoarthritis, bony defects, fracture remodeling and so on. CONCLUSION: Unfortunately, significant hurdles remain and will need to be overcome before tissue engineering using MSCs becomes routine in clinical practice. Thus, further research and understanding are required into the safe and effective sourcing and application of mesenchymal stem cells in musculoskeletal applications.

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.

Orciani, M., et al. (2012). "In vitro evaluation of mesenchymal stem cell isolation possibility from different intra-oral tissues." J Biol Regul Homeost Agents **26**(2 Suppl): 57-63.

Mesenchymal stem cells (MSCs) are of great interest for the regeneration of tissues and organs. Bone marrow is the first sources of MSCs, but in the recent years there has been interest in other tissues for the isolation of these pluripotent cells. In this study, we investigated the features of MSCs isolated from different oral regions in order to evaluate their potential application in the regeneration of damaged maxillofacial tissues. Sampling from human periodontal ligament, dental pulp, maxillary periosteum as well as bone marrow were collected in order to obtain different stem cell populations. Cells were morphologically and immunophenotipically characterized. Their proliferation potential and their ability to differentiate in osteoblasts were also assessed. All tested cell population showed a similar fibroblast-like morphology and superimposable immunophenotype. Slight differences were observed in proliferation and differentiation potential. Cells isolated from human periodontal ligament, dental pulp, maxillary periosteum had the characteristics of stem cells. Considering their peculiar feature they may alternatively represent interesting cell sources in stem cell-based bone/periodontal tissue regeneration approaches.

Otabe, K., et al. (2012). "Comparison of Gingiva, Dental Pulp, and Periodontal Ligament Cells From the Standpoint of Mesenchymal Stem Cell Properties." Cell Med **4**(1): 13-21.

The specific properties of mesenchymal stem cells (MSCs) in oral tissues still remain unknown though their existence has been

previously reported. We collected gingiva, dental pulp, and periodontal ligament tissues from removed teeth and isolated MSCs. These MSCs were compared in terms of their yields per tooth, surface epitopes, and differentiation potentials by patient-matched analysis. For in vivo calcification analysis, rat gingival and dental pulp cells mounted on beta-tricalcium phospateTCP were transplanted into the perivertebral muscle of rats for 6 weeks. Gingival cells and dental pulp cells showed higher yield per tooth than periodontal ligament cells (n=6, $p<0.05$). Yields of periodontal ligament cells were too low for further analysis. Gingival and dental pulp cells expressed MSC markers such as CD44, CD90, and CD166. Gingival and dental pulp cells obtained phenotypes of chondrocytes and adipocytes in vitro. Approximately 60% of the colonies of gingival cells and 40% of the colonies of dental pulp cells were positively stained with alizarin red in vitro, and both gingival and dental pulp cells were calcified in vivo. We clarified properties of MSCs derived from removed teeth. We could obtain a high yield of MSCs with osteogenic potential from gingiva and dental pulp. These results indicate that gingiva and dental pulp are putative cell sources for hard tissue regeneration.

Ozdemir, A. T., et al. (2016). "The paracrine immunomodulatory interactions between the human dental pulp derived mesenchymal stem cells and CD4 T cell subsets." Cell Immunol **310**: 108-115.

Mesenchymal stem cells (MSCs) have strong immunomodulatory properties, however these properties may show some differences according to the tissue type of their isolate. In this study we investigated the paracrine interactions between human DP derived MSCs (hDP-MSCs) and the CD4(+) T helper cell subsets to establish their immunomodulatory mechanisms. We found that the CD4(+)-Tbet(+) (Th1) and CD4(+)-Gata3(+) (Th2) cells were suppressed by the hDP-MSCs, but the CD4(+)-Stat3(+) (Th17) and CD4(+)-CD25(+)-FoxP3(+) (Treg) cells were stimulated. The expressions of T cell specific cytokines interferon gamma (IFN-g), interleukin (IL)-4 and IL-17a decreased, but IL-10 and transforming growth factor beta-1 (TGF-b1) increased with the hDP-MSCs. The expressions of indoleamine-pyrrole 2,3-dioxygenase (IDO), prostaglandin E2 (PGE2), soluble human leukocyte antigen G (sHLA-G) derived from hDP-MSCs slightly increased, but hepatocyte growth factor (HGF) significantly increased in the co-culture groups. According to our findings, the hDP-MSCs can suppress the Th1 and Th2 subsets but stimulate the Th17 and Treg subsets. The Stat3 expression of Th17 cells may have been stimulated by the HGF, and thus the pro-inflammatory Th17 cells may have altered into the immunosuppressive regulatory Th17 cells. Further prospective studies are needed to confirm our findings.

Peng, H., et al. (2016). "Purinergic and Store-Operated Ca(2+) Signaling Mechanisms in Mesenchymal Stem Cells and Their Roles in ATP-Induced Stimulation of Cell Migration." Stem Cells **34**(8): 2102-2114.

ATP is an extrinsic signal that can induce an increase in the cytosolic Ca(2+) level ([Ca(2+)]c) in mesenchymal stem cells (MSCs). However, the cognate intrinsic mechanisms underlying ATP-induced Ca(2+) signaling in MSCs is still contentious, and their importance in MSC migration remains unknown. In this study, we investigated the molecular mechanisms underlying ATP-induced Ca(2+) signaling and their roles in the regulation of cell migration in human dental pulp MSCs (hDP-MSCs). RT-PCR analysis of mRNA transcripts and interrogation of agonist-induced increases in the [Ca(2+)]c support that P2X7, P2Y1 , and P2Y11 receptors participate in ATP-induced Ca(2+) signaling. In addition, following P2Y receptor activation, Ca(2+) release-activated Ca(2+) Orai1/Stim1 channel as a downstream mechanism also plays a significant role in ATP-induced Ca(2+) signaling. ATP concentration-dependently stimulates hDP-MSC migration. Pharmacological and genetic interventions of the expression or function of the P2X7, P2Y1 and P2Y11 receptors, and Orai1/Stim1 channel support critical involvement of these Ca(2+) signaling mechanisms in ATP-induced stimulation of hDP-MSC migration. Taken together, this study provide evidence to show that purinergic P2X7, P2Y1 , and P2Y11 receptors and store-operated Orai1/Stim1 channel represent important molecular mechanisms responsible for ATP-induced Ca(2+) signaling in hDP-MSCs and activation of these mechanisms stimulates hDP-MSC migration. Such information is useful in building a mechanistic understanding of MSC homing in tissue homeostasis and developing more

efficient MSC-based therapeutic applications. Stem Cells 2016;34:2102-2114.

Ren, H., et al. (2016). "Comparative Analysis of Human Mesenchymal Stem Cells from Umbilical Cord, Dental Pulp, and Menstrual Blood as Sources for Cell Therapy." Stem Cells Int **2016**: 3516574.

Although mesenchymal stem cells (MSCs) based therapy has been considered as a promising tool for tissue repair and regeneration, the optimal cell source remains unknown. Umbilical cord (UC), dental pulp (DP), and menstrual blood (MB) are easily accessible sources, which make them attractive candidates for MSCs. The goal of this study was to compare the biological characteristics, including morphology, proliferation, antiapoptosis, multilineage differentiation capacity, and immunophenotype of UC-, DP-, and MB-MSCs in order to provide a theoretical basis for clinical selection and application of these cells. As a result, all UC-, DP-, and MB-MSCs have self-renewal capacity and multipotentiality. However, the UC-MSCs seemed to have higher cell proliferation ability, while DP-MSCs may have significant advantages for osteogenic differentiation, lower cell apoptosis, and senescence. These differences may be associated with the different expression level of cytokines, including vascular endothelial growth factor, fibroblast growth factor, keratinocyte growth factor, and hepatocyte growth factor in each of the MSCs. Comprehensively, our results suggest DP-MSCs may be a desired source for clinical applications of cell therapy.

Riekstina, U., et al. (2009). "Embryonic stem cell marker expression pattern in human mesenchymal stem cells derived from bone marrow, adipose tissue, heart and dermis." Stem Cell Rev **5**(4): 378-386.

Mesenchymal stem cells (MSCs) have been isolated from a variety of human tissues, e.g., bone marrow, adipose tissue, dermis, hair follicles, heart, liver, spleen, dental pulp. Due to their immunomodulatory and regenerative potential MSCs have shown promising results in preclinical and clinical studies for a variety of conditions, such as graft versus host disease (GvHD), Crohn's disease, osteogenesis imperfecta, cartilage damage and myocardial infarction. MSC cultures are composed of heterogeneous cell populations. Complications in defining MSC arise from the fact that different laboratories have employed different tissue sources, extraction, and cultivation methods. Although cell-surface antigens of MSCs have been extensively explored, there is no conclusive evidence that unique stem cells markers are associated with these adult cells. Therefore the aim of this study was to examine expression of embryonic stem cell markers Oct4, Nanog, SOX2, alkaline phosphatase and SSEA-4 in adult mesenchymal stem cell populations derived from bone marrow, adipose tissue, dermis and heart. Furthermore, we tested whether human mesenchymal stem cells preserve tissue-specific differences under in vitro culture conditions. We found that bone marrow MSCs express embryonic stem cell markers Oct4, Nanog, alkaline phosphatase and SSEA-4, adipose tissue and dermis MSCs express Oct4, Nanog, SOX2, alkaline phosphatase and SSEA-4, whereas heart MSCs express Oct4, Nanog, SOX2 and SSEA-4. Our results also indicate that human adult mesenchymal stem cells preserve tissue-specific differences under in vitro culture conditions during early passages, as shown by distinct germ layer and embryonic stem cell marker expression patterns. Studies are now needed to determine the functional role of embryonic stem cell markers Oct4, Nanog and SOX2 in adult human MSCs.

Rodriguez-Lozano, F. J., et al. (2013). "Effects of two low-shrinkage composites on dental stem cells (viability, cell damaged or apoptosis and mesenchymal markers expression)." J Mater Sci Mater Med **24**(4): 979-988.

To investigate the effects of new two low-shrinkage composites SDR((R)) and Venus((R))Bulk Fill on the cell viability, cellular damage and expression of mesenchymal markers on dental stem cells. Specimens from two low-shrinkage composites were eluted with culture medium for 24 h. After 24 h of incubation, cytotoxicity of elutes were evaluated by MTT assay; apoptosis was determined using the DNA-specific fluorochrome Hoechst 33342 and the mesenchymal stem cells markers expression was analyzed by immunofluorescence staining. After 24 h of cell exposure to each extract media, dental stem cells expressed MSCs markers. The interaction among the material and cell line was not significantly correlated [F(1,60) = 2.251, P = 0.39], whereas statistically significant differences among cells lines were observed [F(1,60) = 9.157, P

= 0.004], being dental pulp stem cells more resistant that periodontal ligament stem cells. Also, we did not find any significant effect between the tested materials [F(1,60) = 0.090, P = 0.765]. Furthermore, a very low proportion of exposed cells showed condensed or fragmented nuclei, typical of apoptotic cells at 24 h. The results suggest that SDR((R)) and Venus((R)) Bulk fill and should be considered when selecting an appropriate resin-based dental restorative material.

Shan, L. (2004). FluidMAG iron nanoparticle-labeled mesenchymal stem cells for tracking cell homing to tumors. Molecular Imaging and Contrast Agent Database (MICAD). Bethesda (MD).

Personalized diagnosis and treatment with allogenic or autologous cells are becoming a reality in the field of medicine (1, 2). Cytotoxic or engineered T-cells are under clinical trial for the treatment of hematopoietic or other malignant diseases (3). Contrast agent-tagged macrophages are used as cellular probes to image the early inflammatory processes in macrophage-rich conditions such as inflammation, atherosclerosis, and acute cardiac graft rejection (4). The roles of stem cells are under intensive investigation in therapeutic and regenerative medicine, such as regenerating cardiomyocytes, neurons, bone, and cartilage (1). Genetically modified cells are used to treat genetic disorders (5). With promising results from these studies, a critical issue is how to monitor the temporal and spatial migration and the homing of these cells, as well as the engraftment efficiency and functional capability of the transplanted cells in vivo (6, 7). Histopathological techniques have only been used to obtain information on the fate of implanted cells at the time of animal euthanization or via biopsy or surgery. To track the real-time changes of cell location, viability, and functional status, cell imaging techniques have been introduced during the last few years. Cells of interest are labeled with reporter genes, fluorescent dyes, or other contrast agents that transform the tagged cells into cellular probes or imaging agents (2, 6, 7). The ability to monitor superparamagnetic iron oxide particles (SPIO) with magnetic resonance imaging (MRI) has been utilized in animal models as well as in a few clinical settings to investigate the fate of labeled cells (6-10). The advantages of using MRI for cell tracking include the high spatial resolution with high anatomic background contrast, the lack of exposure to ionizing radiation, and the ability to follow the cells for months, although it is difficult to measure the rate of cell division and to determine whether each progeny shares the SPIO in vivo. In addition, cell labeling with SPIO nanoparticles is generally nontoxic and does not affect the cell proliferation and differentiation capacity, although a few studies have reported that the stem cells labeled with SPIO lose part of their differentiation capacity in a SPIO concentration-dependent manner. An important limitation of MRI is the fact that MRI signals cannot indicate whether cells are dead or alive. It is also unknown whether the MRI signal comes from targeted or labeled cells or from macrophages. Basically, SPIO particles are used to label the target cells by systemic application or by injection into the tissue area of interest to monitor target cell migration after phagocytosis. SPIO are more frequently used to label the cells in vitro by incorporating into the cells directly. Furthermore, SPIO are usually encapsulated by organic polymers to increase their stability and biocompatibility and to allow the chemical modification of their surfaces. The fact is that the uptake of different particles varies largely between different cell types and between particle coatings (6, 7). Msenchymal stem cells (MSCs) represent a heterogeneous subset of pluripotent stromal cells that can be isolated from different adult tissues including adipose tissue, liver, muscle, amniotic fluid, placenta, umbilical cord blood, and dental pulp, although the bone marrow remains the principal source for most preclinical and clinical studies (1, 11, 12). Although MSCs account for only 0.001-0.01% of the total nucleated cells within isolated bone marrow aspirates, they can easily be isolated and expanded in vitro through as many as 40 population doublings after 8-10 weeks of culture (1, 13). These cells exhibit the potential to differentiate into cells of diverse lineages such as adipocytes, chondrocytes, osteocytes, myoblasts, cardiomyocytes, neurons, and astrocytes. In addition, MSCs show tropism or homing to tumors and thus have been used as vehicles for directed cancer delivery (14, 15). The mechanism responsible for the homing of MSCs to tumors is thought to involve chemokine ligands and receptors, as with the recruitment of leukocytes to areas of inflammation. However, unlike with leukocytes, the specific chemokines

responsible for MSC migration are poorly characterized (14, 15). Nevertheless, homing to tumors has been confirmed with traditional immunohistochemistry and other methods in many studies. Loebinger et al. labeled MSCs with fluidMAG iron nanoparticles and imaged homing of the labeled MSCs to tumors with MRI (16). FluidMAG nanoparticles are commercially available ferrofluids consisting of an aqueous dispersion of magnetic iron oxides with a hydrodynamic diameter of 200 nm and a starch coating. The investigators showed that as few as 1,000 labeled MSCs were detected 1 month after their co-injection with breast cancer cells that formed subcutaneous tumors. The investigators further demonstrated that intravenously injected labeled cells could be tracked in vivo to home to multiple lung metastases (16).

Shan, L. (2004). Multimodal, rhodamine B isothiocyanate-incorporated, silica-coated magnetic nanoparticle-labeled human cord blood-derived mesenchymal stem cells for cell tracking. Molecular Imaging and Contrast Agent Database (MICAD). Bethesda (MD).

Personalized diagnosis and treatment with allogenic or autologous cells are becoming a reality in the field of medicine (1, 2). Cytotoxic or engineered T cells are under clinical trial for the treatment of hematopoietic or other malignant diseases (1). Contrast agent-tagged macrophages are used as cellular probes to image the early inflammatory processes in macrophage-rich conditions such as inflammation, atherosclerosis, and acute cardiac graft rejection (2). The roles of stem cells are under intensive investigation in the therapeutic and regenerative medicine such as regenerating cardiomyocytes, neurons, bone, and cartilage (3). Genetically modified cells are used to treat genetic disorders (4). With the promising results from these studies, a critical issue is how to monitor the temporal and spatial migration and the homing of these cells, as well as the engraftment efficiency and functional capability of the transplanted cells in vivo (5, 6). Histopathological techniques have only been used to obtain information on the fate of implanted cells at the time of animal euthanization or via biopsy or surgery. To track the real-time changes of cell location, viability, and functional status, cell imaging techniques have been introduced during the last few years. Cells of interest are labeled with reporter genes, fluorescent dyes, or other contrast agents that transform the tagged cells into cellular probes or imaging agents (5-7). The ability to monitor superparamagnetic iron oxide particles (SPIO) by magnetic resonance imaging (MRI) has been utilized in animal models as well as in a few clinical settings to investigate the fate of labeled cells (5-9). The advantages of using MRI for cell tracking include the high spatial resolution with high anatomic background contrast, the lack of exposure to ionizing radiation, and the ability to follow the cells for months. SPIO particles provide a strong change in signal per unit of metal, in particular on T2- and T2*-weight images. In addition, cell labeling with SPIO nanoparticles is generally nontoxic and does not affect the cell proliferation and differentiation capacity, although a few studies have reported that the stem cells labeled with SPIO lose part of their differentiation capacity in a SPIO concentration-dependent manner (8, 9). An important limitation of MRI is the fact that MRI signals cannot indicate whether cells are dead or alive. It is also unknown whether the MRI signal comes from targeted or labeled cells or from macrophages. Basically, SPIO particles are used to label the target cells by systemic application or by injecting into the tissue area of interest to monitor target cell migration after phagocytosis. SPIO are more frequently used to label the cells in vitro by incorporating into the cells directly. Furthermore, SPIO are usually encapsulated by organic polymers to increase their stability and bio-compatibility, and allow the chemical modification of their surfaces. The fact is that the uptake of different particles varies largely between different cell types (5, 6). Mesenchymal stem cells (MSCs) represent a heterogeneous subset of pluripotent stromal cells that can be isolated from different adult tissues including adipose tissue, liver, muscle, amniotic fluid, placenta, umbilical cord blood, and dental pulp, although the bone marrow remains the principal source for most preclinical and clinical studies (3, 10, 11). Although MSCs account for only 0.01-0.001% of the total nucleated cells within isolated bone marrow aspirates, they can easily be isolated and expanded in vitro through as many as 40 population doublings in ~8-10 weeks of culture (12). These cells exhibit the potential to differentiate into cells of diverse lineages, such as adipocytes, chondrocytes, osteocytes, myoblasts, cardiomyocytes,

neurons, and astrocytes. In addition, MSCs possess remarkable immunosuppressive properties, and they have been shown to be effective against tumor cell growth (13, 14). Yoon et al. generated multimodal, rhodamine B isothiocyanate (RITC)-labeled, silica-coated magnetic nanoparticles (MNPs@SiO2(RITC)) and Park et al. labeled the MSCs with the nanoparticles and successfully tracked the labeled cells transplanted into the subcutaneous tissue and liver of the mice (7, 15). Their results indicate that MNPs@SiO2(RITC) are biocompatible and useful for human MSC labeling and cell tracking with multimodality imaging.

Strojny, C., et al. (2015). "Interferon Gamma-treated Dental Pulp Stem Cells Promote Human Mesenchymal Stem Cell Migration In Vitro." J Endod **41**(8): 1259-1264.

INTRODUCTION: Chronic inflammation disrupts dental pulp regeneration by disintegrating the recruitment process of progenitors for repair. Bone marrow-derived mesenchymal stem cells (BM-MSCs) share the common features with dental pulp stem cells (DPSCs). The aim of the study was to investigate the migration of BM-MSCs toward DPSCs in response to inflammatory chemoattractants. Additionally, our studies also delineated the signaling mechanisms from BM-MSCs in mediating the proliferation and differentiation of DPSCs in vitro. METHODS: Human DPSCs and BM-MSCs between passages 2 and 4 were used and were grown in odontogenic differentiation medium. Mineralization was determined by alizarin red staining analysis. Migration was assessed using crystal violet staining in cells grown in Boyden chamber Transwell inserts (Corning Inc Foundation, Tewksbury, MA). The mineralization potential of DPSCs was evaluated using alkaline phosphatase activity assay. Real-time polymerase chain reaction analysis was performed to assess the gene expression profile of chemokine (C-X-C motif) ligand (Cxcl) 3, 5, 6, 10, 11, 12, 14, and 16; stromal cell-derived factor (SDF) alpha; vascular endothelial growth factor; and fibroblast growth factor. RESULTS: Interferon gamma (FN-gamma) treatment significantly abrogated the differentiation potential of DPSCs as shown by using alizarin red and alkaline phosphatase activity analysis. An increase in the migration of BM-MSCs was documented when cocultured with IFN-gamma-treated DPSCs. RNA expression studies showed an increase in the levels of Cxcl6 and Cxcl12 in BM-MSCs when cocultured with IFN-gamma-treated DPSCs. Additionally, an up-regulation of proangiogenic factors vascular endothelial growth factor and fibroblast growth factor were observed in DPSCs exposed to IFN-gamma. CONCLUSIONS: Our findings indicate that inflamed IFN-gamma-treated DPSCs release factors (presumably Cxcl6 and 12) that contribute to the homing of MSCs. This model might provide a potential research tool for studying MSC-DPSC cross talk and for future studies involving the recruitment and sustainability of progenitor stem cells sustaining the inflammatory cascade to treat pulp inflammation.

Tatullo, M., et al. (2015). "Dental Pulp Stem Cells and Human Periapical Cyst Mesenchymal Stem Cells in Bone Tissue Regeneration: Comparison of Basal and Osteogenic Differentiated Gene Expression of a Newly Discovered Mesenchymal Stem Cell Lineage." J Biol Regul Homeost Agents **29**(3): 713-718.

Bone regeneration is an interesting field of biomedicine. The most recent studies are aimed to achieve a bone regeneration using mesenchymal stem cells (MSCs) taken from more accessible sites: oral and dental tissues have been widely investigated as a rich accessible source of MSCs. Dental Pulp Stem Cells (DPSCs) and human Periapical Cysts Mesenchymal Stem Cells (hPCy-MSCs) represent the new generation MSCs. The aim of this study is to compare the gene expression of these two innovative cell types to highlight the advantages of their use in bone regeneration. The harvesting, culturing and differentiating of cells isolated from dental pulp as well as from periapical cystic tissue were carried out as described in previously published reports. qRT-PCR analyses were performed on osteogenic genes in undifferentiated and osteogenic differentiated cells of DPSC and hPCy-MSC lineage. Real-time RT-PCR data suggested that both DPSCs and hPCy-MSCs cultured in osteogenic media are able to differentiate into osteoblast/odontoblast-like cells: however, some differences indicated that DPSCs seem to be directed more towards dentinogenesis, while hPCy-MSCs seem to be directed more towards osteogenesis.

Tatullo, M., et al. (2016). "Mechanical influence of tissue culture plates and extracellular matrix on mesenchymal stem cell behavior: A topical review." Int J Immunopathol Pharmacol **29**(1): 3-8.

Tissue engineering applications need a continuous development of new biomaterials able to generate an ideal cell-extracellular matrix interaction. The stem cell fate is regulated by several factors, such as growth factors or transcription factors. The most recent literature has reported several publications able to demonstrate that environmental factors also contribute to the regulation of stem cell behavior, leading to the opinion that the environment plays the major role in the cell differentiation.The interaction between mesenchymal stem cells (MSCs) and extracellular environment has been widely described, and it has a crucial role in regulating the cell phenotype. In our laboratory (Tecnologica Research Institute, Crotone, Italy), we have recently studied how several physical factors influence the distribution and the morphology of MSCs isolated from dental pulp, and how they are able to regulate stem cell differentiation. Mechanical and geometrical factors are only a small part of the environmental factors able to influence stem cell behavior, however, this influence should be properly known: in fact, this assumption must be clearly considered during those studies involving MSCs; furthermore, these interactions should be considered as an important bias that involves an high number of studies on the MSCs, since in worldwide laboratories the scientists mostly use tissue culture plates for their experiments.

Trubiani, O., et al. (2012). "Overexpression of interleukin-6 and -8, cell growth inhibition and morphological changes in 2-hydroxyethyl methacrylate-treated human dental pulp mesenchymal stem cells." Int Endod J **45**(1): 19-25.

AIM: To evaluate morphological features, cell growth and interleukin-6 (IL-6) and interleukin-8 (IL-8) secretion in expanded ex vivo human dental pulp mesenchymal stem cells (DP-MSCs) after exposure to 2-hydroxyethyl methacrylate (HEMA). METHODOLOGY: Dental pulp mesenchymal stem cells were derived from the dental pulps of 10 young donors. After in vitro isolation, DP-MSCs were treated with 3 and 5 mmol L(-1) HEMA, and after 24, 48 and 72 h of incubation, their morphological features, cell growth, IL-6 and IL-8 secretion were analysed. Differences in the cell growth and in the interleukin secretion were analysed for statistical significance with two-way anova tests and the Holm-Sidak method for multiple comparisons. RESULTS: Dental pulp mesenchymal stem cells revealed a decrease in cell growth with both treatments ($P < 0.05$), more evident at 5 mmol L(-1) . Microscopic analysis displayed extensive cytotoxic effects in treated cells, which lost their fibroblastoid features and became retracted, even roundish, with a large number of granules. An up-regulation of IL-6 and IL-8 in treated cells cytokines was evident ($P < 0.05$). CONCLUSIONS: 2-Hydroxyethyl methacrylate exhibited cytotoxicity, inhibited cell growth and induced morphological changes in cultured DP-MSCs. Moreover, in treated samples, an up-regulation of soluble mediators of inflammation such as IL-6 and IL-8 cytokines was found. The direct application of HEMA potentially induces an inflammation process that could be the starting point for toxic response and cell damage in DP-MSCs.

Wei, F., et al. (2013). "Functional tooth restoration by allogeneic mesenchymal stem cell-based bio-root regeneration in swine." Stem Cells Dev **22**(12): 1752-1762.

Our previous proof-of-concept study showed the feasibility of regenerating the dental stem cell-based bioengineered tooth root (bio-root) structure in a large animal model. Here, we used allogeneic dental mesenchymal stem cells to regenerate bio-root, and then installed a crown on the bio-root to restore tooth function. A root shape hydroxyapatite tricalcium phosphate scaffold containing dental pulp stem cells was covered by a Vc-induced periodontal ligament stem cell sheet and implanted into a newly generated jaw bone implant socket. Six months after implantation, a prefabricated porcelain crown was cemented to the implant and subjected to tooth function. Clinical, radiological, histological, ultrastructural, systemic immunological evaluations and mechanical properties were analyzed for dynamic changes in the bio-root structure. The regenerated bio-root exhibited characteristics of a normal tooth after 6 months of use, including dentinal tubule-like and functional periodontal ligament-like structures. No immunological response to the bio-roots was observed. We developed a standard stem cell procedure for

bio-root regeneration to restore adult tooth function. This study is the first to successfully regenerate a functional bio-root structure for artificial crown restoration by using allogeneic dental stem cells and Vc-induced cell sheet, and assess the recipient immune response in a preclinical model.

Yamada, Y., et al. (2006). "Cluster analysis and gene expression profiles: a cDNA microarray system-based comparison between human dental pulp stem cells (hDPSCs) and human mesenchymal stem cells (hMSCs) for tissue engineering cell therapy." Biomaterials **27**(20): 3766-3781.

We investigated gene expression patterns and functional classifications regarding the clusters of human dental pulp stem cells (hDPSCs) and human mesenchymal stem cells (hMSCs)--which possess a multipotent ability--because little is known about the precise moleculobiological clues by which these cells activate their differentiating ability or functionality to eventually form dentin and bone, respectively. We first verified the expressions of the alkaline phosphatase (ALP) gene, dentin matrix protein 1 (DMP-1), and dentinsialophosphoprotein (DSPP) by real-time reverse-transcriptase polymerase chain reaction (RT-PCR) and consequently discovered the high expressions of these genes. Total RNA was also followed by hybridization with a human microarray system consisting of 12,814 genes. Analyses of gene expression patterns indicated several genes which encode extracellular matrix components, cell adhesion molecules, growth factors, and transcription regulators. Functional and clustering analyses of differences in gene expression levels revealed cell signaling, cell communication, or cell metabolism. In the future, information on the gene expression patterns of hDPSCs and hMSCs might be useful in determining the detailed functional roles of the relevant genes and applicable to stem cell therapies, and these cells could also be used as multipotent cell sources for gene technology and tissue engineering technology.

Yamada, Y., et al. (2010). "A feasibility of useful cell-based therapy by bone regeneration with deciduous tooth stem cells, dental pulp stem cells, or bone-marrow-derived mesenchymal stem cells for clinical study using tissue engineering technology." Tissue Eng Part A **16**(6): 1891-1900.

This study investigated the effect of bone regeneration with dental pulp stem cells (DPSCs), deciduous tooth stem cells (DTSCs), or bone-marrow-derived mesenchymal stem cells (BMMSCs) for clinical study on hydroxyapatite-coated osseointegrated dental implants, using tissue engineering technology. In vitro, human DPSCs and DTSCs expressed STRO-1, CD13, CD29, CD 44, CD73, and osteogenic marker genes such as alkaline phosphatase, Runx2, and osteocalcin. In vivo, prepared bone defect model was implanted using graft materials as follows: platelet-rich plasma (PRP), PRP and canine BMMSCs (cBMMSCs), PRP and canine DPSCs (cDPSCs), PRP and puppy DTSCs (pDTSCs), and control (defect only). After 8 weeks, the dental implants were installed, and 16 weeks later the sections were evaluated histologically and histometrically. The cBMMSCs/PRP, cDPSCs/PRP, and pDTSCs/PRP groups had well-formed mature bone and neovascularization. Histometrically, the bone-implant contact was significantly different between the cBMMSCs/PRP, cDPSCs/PRP, pDTSCs/PRP groups, and the control and PRP groups ($p < 0.01$). These results demonstrated that these stem cells with PRP have the ability to form bone, and this bone formation activity might be useful for osseointegrated hydroxyapatite-coated dental implants with good levels of bone-implant contact.

Yang, X., et al. (2012). "WITHDRAWN: The mesenchymal stem cell potential of human dental pulp derived cells transfected with embryonic transcription factor Oct-4." Biomaterials.

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Yu, J., et al. (2008). "Epithelial-mesenchymal cell ratios can determine the crown morphogenesis of dental pulp stem cells." Stem Cells Dev **17**(3): 475-482.

Although dental pulp stem cells (DPSC) have been isolated from adult dental pulp tissues, knowledge on how to use them to make teeth lags behind. To date, little is known about the effects of epithelial-mesenchymal cell ratios on the bioengineered odontogenesis mediated by DPSCs. In this study, we investigated the effects of apical bud cells (ABC) from dental epithelial stem cell niche of rat incisors on the differentiation and morphogenesis of molar

DPSCs at different proportions (DPSC/ABC cell ratios=1:10, 1:3, 1:1, 3:1, 10:1, respectively). In vitro mixed DPSCs/ABCs at 1:1, 1:3, and 3:1 ratios displayed several crucial characteristics of odontoblast/ameloblast lineages, as indicated by accelerated mineralization, upregulated alkaline phosphatase activity, protein/gene expression for dentin sialophosphoprotein and ameloblastin. In vivo transplantation of reassociated DPSC and ABC pellets at different ratios was also carried out. Histological analyses demonstrated that only DPSC/ABC recombinants at 1:1 ratio generated typical molar crown-shaped structures, whereas recombinations at other ratios presented an atypical crown morphogenesis with unbalanced distribution of amelogenesis and dentinogenesis. Together, these findings revealed that the proportions of dental epithelial and mesenchymal cell populations can determine the odontogenic differentiation of DPSCs/ABCs in vitro as well as the bioengineered tooth morphogenesis in vivo.

Yuan, G. H., et al. (2010). "Potential Role of Dentin Sialoprotein by Inducing Dental Pulp Mesenchymal Stem Cell Differentiation and Mineralization for Dental Tissue Repair." Dent Hypotheses **1**(2): 69-75.

INTRODUCTION: Dentin sialoprotein (DSP) is a dentin extracellular matrix protein, a unique marker of dentinogenesis and plays a vital role in odontoblast differentiation and dentin mineralization. Recently, studies have shown that DSP induces differentiation and mineralization of periodontal ligament stem cells and dental papilla mesenchymal cells in vitro and rescues dentin deficiency and increases enamel mineralization in animal models. THE HYPOTHESIS: DSP as a nature therapeutic agent stimulates dental tissue repair by inducing endogenous dental pulp mesenchymal stem/progenitor cells into odontoblast-like cells to synthesize and to secrete dentin extracellular matrix forming new tertiary dentin as well as to regenerate a functional dentin-pulp complex. As DSP is a nature protein, and clinical procedure for DSP therapy is easy and simple, application of DSP may provide a new avenue for dentists with additional option for the treatment of substantially damaged vital teeth. EVALUATION OF THE HYPOTHESIS: Dental caries is the most common dental disease. Deep caries and pulp exposure have been treated by various restorative materials with limited success. One promising approach is dental pulp stem/progenitor-based therapies to regenerate dentin-pulp complex and restore its functions by DSP induction in vivo.

Zeidan-Chulia, F. and M. Noda (2009). ""Opening" the mesenchymal stem cell tool box." Eur J Dent **3**(3): 240-249.

Adult mesenchymal stem cells (MSCs) are adherent stromal cells able to self-renew and differentiate into a wide variety of cells and tissues. MSCs can be obtained from distinct tissue sources and have turned out to be successfully manipulated in vitro. As adult stem cells, MSCs are less tumorigenic than their embryonic correlatives and posses another unique characteristic which is their almost null immunogenicity. Moreover, these cells seem to be immunosuppressive in vitro. These facts together with others became MSCs a promising subject of study for future approaches in bioengineering and cell-based therapy. On the other hand, new strategies to achieve long-term integration as well as efficient differentiation of these cells at the area of the lesion are still challenging, and the signalling pathways ruling these processes are not completely well characterized. In this review, we are going summarize the general landscape and current status of the MSC tool as well as their wide potential in tissue engineering, from neuronal to tooth replacement. Highlights and pitfalls for further clinical applications will be discussed.

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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]. Abbas, O. L., et al. (2018). "Comparative Analysis of Mesenchymal Stem Cells from Bone Marrow, Adipose Tissue, and Dental Pulp as Sources of Cell Therapy for Zone of Stasis Burns." J Invest Surg: 1-14.

[17]. Akazawa, Y., et al. (2015). "Recruitment of mesenchymal stem cells by stromal cell-derived factor 1alpha in pulp cells from deciduous teeth." Int J Mol Med **36**(2): 442-448.

[18]. Ansari, S., et al. (2017). "Hydrogel elasticity and microarchitecture regulate dental-derived mesenchymal stem cell-host immune system cross-talk." Acta Biomater **60**: 181-189.

[19]. Bose, B., et al. (2018). "Breast Cancer Stem Cell Therapeutics, Multiple Strategies Versus Using Engineered Mesenchymal Stem Cells With Notch Inhibitory Properties: Possibilities and Perspectives." J Cell Biochem **119**(1): 141-149.

[20]. Carbone, A., et al. (2016). "Adipose-derived mesenchymal stromal (stem) cells differentiate to osteoblast and chondroblast lineages upon incubation with conditioned media from dental pulp stem cell-derived osteoblasts and auricle cartilage chondrocytes." J Biol Regul Homeost Agents **30**(1): 111-122.

[21]. Dehghani Nazhvani, A., et al. (2015). "Identification of Mesenchymal Stem Cell Marker STRO-1 in Oral Reactive Lesions by Immunofluorescence Method." J Dent (Shiraz) **16**(3 Suppl): 246-250.

[22]. Di Scipio, F., et al. (2014). "Injured cardiomyocytes promote dental pulp mesenchymal stem cell homing." Biochim Biophys Acta **1840**(7): 2152-2161.

[23]. El Omar, R., et al. (2014). "Umbilical cord mesenchymal stem cells: the new gold standard for mesenchymal stem cell-based therapies?" Tissue Eng Part B Rev **20**(5): 523-544.

[24]. Gagari, E., et al. (2006). "Expression of stem cell factor and its receptor, c-kit, in human oral mesenchymal cells." Eur J Oral Sci **114**(5): 409-415.

[25]. Ginani, F., et al. (2015). "Effect of low-level laser therapy on mesenchymal stem cell proliferation: a systematic review." Lasers Med Sci **30**(8): 2189-2194.

[26]. Gonzalez-King, H., et al. (2017). "Hypoxia Inducible Factor-1alpha Potentiates Jagged 1-Mediated Angiogenesis by Mesenchymal Stem Cell-Derived Exosomes." Stem Cells **35**(7): 1747-1759.

[27]. Hatlapatka, T., et al. (2011). "Optimization of culture conditions for the expansion of umbilical cord-derived mesenchymal stem or stromal cell-like cells using xeno-free culture conditions." Tissue Eng Part C Methods **17**(4): 485-493.

[28]. Jewett, A., et al. (2010). "Strategies to rescue mesenchymal stem cells (MSCs) and dental pulp stem cells (DPSCs) from NK cell mediated cytotoxicity." PLoS One **5**(3): e9874.

[29]. Karaoz, E., et al. (2011). "Human dental pulp stem cells demonstrate better neural and epithelial stem cell properties than bone marrow-derived mesenchymal stem cells." Histochem Cell Biol **136**(4): 455-473.

[30]. Kawazoe, Y., et al. (2008). "Activation of the FGF signaling pathway and subsequent induction of mesenchymal stem cell differentiation by inorganic polyphosphate." Int J Biol Sci **4**(1): 37-47.

[31]. 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.

[32]. Lapthanasupkul, P., et al. (2012). "Ring1a/b polycomb proteins regulate the mesenchymal stem cell niche in continuously growing incisors." Dev Biol **367**(2): 140-153.

[33]. Lei, M., et al. (2014). "Mesenchymal stem cell characteristics of dental pulp and periodontal ligament stem cells after in vivo transplantation." Biomaterials **35**(24): 6332-6343.

[34]. Marei, M. K. and R. M. El Backly (2018). "Dental Mesenchymal Stem Cell-Based Translational Regenerative Dentistry: From Artificial to Biological Replacement." Front Bioeng Biotechnol **6**: 49.

[35]. Mrozik, K. M., et al. (2010). "Proteomic characterization of mesenchymal stem cell-like populations derived from ovine periodontal ligament, dental pulp, and bone marrow: analysis of differentially expressed proteins." Stem Cells Dev **19**(10): 1485-1499.

[36]. Murakami, M., et al. (2015). "Trophic Effects and Regenerative Potential of Mobilized Mesenchymal Stem Cells From Bone Marrow and Adipose Tissue as Alternative Cell Sources for Pulp/Dentin Regeneration." Cell Transplant **24**(9): 1753-1765.

[37]. Nancarrow-Lei, R., et al. (2017). "A Systemic Review of Adult Mesenchymal Stem Cell Sources and their Multilineage Differentiation Potential Relevant to Musculoskeletal Tissue Repair and Regeneration." Curr Stem Cell Res Ther **12**(8): 601-610.

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

[39]. Orciani, M., et al. (2012). "In vitro evaluation of mesenchymal stem cell isolation possibility from different intra-oral tissues." J Biol Regul Homeost Agents **26**(2 Suppl): 57-63.

[40]. Otabe, K., et al. (2012). "Comparison of Gingiva, Dental Pulp, and Periodontal Ligament Cells From the Standpoint of Mesenchymal Stem Cell Properties." Cell Med **4**(1): 13-21.

[41]. Ozdemir, A. T., et al. (2016). "The paracrine immunomodulatory interactions between the human dental pulp derived mesenchymal stem cells and CD4 T cell subsets." Cell Immunol **310**: 108-115.

[42]. Peng, H., et al. (2016). "Purinergic and Store-Operated Ca(2+) Signaling Mechanisms in Mesenchymal Stem Cells and Their Roles in ATP-Induced Stimulation of Cell Migration." Stem Cells **34**(8): 2102-2114.

[43]. Ren, H., et al. (2016). "Comparative Analysis of Human Mesenchymal Stem Cells from Umbilical Cord, Dental Pulp, and Menstrual Blood as Sources for Cell Therapy." Stem Cells Int **2016**: 3516574.

[44]. Riekstina, U., et al. (2009). "Embryonic stem cell marker expression pattern in human mesenchymal stem cells derived from bone marrow, adipose tissue, heart and dermis." Stem Cell Rev **5**(4): 378-386.

[45]. Rodriguez-Lozano, F. J., et al. (2013). "Effects of two low-shrinkage composites on dental stem cells (viability, cell damaged or apoptosis and mesenchymal markers expression)." J Mater Sci Mater Med **24**(4): 979-988.

[46]. Shan, L. (2004). FluidMAG iron nanoparticle-labeled mesenchymal stem cells for tracking cell homing to tumors. Molecular Imaging and Contrast Agent Database (MICAD). Bethesda (MD).

[47]. Shan, L. (2004). Multimodal, rhodamine B isothiocyanate-incorporated, silica-coated magnetic nanoparticle-labeled human cord blood-derived mesenchymal stem cells for cell tracking. Molecular Imaging and Contrast Agent Database (MICAD). Bethesda (MD).

[48]. Strojny, C., et al. (2015). "Interferon Gamma-treated Dental Pulp Stem Cells Promote Human Mesenchymal Stem Cell Migration In Vitro." J Endod **41**(8): 1259-1264.

[49]. Tatullo, M., et al. (2015). "Dental Pulp Stem Cells and Human Periapical Cyst Mesenchymal Stem Cells in Bone Tissue Regeneration: Comparison of Basal and Osteogenic Differentiated Gene Expression of a Newly Discovered Mesenchymal Stem Cell Lineage." J Biol Regul Homeost Agents **29**(3): 713-718.

[50]. Tatullo, M., et al. (2016). "Mechanical influence of tissue culture plates and extracellular matrix on mesenchymal stem cell behavior: A topical review." Int J Immunopathol Pharmacol **29**(1): 3-8.

[51]. Trubiani, O., et al. (2012). "Overexpression of interleukin-6 and -8, cell growth inhibition and morphological changes in 2-hydroxyethyl methacrylate-treated human dental pulp mesenchymal stem cells." Int Endod J **45**(1): 19-25.

[52]. Wei, F., et al. (2013). "Functional tooth restoration by allogeneic mesenchymal stem cell-based bio-root regeneration in swine." Stem Cells Dev **22**(12): 1752-1762.

[53]. Yamada, Y., et al. (2006). "Cluster analysis and gene expression profiles: a cDNA microarray system-based comparison between human dental pulp stem cells (hDPSCs) and human mesenchymal stem cells (hMSCs) for tissue engineering cell therapy." Biomaterials **27**(20): 3766-3781.

[54]. Yamada, Y., et al. (2010). "A feasibility of useful cell-based therapy by bone regeneration with deciduous tooth stem cells, dental pulp stem cells, or bone-marrow-derived mesenchymal stem cells for clinical study using tissue engineering technology." Tissue Eng Part A **16**(6): 1891-1900.

[55]. Yang, X., et al. (2012). "WITHDRAWN: The mesenchymal stem cell potential of human dental

pulp derived cells transfected with embryonic transcription factor Oct-4." Biomaterials.

[56]. Yu, J., et al. (2008). "Epithelial-mesenchymal cell ratios can determine the crown morphogenesis of dental pulp stem cells." Stem Cells Dev **17**(3): 475-482.

[57]. Yuan, G. H., et al. (2010). "Potential Role of Dentin Sialoprotein by Inducing Dental Pulp Mesenchymal Stem Cell Differentiation and Mineralization for Dental Tissue Repair." Dent Hypotheses **1**(2): 69-75.

[58]. Zeidan-Chulia, F. and M. Noda (2009). ""Opening" the mesenchymal stem cell tool box." Eur J Dent **3**(3): 240-249.

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