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Stem Cell

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Stem Cell Multipotent Research Literatures

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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; multipotent; 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.

Multipotent stem cells can differentiate into a number of cell types, but only those of a closely related family of cells.[1]

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

Al Battah, F., et al. (2011). "Evaluation of the multipotent character of human adipose tissue-derived stem cells isolated by Ficoll gradient centrifugation and red blood cell lysis treatment." Toxicol In Vitro **25**(6): 1224-1230.

In the present study, the multipotent potential of two differential isolated human adipose-derived stem cell (hADSC) populations was evaluated. More specifically, hADSC isolated by means of classical Ficoll (F) gradient centrifugation were compared to hADSC isolated by means of red blood cell (RBC) lysis treatment and subsequent cultivation as 3D spheres. No significant difference in the genotypic expression of the multipotent markers Oct-4, Sox-2, Nanog, Klf-4 and cMyc could be observed between both isolation methods. Upon adipogenic and osteogenic differentiation, both hADSC populations showed lipid droplet accumulation and mineral deposition, respectively. Although, a more pronounced mineral deposition was observed in hADSC-RBC, suggesting a higher osteogenic potential. Upon exposure to keratinogenic media, both hADSC populations expressed the keratinocyte markers filaggrin and involucrin, evidencing a successful keratinogenic differentiation. Yet, no differences in expression were observed between the distinctive isolation procedures. Finally, upon exposure to neurogenic differentiation media, a significant difference in marker expression was observed. Indeed, hADSC-RBC only expressed vimentin and nestin, whereas hADSC-F expressed vimentin, nestin, NF-200, MBP and TH, suggesting a higher neurogenic potential. In summary, our data suggest that the choice of the most efficient isolation procedure of hADSC depends on the differentiated cell type ultimately required.

Alexanian, A. R. and S. N. Kurpad (2005). "Quiescent neural cells regain multipotent stem cell characteristics influenced by adult neural stem cells in co-culture." Exp Neurol **191**(1): 193-197.

The source of cells participating in central nervous system (CNS) tissue repair and regeneration is poorly defined. One possible source is quiescent neural cells that can persist in CNS in the form of dormant progenitors or highly specialized cell types. Under appropriate conditions, these quiescent cells may be

capable of re-entering the mitotic cell cycle and contributing to the stem cell pool. The aim of this study was to determine whether in vitro differentiated neural stem cells (NSC) can regain their multipotent-like stem cell characteristics in co-culture with NSC. To this end, we induced neural differentiation by plating NSC, derived from the periventricular subependymal zone (SEZ) of ROSA26 transgenic mice in Neurobasal A/B27 medium in the absence of bFGF. Under these conditions, NSC differentiated into neurons, glia, and oligodendrocytes. While the level of Nestin expression was downregulated, persistence of dormant progenitors could not be ruled out. However, further addition of bFGF or bFGF/EGF with conditioned medium derived from adult NSC did not induce any noticeable cell proliferation. In another experiment, differentiated neural cells were cultured with adult NSC, isolated from the hippocampus of Balb/c mice, in the presence bFGF. This resulted in proliferating colonies of ROSA26 derived cells that mimicked NSC in their morphology, growth kinetics, and expressed NSC marker proteins. The average nuclear area and DAPI fluorescence intensity of these cells were similar to that of NSC grown alone. We conclude that reactivation of quiescent neural cells can be initiated by NSC-associated short-range cues but not by cell fusion.

Alshabibi, M. A., et al. (2017). "Mesenchymal Stem/Multipotent Stromal Cells from Human Decidua Basalis Reduce Endothelial Cell Activation." Stem Cells Dev **26**(18): 1355-1373.

Recently, we reported the isolation and characterization of mesenchymal stem cells from the decidua basalis of human placenta (DBMSCs). These cells express a unique combination of molecules involved in many important cellular functions, which make them good candidates for cell-based therapies. The endothelium is a highly specialized, metabolically active interface between blood and the underlying tissues. Inflammatory factors stimulate the endothelium to undergo a change to a proinflammatory and procoagulant state (ie, endothelial cell activation). An initial response to endothelial cell activation is monocyte adhesion. Activation typically involves increased proliferation and enhanced expression of adhesion and inflammatory markers by endothelial cells. Sustained endothelial cell activation leads to a type of damage to the body associated with inflammatory diseases, such as atherosclerosis. In this study, we examined the ability of DBMSCs to protect endothelial cells from activation through monocyte adhesion, by modulating endothelial proliferation, migration, adhesion, and inflammatory marker expression. Endothelial cells were cocultured with DBMSCs, monocytes, monocyte-pretreated with DBMSCs and DBMSC-pretreated with monocytes were also evaluated. Monocyte adhesion to endothelial cells was examined following treatment with DBMSCs. Expression of endothelial cell adhesion and inflammatory markers was also analyzed. The interaction between DBMSCs and monocytes reduced endothelial cell proliferation and monocyte adhesion to endothelial cells. In contrast, endothelial cell migration increased in response to DBMSCs and monocytes. Endothelial cell expression of adhesion and inflammatory molecules was reduced by DBMSCs and DBMSC-pretreated with monocytes. The mechanism of reduced endothelial proliferation involved enhanced phosphorylation of the tumor suppressor protein p53. Our study shows for the first time that DBMSCs protect endothelial cells from activation by inflammation triggered by monocyte adhesion and increased endothelial cell proliferation. These events are manifest in inflammatory diseases, such as atherosclerosis. Therefore, our results suggest that DBMSCs could be usefully employed as a therapeutic strategy for atherosclerosis.

Anzai, H., et al. (1999). "Self-renewal and differentiation of a basic fibroblast growth factor-dependent multipotent hematopoietic cell line derived from embryonic stem cells." Dev Growth Differ **41**(1): 51-58.

Despite the accumulation of informat on on the origin of hematopoietic stem cells, it is still unclear how these cells are generated in ontogeny. Isolation of cell lines equivalent to early embryonic hematopoietic progenitor cells can be helpful. A multipotent hematopoietic progenitor cell line, A-6, was isolated from H-1 embryonic stem (ES) cells. The self-renewal of A-6 cells was supported by basic-fibroblast growth factor (b-FGF) and their differentiation into definitive erythroid cells, granulocytes and macrophages was induced after co-culture with ST-2 stromal cells. A-6 cells were positive for the surface markers of hematopoietic stem cell, c-kit, CD31, CD34, Flt3/Flk2, PgP-1, and HSA, but were negative for that of the differentiated cells. Reverse transcription-polymerase chain reaction analysis showed that A-6 cells produced mRNA from SCL/tal-1 and GATA-2 genes. Among various cytokines examined, on y stem cell factor (SCF) and Flt3/Flk2 ligand (FL) supported the proliferation of A-6 cells instead of b-FGF. The FL, as well as b-FGF, supported the self-renewal of A-6 cells, whereas SCF induced differentiation into myeloid cells. A-6 cells will be useful for the characterization of hematopoietic progenitor cells derived from ES cells and provide a model system to realize the control mechanisms between self-renewal and different ation of hematopoietic stem cells.

Babenko, V. A., et al. (2018). "Miro1 Enhances Mitochondria Transfer from Multipotent Mesenchymal Stem Cells (MMSC) to Neural Cells and Improves the Efficacy of Cell Recovery." Molecules **23**(3).

A recently discovered key role of reactive oxygen species (ROS) in mitochondrial traffic has opened a wide alley for studying the interactions between cells, including stem cells. Since its discovery in 2006, intercellular mitochondria transport has been intensively studied in different cellular models as a basis for cell therapy, since the potential of replacing malfunctioning organelles appears to be very promising. In this study, we explored the transfer of mitochondria from multipotent mesenchymal stem cells (MMSC) to neural cells and analyzed its efficacy under normal conditions and upon induction of mitochondrial damage. We found that mitochondria were transferred from the MMSC to astrocytes in a more efficient manner when the astrocytes were exposed to ischemic damage associated with elevated ROS levels. Such transport of mitochondria restored the bioenergetics of the recipient cells and stimulated their proliferation. The introduction of MMSC with overexpressed Miro1 in animals that had undergone an experimental stroke led to significantly improved recovery of neurological functions. Our data suggest that mitochondrial impairment in differentiated cells can be compensated by receiving healthy mitochondria from MMSC. We demonstrate a key role of Miro1, which promotes the mitochondrial transfer from MMSC and suggest that the genetic modification of stem cells can improve the therapies for the injured brain.

Barbet, R., et al. (2012). "Expression of the 49 human ATP binding cassette (ABC) genes in pluripotent embryonic stem cells and in early- and late-stage multipotent mesenchymal stem cells: possible role of ABC plasma membrane transporters in maintaining human stem cell pluripotency." Cell Cycle **11**(8): 1611-1620.

The 49-member human ATP binding cassette (ABC) gene family encodes 44 membrane transporters for lipids, ions, peptides or xenobiotics, four translation factors without transport activity, as they lack transmembrane domains, and one pseudogene. To understand the roles of ABC genes in pluripotency and multipotency, we performed a sensitive qRT-PCR analysis of their expression in embryonic stem cells (hESCs), bone marrow-derived mesenchymal stem cells (hMSCs) and hESC-derived hMSCs (hES-MSCs). We confirm that hES-MSCs represent an intermediate developmental stage between hESCs and hMSCs. We observed that 44 ABCs were significantly expressed in hESCs, 37 in hES-MSCs and 35 in hMSCs. These variations are mainly due to plasma membrane transporters with low but significant gene expression: 18 are expressed in hESCs compared with 16 in hES-MSCs and 8 in hMSCs, suggesting important roles in pluripotency. Several of these ABCs shared similar substrates but differ regarding gene regulation. ABCA13 and ABCB4, similarly to ABCB1, could be new markers to select primitive hMSCs with specific plasma membrane transporter (low) phenotypes. ABC proteins performing basal intracellular functions, including translation factors and mitochondrial heme transporters, showed the highest constant gene expression among the three populations. Peptide transporters in the endoplasmic reticulum, Golgi and lysosome were well expressed in hESCs and slightly upregulated in hMSCs, which play important roles during the development of stem cell niches in bone marrow or meningeal tissue. These results will be useful to study specific cell cycle regulation of pluripotent stem cells or ABC dysregulation in complex pathologies, such as cancers or neurological disorders.

Berking, S. (1979). "Control of nerve cell formation from multipotent stem cells in Hydra." J Cell Sci **40**: 193-205.

Feeding of starved animals provides a very short signal which determines stem cells to differentiate into nerve cells after the next mitosis. Only those stem cells become determined which are just in the middle of their S-phase at the time of feeding. Stem cells of any other stage of the cycle do not become determined. Nerve cell determination is suppressed by very low concentrations of an endogenous inhibitor. The inhibitor exerts its effect only during the first half of the S-phase, not before and not after this period. Based on these finding it is proposed that stem cells are susceptible to 2 different signals during the first half of their S-phase; one signal allows the development into nerve cells, the other prevents this development. Within this period the decision whether to become a nerve cell or not is reversible. It becomes fixed at the end of this period.

Cao, K., et al. (2017). "Monoclonal antibodies targeting non-small cell lung cancer stem-like cells by multipotent cancer stem cell monoclonal antibody library." Int J Oncol **50**(2): 587-596.

Cancer stem cells (CSCs) are a rare subset of cancer cells that play a significant role in cancer initiation, spreading, and recurrence. In this study, a subpopulation of lung cancer stem-like cells (LCSLCs) was identified from non-small cell lung carcinoma cell lines, SPCA-1 and A549, using serum-free suspension sphere-forming culture method. A monoclonal antibody library was constructed using immunized BLAB/c mice with the multipotent CSC cell line T3A-A3. Flow cytometry analysis showed that 33 mAbs targeted antigens can be enriched in sphere cells compared with the parental cells of SPCA-1 and A549 cell lines. Then, we performed functional antibody screening including sphere-forming inhibiting and invasion inhibiting assay. The results showed that two antibodies, 12C7 and 9B8, notably suppressed the self-renewal and invasion of LCSLCs. Fluorescence-

activated cell sorting (FACs) found that the positive cells recognized by mAbs, 12C7 or 9B8, displayed features of LCSLCs. Interestingly, we found that these two antibodies recognized different subsets of cells and their combination effect was superior to the individual effect both in vitro and in vivo. Tissue microarrays were applied to detect the expression of the antigens targeted by these two antibodies. The positive expression of 12C7 and 9B8 targeted antigen was 84.4 and 82.5%, respectively, which was significantly higher than that in the non-tumor lung tissues. In conclusion, we screened two potential therapeutic antibodies that target different subsets of LCSLCs.

Chikhovskaya, J. V., et al. (2014). "Mesenchymal origin of multipotent human testis-derived stem cells in human testicular cell cultures." Mol Hum Reprod **20**(2): 155-167.

In contrast to mouse germ cell-derived pluripotent stem cells, the pluripotent state of human testis-derived embryonic stem cell (ESC)-like that spontaneously arise in primary testicular cell cultures remains controversial. Recent studies have shown that these cells closely resemble multipotent mesenchymal stem cells (MSCs), raising the question of their origin and designating these cell populations as multipotent human testis-derived stem cells (mhtSCs) rather than truly ESC-like cells. Here, we evaluate the origin of mhtSCs in vitro by culturing selected testicular cell types. We demonstrate that mhtSCs can be obtained equally efficiently in cultures of pure testicular somatic cells devoid of germ cells. Conversely, cultures with a purified population of germ cells/spermatogonia do not produce any mhtSCs. Based on common molecular characteristics of the somatic starting population and mhtSCs, we conclude that mhtSCs colonies originate from somatic mesenchymal progenitors present in primary testicular cell cultures and do not arise from germ cells undergoing incomplete reprogramming in vitro.

Dihazi, H., et al. (2011). "Multipotent adult germline stem cells and embryonic stem cells functional proteomics revealed an important role of eukaryotic initiation factor 5A (Eif5a) in stem cell differentiation." J Proteome Res **10**(4): 1962-1973.

Multipotent adult germline stem cells (maGSCs) are pluripotent cells that can be differentiated into somatic cells of the three primary germ layers. To highlight the protein profile changes associated with stem cell differentiation, retinoic acid (RA) treated mouse stem cells (maGSCs and ESCs) were compared to nontreated stem cells. 2-DE and DIGE reference maps were created, and differentially expressed proteins were further processed for identification. In both stem cell types, the RA induced differentiation resulted in an alteration of 36 proteins of which 18 were down-regulated and might be potential pluripotency associated proteins, whereas the other 18 proteins were up-regulated. These might be correlated to stem cell differentiation. Surprisingly, eukaryotic initiation factor 5A (Eif5a), a protein which is essential for cell proliferation and differentiation, was significantly down-regulated under RA treatment. A time-dependent investigation of Eif5a showed that the RA treatment of stem cells resulted in a significant up-regulation of the Eif5a in the first 48 h followed by a progressive down-regulation thereafter. This effect could be blocked by the hypusination inhibitor ciclopirox olamine (CPX). The alteration of Eif5a hypusination, as confirmed by mass spectrometry, exerts an antiproliferative effect on ESCs and maGSCs in vitro, but does not affect the cell pluripotency. Our data highlights the important role of Eif5a and its hypusination for stem cell differentiation and proliferation.

Freitas, C. S. and S. R. Dalmau (2006). "Multiple sources of non-embryonic multipotent stem cells: processed lipoaspirates and dermis as promising alternatives to bone-marrow-derived cell therapies." Cell Tissue Res **325**(3): 403-411.

A body of evidence points to the existence of stem cell stores in adult tissues, in addition to the well-known hematopoietic stem cells from bone marrow. Many reports describe the ability of these multipotent cells (developmentally non-compromised with their organs of origin) to give rise to many different cell types in response to specific stimuli. This apparent plasticity provides new perspectives in tissue engineering and suggests the usefulness of these cells in future protocols of autologous transplantation, gene therapy, and tissue reconstitution in a number of pathological processes. Lipoaspirates and dermis represent accessible sources for obtaining such cells, with minimal discomfort to the donor, and might be promising candidates for cell therapy procedures once their features are experimentally accessed. The intention of the present work has been to gather reports on the phenotypic characteristics, profile, and plastic potential of these stem cells.

Han, X. D., et al. (1995). "Identification of a unique membrane-bound molecule on a hemopoietic stem cell line and on multipotent progenitor cells." Proc Natl Acad Sci U S A **92**(24): 11014-11018.

Hemopoietic stem cells are a distinct population of cells that can differentiate into multilineages of hemopoietic cells and have long-term repopulation capability. A few membrane-bound molecules have been found to be preferentially, but not uniquely, present on the surface of these primitive cells. We report here the identification of a unique 105-kDa glycoprotein on the surface of hemopoietic stem cell line BL3. This molecule, recognized by the absorbed antiserum, is not present on the surface of myeloid

progenitors 32D and FDC-P1 cells, EL4 T cells, and NIH 3T3 fibroblasts. This antiserum can also be used to block the proliferation of BL3 cells even in the presence of mitogen-stimulated spleen cell conditioned medium, which is known to have a stimulating activity on BL3 cells. It can also inhibit development of in vitro, fetal liver cell-derived multilineage colonies, but not other types of colonies, and of in vivo bone marrow cell-derived colony-forming unit spleen foci. These data suggest that gp105 plays an important role in hemopoietic stem cell differentiation.

Holstein, T. W. and C. N. David (1990). "Putative intermediates in the nerve cell differentiation pathway in hydra have properties of multipotent stem cells." Dev Biol **142**(2): 401-405.

We have investigated the properties of nerve cell precursors in hydra by analyzing the differentiation and proliferation capacity of interstitial cells in the peduncle of Hydra oligactis, which is a region of active nerve cell differentiation. Our results indicate that about 50% of the interstitial cells in the peduncle can grow rapidly and also give rise to nematocyte precursors when transplanted into a gastric environment. If these cells were committed nerve cell precursors, one would not expect them to differentiate into nematocytes nor to proliferate apparently without limit. Therefore we conclude that cycling interstitial cells in peduncles are not intermediates in the nerve cell differentiation pathway but are stem cells. The remaining interstitial cells in the peduncle are in G1 and have the properties of committed nerve cell precursors (Holstein and David, 1986). Thus, the interstitial cell population in the peduncle contains both stem cells and noncycling nerve precursors. The presence of stem cells in this region makes it likely that these cells are the immediate targets of signals which give rise to nerve cells.

Hsiao, F. S., et al. (2011). "Toward an ideal animal model to trace donor cell fates after stem cell therapy: production of stably labeled multipotent mesenchymal stem cells from bone marrow of transgenic pigs harboring enhanced green fluorescence protein gene." J Anim Sci **89**(11): 3460-3472.

The discovery of postnatal mesenchymal stem cells (MSC) with their general multipotentiality has fueled much interest in the development of cell-based therapies. Proper identification of transplanted MSC is crucial for evaluating donor cell distribution, differentiation, and migration. Lack of an efficient marker of transplanted MSC has precluded our understanding of MSC-related regenerative studies, especially in large animal models such as pigs. In the present study, we produced transgenic pigs harboring an enhanced green fluorescent protein (EGFP) gene. The pigs provide a reliable and reproducible source for obtaining stable EGFP-labeled MSC, which is very useful for donor cell tracking after transplantation. The undifferentiated EGFP-tagged MSC expressed a greater quantity of EGFP while maintaining MSC multipotentiality. These cells exhibited homogeneous surface epitopes and possessed classic trilineage differentiation potential into osteogenic, adipogenic, and chondrogenic lineages, with robust EGFP expression maintained in all differentiated progeny. Injection of donor MSC can dramatically increase the thickness of infarcted myocardium and improve cardiac function in mice. Moreover, the MSC, with their strong EGFP expression, can be easily distinguished from the background autofluorescence in myocardial infarcts. We demonstrated an efficient, effective, and easy way to identify MSC after long-term culture and transplantation. With the transgenic model, we were able to obtain stem or progenitor cells in earlier passages compared with the transfection of traceable markers into established MSC. Because the integration site of the transgene was the same for all cells, we lessened the potential for positional effects and the heterogeneity of the stem cells. The EGFP-transgenic pigs may serve as useful biomedical and agricultural models of somatic stem cell biology.

Izadyar, F., et al. (2008). "Generation of multipotent cell lines from a distinct population of male germ line stem cells." Reproduction **135**(6): 771-784.

Spermatogonial stem cells (SSCs) maintain spermatogenesis by self-renewal and generation of spermatogonia committed to differentiation. Under certain in vitro conditions, SSCs from both neonatal and adult mouse testis can reportedly generate multipotent germ cell (mGC) lines that have characteristics and differentiation potential similar to embryonic stem (ES) cells. However, mGCs generated in different laboratories showed different germ cell characteristics, i.e., some retain their SSC properties and some have lost them completely. This raises an important question: whether mGC lines have been generated from different subpopulations in the mouse testes. To unambiguously identify and track germ line stem cells, we utilized a transgenic mouse model expressing green fluorescence protein under the control of a germ cell-specific Pou5f1 (Oct4) promoter. We found two distinct populations among the germ line stem cells with regard to their expression of transcription factor Pou5f1 and c-Kit receptor. Only the POU5F1+/c-Kit+ subset of mouse germ line stem cells, when isolated from either neonatal or adult testes and cultured in a complex mixture of growth factors, generates cell lines that express pluripotent ES markers, i.e., Pou5f1, Nanog, Sox2, Rex1, Dppa5, SSEA-1, and alkaline phosphatase, exhibit high telomerase activity, and differentiate into multiple lineages, including beating cardiomyocytes, neural cells, and chondrocytes. These data clearly show the existence of two distinct

populations within germ line stem cells: one destined to become SSC and the other with the ability to generate multipotent cell lines with some pluripotent characteristics. These findings raise interesting questions about the relativity of pluripotency and the plasticity of germ line stem cells.

Jung, Y. H., et al. (2010). "Glial cell line-derived neurotrophic factor alters the growth characteristics and genomic imprinting of mouse multipotent adult germline stem cells." Exp Cell Res **316**(5): 747-761.

This study evaluated the essentiality of glial cell line-derived neurotrophic factor (GDNF) for in vitro culture of established mouse multipotent adult germline stem (maGS) cell lines by culturing them in the presence of GDNF, leukemia inhibitory factor (LIF) or both. We show that, in the absence of LIF, GDNF slows the proliferation of maGS cells and result in smaller sized colonies without any change in distribution of cells to different cell-cycle stages, expression of pluripotency genes and in vitro differentiation potential. Furthermore, in the absence of LIF, GDNF increased the expression of male germ-line genes and repopulated the empty seminiferous tubule of W/W(v) mutant mouse without the formation of teratoma. GDNF also altered the genomic imprinting of Igf2, Peg1, and H19 genes but had no effect on DNA methylation of Oct4, Nanog and Stra8 genes. However, these effects of GDNF were masked in the presence of LIF. GDNF also did not interfere with the multipotency of maGS cells if they are cultured in the presence of LIF. In conclusion, our results suggest that, in the absence of LIF, GDNF alters the growth characteristics of maGS cells and partially impart them some of the germline stem (GS) cell-like characteristics.

Kallekleiv, M., et al. (2016). "Co-transplantation of multipotent mesenchymal stromal cells in allogeneic hematopoietic stem cell transplantation: A systematic review and meta-analysis." Cytotherapy **18**(2): 172-185.

BACKGROUND AIMS: Allogeneic hematopoietic stem cell transplantation (HSCT) is a potentially curative treatment option for patients with hematological malignancies. Co-transplantation of multipotent mesenchymal stromal cells (MSCs) during allogeneic HSCT has been explored to enhance engraftment and decrease the risk of graft-versus-host disease (GVHD). We aimed to identify, evaluate and summarize the findings of all relevant controlled clinical studies to determine the potential benefits of MSC infusion during allogeneic HSCT, with regard to the outcomes engraftment, GVHD, post-transplant relapse and survival. METHODS: We conducted a systematic search of electronic databases for relevant controlled clinical studies. Studies included patients of all ages with hematological malignancies receiving allogeneic HSCT with or without infusion of MSCs within a 24-h time frame of transplantation. RESULTS: Nine studies met our inclusion criteria, including three randomized, one non-randomized and five historically controlled trials, representing a total of 309 patients. Our meta-analyses did not reveal any statistically significant differences in donor engraftment or GVHD. A review of data regarding relapse and overall survival may result in a positive attitude toward intervention with MSCs, but due to heterogeneous reporting, it is difficult to draw any strict conclusions. None of the studies had overall serious risks of bias, but the quality of the evidence is low. CONCLUSIONS: Meta-analysis did not reveal any statistically significant effects of MSC co-transplantation, but the results must be interpreted with caution because of the weak study design and small study populations. We discuss further needs to explore the potential effects of MSCs in a HSCT setting.

Kamiya, K. and K. Ikeda (2011). "[Inner ear cell therapy for hereditary deafness with multipotent stem cells]." Nihon Rinsho **69**(12): 2215-2219.

Congenital deafness affects about 1 in 1000 children and the half of them have genetic background such as connexin26 gene mutation. The strategy to rescue such hereditary deafness has not been developed yet. Inner ear cell therapy for hereditary deafness has been studied using some laboratory animals and multipotent stem cells, although the successful reports for the hearing recovery accompanied with supplementation of the normal functional cells followed by tissue repair and recovery of the cellular/molecular functions have been still few. To succeed in hearing recovery by inner ear cell therapy, appropriate cell type, surgical approach and the stem cell homing system to the niche are thought to be required.

Kawase, Y., et al. (2004). "Characterization of multipotent adult stem cells from the skin: transforming growth factor-beta (TGF-beta) facilitates cell growth." Exp Cell Res **295**(1): 194-203.

Recently, adult stem cells have been isolated from the skin and designated as skin-derived precursors (SKPs). These SKPs, cultured in vitro, can give rise to neurons, glia, smooth muscle cells, and adipocytes. In the current study, we confirmed the clonal expansion of SKPs using a sphere-forming culture system in a medium containing methylcellulose. Among the growth factors, only transforming growth factor-beta (TGF-beta) was revealed to uniquely facilitate the sphere formation and proliferation of the SKPs in combination with EGF and bFGF. In addition, TGF-beta did not alter phenotypical characteristics of the SKPs under sphere-forming conditions. The effect of TGF-beta on sphere formation was not observed in neural stem cells, which expressed a different set of cell surface markers from SKPs, suggesting that SKPs have distinct features. Although the number of SKPs

decreased with age, TGF-beta increased the sphere colony formation and proliferation in all ages. These results suggest that SKPs maintained in the presence of TGF-beta during culture are of potential use in cell-replacement therapies employing adult tissue sources.

Kelsh, R. N., et al. (2017). "Zebrafish adult pigment stem cells are multipotent and form pigment cells by a progressive fate restriction process: Clonal analysis identifies shared origin of all pigment cell types." Bioessays **39**(3).

Skin pigment pattern formation is a paradigmatic example of pattern formation. In zebrafish, the adult body stripes are generated by coordinated rearrangement of three distinct pigment cell-types, black melanocytes, shiny iridophores and yellow xanthophores. A stem cell origin of melanocytes and iridophores has been proposed although the potency of those stem cells has remained unclear. Xanthophores, however, seemed to originate predominantly from proliferation of embryonic xanthophores. Now, data from Singh et al. shows that all three cell-types derive from shared stem cells, and that these cells generate peripheral neural cell-types too. Furthermore, clonal compositions are best explained by a progressive fate restriction model generating the individual cell-types. The numbers of adult pigment stem cells associated with the dorsal root ganglia remain low, but progenitor numbers increase significantly during larval development up to metamorphosis, likely via production of partially restricted progenitors on the spinal nerves.

Kennedy, E., et al. (2014). "Adult vascular smooth muscle cells in culture express neural stem cell markers typical of resident multipotent vascular stem cells." Cell Tissue Res **358**(1): 203-216.

Differentiation of resident multipotent vascular stem cells (MVSCs) or de-differentiation of vascular smooth muscle cells (vSMCs) might be responsible for the SMC phenotype that plays a major role in vascular diseases such as arteriosclerosis and restenosis. We examined vSMCs from three different species (rat, murine and bovine) to establish whether they exhibit neural stem cell characteristics typical of MVSCs. We determined their SMC differentiation, neural stem cell marker expression and multipotency following induction in vitro by using immunocytochemistry, confocal microscopy, fluorescence-activated cell sorting analysis and quantitative real-time polymerase chain reaction. MVSCs isolated from rat aortic explants, enzymatically dispersed rat SMCs and rat bone-marrow-derived mesenchymal stem cells served as controls. Murine carotid artery lysates and primary rat aortic vSMCs were both myosin-heavy-chain-positive but weakly expressed the neural crest stem cell marker, Sox10. Each vSMC line examined expressed SMC differentiation markers (smooth muscle alpha-actin, myosin heavy chain and calponin), neural crest stem cell markers (Sox10(+), Sox17(+)) and a glia marker (S100beta(+)). Serum deprivation significantly increased calponin and myosin heavy chain expression and decreased stem cell marker expression, when compared with serum-rich conditions. vSMCs did not differentiate to adipocytes or osteoblasts following adipogenic or osteogenic inductive stimulation, respectively, or respond to transforming growth factor-beta1 or Notch following gamma-secretase inhibition. Thus, vascular SMCs in culture express neural stem cell markers typical of MVSCs, concomitant with SMC differentiation markers, but do not retain their multipotency. The ultimate origin of these cells might have important implications for their use in investigations of vascular proliferative disease in vitro.

Kim, S. W., et al. (2006). "Successful stem cell therapy using umbilical cord blood-derived multipotent stem cells for Buerger's disease and ischemic limb disease animal model." Stem Cells **24**(6): 1620-1626.

Buerger's disease, also known as thromboangiitis obliterans, is a nonatherosclerotic, inflammatory, vasoocclusive disease. It is characterized pathologically as a panangiitis of medium and small blood vessels, including both arteries and adjacent veins, especially the distal extremities (the feet and the hands). There is no curative medication or surgery for this disease. In the present study, we transplanted human leukocyte antigen-matched human umbilical cord blood (UCB)-derived mesenchymal stem cells (MSCs) into four men with Buerger's disease who had already received medical treatment and surgical therapies. After the stem cell transplantation, ischemic rest pain suddenly disappeared from their affected extremities. The necrotic skin lesions were healed within 4 weeks. In the follow-up angiography, digital capillaries were increased in number and size. In addition, vascular resistance in the affected extremities, compared with the preoperative examination, was markedly decreased due to improvement of the peripheral circulation. Because an animal model of Buerger's disease is absent and also to understand human results, we transplanted human UCB-derived MSCs to athymic nude mice with hind limb ischemia by femoral artery ligation. Up to 60% of the hind limbs were salvaged in the femoral artery-ligated animals. By in situ hybridization, the human UCB-derived MSCs were detected in the arterial walls of the ischemic hind limb in the treated group. Therefore, it is suggested that human UCB-derived MSC transplantation may be a new and useful therapeutic armament for Buerger's disease and similar ischemic diseases.

Klein, D. (2016). "Vascular Wall-Resident Multipotent Stem Cells of Mesenchymal Nature within the Process of Vascular Remodeling: Cellular Basis, Clinical

Relevance, and Implications for Stem Cell Therapy." Stem Cells Int **2016**: 1905846.

Until some years ago, the bone marrow and the endothelial cell compartment lining the vessel lumen (subendothelial space) were thought to be the only sources providing vascular progenitor cells. Now, the vessel wall, in particular, the vascular adventitia, has been established as a niche for different types of stem and progenitor cells with the capacity to differentiate into both vascular and nonvascular cells. Herein, vascular wall-resident multipotent stem cells of mesenchymal nature (VW-MPSCs) have gained importance because of their large range of differentiation in combination with their distribution throughout the postnatal organism which is related to their existence in the adventitial niche, respectively. In general, mesenchymal stem cells, also designated as mesenchymal stromal cells (MSCs), contribute to the maintenance of organ integrity by their ability to replace defunct cells or secrete cytokines locally and thus support repair and healing processes of the affected tissues. This review will focus on the central role of VW-MPSCs within vascular reconstructing processes (vascular remodeling) which are absolute prerequisite to preserve the sensitive relationship between resilience and stability of the vessel wall. Further, a particular advantage for the therapeutic application of VW-MPSCs for improving vascular function or preventing vascular damage will be discussed.

Klein, D., et al. (2013). "Hox genes are involved in vascular wall-resident multipotent stem cell differentiation into smooth muscle cells." Sci Rep **3**: 2178.

Human vascular wall-resident CD44+ multipotent stem cells (VW-MPSCs) within the vascular adventitia are capable to differentiate into pericytes and smooth muscle cells (SMC). This study demonstrates HOX-dependent differentiation of CD44(+) VW-MPSCs into SMC that involves epigenetic modification of transgelin as a down-stream regulated gene. First, HOXB7, HOXC6 and HOXC8 were identified to be differentially expressed in VW-MPSCs as compared to terminal differentiated human aortic SMC, endothelial cells and undifferentiated pluripotent embryonic stem cells. Silencing these HOX genes in VW-MPSCs significantly reduced their sprouting capacity and increased expression of the SMC markers transgelin and calponin and the histone gene histone H1. Furthermore, the methylation pattern of the TAGLN promoter was altered. In summary, our findings suggest a role for certain HOX genes in regulating differentiation of human VW-MPSC into SMCs that involves epigenetic mechanisms. This is critical for understanding VW-MPSC-dependent vascular disease processes such as neointima formation and tumor vascularization.

Klimmeck, D., et al. (2012). "Proteomic cornerstones of hematopoietic stem cell differentiation: distinct signatures of multipotent progenitors and myeloid committed cells." Mol Cell Proteomics **11**(8): 286-302.

Regenerative tissues such as the skin epidermis, the intestinal mucosa or the hematopoietic system are organized in a hierarchical manner with stem cells building the top of this hierarchy. Somatic stem cells harbor the highest self-renewal activity and generate a series of multipotent progenitors which differentiate into lineage committed progenitors and subsequently mature cells. In this report, we applied an in-depth quantitative proteomic approach to analyze and compare the full proteomes of ex vivo isolated and FACS-sorted populations highly enriched for either multipotent hematopoietic stem/progenitor cells (HSPCs, Lin(neg)Sca-1(+)c-Kit(+)) or myeloid committed precursors (Lin(neg)Sca-1(-)c-Kit(+)). By employing stable isotope dimethyl labeling and high-resolution mass spectrometry, more than 5000 proteins were quantified. From biological triplicate experiments subjected to rigorous statistical evaluation, 893 proteins were found differentially expressed between multipotent and myeloid committed cells. The differential protein content in these cell populations points to a distinct structural organization of the cytoskeleton including remodeling activity. In addition, we found a marked difference in the expression of metabolic enzymes, including a clear shift of specific protein isoforms of the glycolytic pathway. Proteins involved in translation showed a collective higher expression in myeloid progenitors, indicating an increased translational activity. Strikingly, the data uncover a unique signature related to immune defense mechanisms, centering on the RIG-I and type-1 interferon response systems, which are installed in multipotent progenitors but not evident in myeloid committed cells. This suggests that specific, and so far unrecognized, mechanisms protect these immature cells before they mature. In conclusion, this study indicates that the transition of hematopoietic stem/progenitors toward myeloid commitment is accompanied by a profound change in processing of cellular resources, adding novel insights into the molecular mechanisms at the interface between multipotency and lineage commitment.

Lee, S. W., et al. (2018). "The Therapeutic Effect of Human Embryonic Stem Cell-Derived Multipotent Mesenchymal Stem Cells on Chemical-Induced Cystitis in Rats." Int Neurourol J **22**(Suppl 1): S34-45.

PURPOSE: To evaluate the therapeutic effect of human embryonic stem cell (hESC)-derived multipotent mesenchymal stem cells (M-MSCs) on ketamine-induced cystitis (KC) in rats. METHODS: To

induce KC, 10-week-old female rats were injected with 25-mg/kg ketamine hydrochloride twice weekly for 12 weeks. In the sham group, phosphate buffered saline (PBS) was injected instead of ketamine. One week after the final injection of ketamine, the indicated doses (0.25, 0.5, and 1x10(6) cells) of M-MSCs (KC+M-MSC group) or PBS vehicle (KC group) were directly injected into the bladder wall. One week after M-MSC injection, the therapeutic outcomes were evaluated via cystometry, histological analyses, and measurement of gene expression. Next, we compared the efficacy of M-MSCs at a low dose (1x10(5) cells) to that of an identical dose of adult bone marrow (BM)-derived MSCs. RESULTS: Rats in the KC group exhibited increased voiding frequency and reduced bladder capacity compared to rats of the sham group. However, these parameters recovered after transplantation of M-MSCs at all doses tested. KC bladders exhibited markedly increased mast cell infiltration, apoptosis, and tissue fibrosis. Administration of M-MSCs significantly reversed these characteristic histological alterations. Gene expression analyses indicated that several genes associated with tissue fibrosis were markedly upregulated in KC bladders. However the expression of these genes was significantly suppressed by the administration of M-MSCs. Importantly, M-MSCs ameliorated bladder deterioration in KC rats after injection of a low dose (1x10(5)) of cells, at which point BM-derived MSCs did not substantially improve bladder function. CONCLUSIONS: This study demonstrates for the first time the therapeutic efficacy of hESC-derived M-MSCs on KC in rats. M-MSCs restored bladder function more effectively than did BM-derived MSCs, protecting against abnormal changes including mast cell infiltration, apoptosis and fibrotic damage.

Li, M., et al. (2014). "Multipotent neural crest stem cell-like cells from rat vibrissa dermal papilla induce neuronal differentiation of PC12 cells." Biomed Res Int **2014**: 186239.

Bone marrow mesenchymal stem cells (BMSCs) transplants have been approved for treating central nervous system (CNS) injuries and diseases; however, their clinical applications are limited. Here, we model the therapeutic potential of dermal papilla cells (DPCs) in vitro. DPCs were isolated from rat vibrissae and characterized by immunocytofluorescence, RT-PCR, and multidifferentiation assays. We examined whether these cells could secrete neurotrophic factors (NTFs) by using cocultures of rat pheochromocytoma cells (PC12) with conditioned medium and ELISA assay. DPCs expressed Sox10, P75, Nestin, Sox9, and differentiated into adipocytes, osteoblasts, smooth muscle cells, and neurons under specific inducing conditions. The DPC-conditioned medium (DPC-CM) induced neuronal differentiation of PC12 cells and promoted neurite outgrowth. Results of ELISA assay showed that compared to BMSCs, DPCs secreted more brain-derived neurotrophic factor (BDNF) and glial cell line-derived neurotrophic factor (GDNF). Moreover, we observed that, compared with the total DPC population, sphere-forming DPCs expressed higher levels of Nestin and P75 and secreted greater amounts of GDNF. The DPCs from craniofacial hair follicle papilla may be a new and promising source for treating CNS injuries and diseases.

Lim, M. N., et al. (2012). "Ex vivo expanded SSEA-4+ human limbal stromal cells are multipotent and do not express other embryonic stem cell markers." Mol Vis **18**: 1289-1300.

PURPOSE: The presence of multipotent human limbal stromal cells resembling mesenchymal stromal cells (MSC) provides new insights to the characteristic of these cells and its therapeutic potential. However, little is known about the expression of stage-specific embryonic antigen 4 (SSEA-4) and the embryonic stem cell (ESC)-like properties of these cells. We studied the expression of SSEA-4 surface protein and the various ESC and MSC markers in the ex vivo cultured limbal stromal cells. The phenotypes and multipotent differentiation potential of these cells were also evaluated. METHODS: Limbal stromal cells were derived from corneoscleral rims. The SSEA-4(+) and SSEA-4(-) limbal stromal cells were sorted by fluorescence-activated cells sorting (FACS). Isolated cells were expanded and reanalyzed for their expression of SSEA-4. Expression of MSC and ESC markers on these cells were also analyzed by FACS. In addition, expression of limbal epithelial and corneal stromal proteins such as ATP-binding cassette sub-family G member 2 (ABCG2), tumour protein p63 (p63), paired box 6 (Pax6), cytokeratin 3 (AE5), cytokeratin 10, and keratocan sulfate were evaluated either by immunofluorecence staining or reverse transcription polymerase chain reaction. Appropriate induction medium was used to differentiate these cells into adipocytes, osteocytes, and chondrocytes. RESULTS: Expanded limbal stromal cells expressed the majority of mesenchymal markers. These cells were negative for ABCG2, p63, Pax6, AE-5, and keratocan sulfate. After passaged, a subpopulation of these cells showed low expression of SSEA-4 but were negative for other important ESC surface markers such as Tra-1-60, Tra-1-81, and transcription factors like octamer-binding transcription factor 4 (Oct4), SRY(sex determining region Y)-box 2 (Sox2), and Nanog. Early passaged cells when induced were able to differentiate into adipocytes, osteocytes and chondrocytes. CONCLUSIONS: The expanded limbal stromal cells showed features of multipotent MSC. Our study confirmed the expression of SSEA-4 by a

subpopulation of cultured limbal stromal cells. However, despite the expression of SSEA-4, these cells did not express any other markers of ESC. Therefore, we conclude that the cells did not show properties of ESC.

Luyckx, A., et al. (2011). "Oct4-negative multipotent adult progenitor cells and mesenchymal stem cells as regulators of T-cell alloreactivity in mice." Immunol Lett **137**(1-2): 78-81.

Multipotent adult progenitor cells (MAPC) are clinically being explored as an alternative to mesenchymal stem cells (MSC) for the immunomodulatory control of graft-versus-host disease (GvHD). Here, we performed an explorative study of the immunomodulatory potential of mouse MAPC (mMAPC), in comparison with that of MSC (mMSC) using experimental models of T-cell alloreactivity. Suppressive effects of Oct4-expressing mMAPC have been described previously; here, we studied mMAPC expressing low to no Oct4 ('mClone-3'), recently shown to be most representative for the human MAPC counterpart. mClone-3 and mMSC exhibited similar immunophenotype and in vitro immunogenic behavior. Allogeneic T-cell<-->dendritic cell-proliferation assays showed strong dose-dependent T-cell-suppressive effects of both mClone-3 and mMSC. In a popliteal lymph node assay, mClone-3 and mMSC equally suppressed in vivo alloreactive T-cell expansion. We conclude that mouse MAPC and MSC exhibit similar immunosuppressive behavior in in vitro and local in vivo GvHD assays.

Mahmood, A., et al. (2011). "In vitro differentiation and maturation of human embryonic stem cell into multipotent cells." Stem Cells Int **2011**: 735420.

Human embryonic stem cells (hESCs), which have the potential to generate virtually any differentiated progeny, are an attractive cell source for transplantation therapy, regenerative medicine, and tissue engineering. To realize this potential, it is essential to be able to control ESC differentiation and to direct the development of these cells along specific pathways. Basic science in the field of embryonic development, stem cell differentiation, and tissue engineering has offered important insights into key pathways and scaffolds that regulate hESC differentiation, which have produced advances in modeling gastrulation in culture and in the efficient induction of endoderm, mesoderm, ectoderm, and many of their downstream derivatives. These findings have lead to identification of several pathways controlling the differentiation of hESCs into mesodermal derivatives such as myoblasts, mesenchymal cells, osteoblasts, chondrocytes, adipocytes, as well as hemangioblastic derivatives. The next challenge will be to demonstrate the functional utility of these cells, both in vitro and in preclinical models of bone and vascular diseases.

Matulka, L. A., et al. (2007). "Parity-induced mammary epithelial cells are multipotent and express cell surface markers associated with stem cells." Dev Biol **303**(1): 29-44.

Parity-induced mammary epithelial cells (PI-MECs) are defined as a pregnancy hormone-responsive cell population that activates the promoter of late milk protein genes during the second half of pregnancy and lactation. However, unlike their terminally differentiated counterparts, these cells do not undergo programmed cell death during post-lactational remodeling of the gland. We previously demonstrated that upon transplantation into an epithelial-free mammary fat pad, PI-MECs exhibited two important features of multipotent mammary epithelial progenitors: a) self-renewal, and b) contribution to ductal and alveolar morphogenesis. In this new report, we introduce a new method to viably label PI-MECs. Using this methodology, we analyzed the requirement of ovarian hormones for the maintenance of this epithelial subtype in the involuted mammary gland. Furthermore, we examined the expression of putative stem cell markers and found that a portion of GFP-labeled PI-MECs were part of the CD24(+)/CD49f(high) mammary epithelial subtype, which has recently been suggested to contain multipotent stem cells. Subsequently, we demonstrated that isolated PI-MECs were able to form mammospheres in culture, and upon transplantation, these purified epithelial cells were capable of establishing a fully functional mammary gland. These observations suggest that PI-MECs contain multipotent progenitors that are able to self renew and generate diverse epithelial lineages present in the murine mammary gland.

Motohashi, T., et al. (2007). "Multipotent cell fate of neural crest-like cells derived from embryonic stem cells." Stem Cells **25**(2): 402-410.

Neural crest cells migrate throughout the embryo and differentiate into diverse derivatives: the peripheral neurons, cranial mesenchymal cells, and melanocytes. Because the neural crest cells have critical roles in organogenesis, detailed elucidation of neural crest cell differentiation is important in developmental biology. We recently reported that melanocytes could be induced from mouse ESCs. Here, we improved the culture system and showed the existence of neural crest-like precursors. The addition of retinoic acid to the culture medium reduced the hematopoiesis and promoted the expression of the neural crest marker genes. The colonies formed contained neural crest cell derivatives: neurons and glial cells, together with melanocytes. This suggested that neural crest-like cells assuming multiple cell fates

had been generated in these present cultures. To isolate the neural crest-like cells, we analyzed the expression of c-Kit, a cell-surface protein expressed in the early stage of neural crest cells in vivo. The c-Kit-positive (c-Kit(+)) cells appeared as early as day 9 of the culture period and expressed the transcriptional factors Sox10 and Snail, which are expressed in neural crest cells. When the c-Kit(+) cells were separated from the cultures and recultured, they frequently formed colonies containing neurons, glial cells, and melanocytes. Even a single c-Kit(+) cell formed colonies that contained these three cell types, confirming their multipotential cell fate. The c-Kit(+) cells were also capable of migrating along neural crest migratory pathways in vivo. These results indicate that the c-Kit(+) cells isolated from melanocyte-differentiating cultures of ESCs are closely related to neural crest cells.

Muller, I., et al. (2008). "Application of multipotent mesenchymal stromal cells in pediatric patients following allogeneic stem cell transplantation." Blood Cells Mol Dis **40**(1): 25-32.

Multipotent mesenchymal stromal cells (MSC) have immunomodulatory effects. The aim of this study was to demonstrate safety and feasibility of MSC transfusion in pediatric patients who had undergone allogeneic stem cell transplantation from MMFD, MUD, MMUD and MSD. Patients with posttransplant complications based on deregulated immune effector cells who may benefit from an immunomodulatory effect of MSC had been selected. MSC were isolated from the hematopoietic stem cell donors in five cases and from a third party parental donor in two cases. We transfused ex vivo-expanded MSC in 11 doses into seven pediatric patients. Cell doses were escalated based on availability from 0.4x10(6) to 3.0x10(6) per kg bodyweight No adverse effects were detected with a maximum follow-up of 29 months. One out of three patients showed slight improvement of chronic GVHD. Two patients with severe acute GvHD did not progress to cGvHD. One patient received MSC to stabilize graft function after secondary haploidentical transplantation. One patient recovered from trilineage failure due to severe hemophagocytosis. This is the first case of a pediatric patient treated with MSC for trilineage failure after haploidentical stem cell transplantation from her father. We report the first series of 11 transfusions of expanded MSC in pediatric patients with immunological complications after allogeneic transplantation. Transfusion of MSC was safe and encouraging improvements in some patients were observed.

Nakajima, H., et al. (2010). "TIMP-3 recruits quiescent hematopoietic stem cells into active cell cycle and expands multipotent progenitor pool." Blood **116**(22): 4474-4482.

Regulating transition of hematopoietic stem cells (HSCs) between quiescent and cycling states is critical for maintaining homeostasis of blood cell production. The cycling states of HSCs are regulated by the extracellular factors such as cytokines and extracellular matrix; however, the molecular circuitry for such regulation remains elusive. Here we show that tissue inhibitor of metalloproteinase-3 (TIMP-3), an endogenous regulator of metalloproteinases, stimulates HSC proliferation by recruiting quiescent HSCs into the cell cycle. Myelosuppression induced TIMP-3 in the bone marrow before hematopoietic recovery. Interestingly, TIMP-3 enhanced proliferation of HSCs and promoted expansion of multipotent progenitors, which was achieved by stimulating cell-cycle entry of quiescent HSCs without compensating their long-term repopulating activity. Surprisingly, this effect did not require metalloproteinase inhibitory activity of TIMP-3 and was possibly mediated through a direct inhibition of angiopoietin-1 signaling, a critical mediator for HSC quiescence. Furthermore, bone marrow recovery from myelosuppression was accelerated by over-expression of TIMP-3, and in turn, impaired in TIMP-3-deficient animals. These results suggest that TIMP-3 may act as a molecular cue in response to myelosuppression for recruiting dormant HSCs into active cell cycle and may be clinically useful for facilitating hematopoietic recovery after chemotherapy or ex vivo expansion of HSCs.

Ohlstein, B. and A. Spradling (2007). "Multipotent Drosophila intestinal stem cells specify daughter cell fates by differential notch signaling." Science **315**(5814): 988-992.

The adult Drosophila midgut contains multipotent intestinal stem cells (ISCs) scattered along its basement membrane that have been shown by lineage analysis to generate both enterocytes and enteroendocrine cells. ISCs containing high levels of cytoplasmic Delta-rich vesicles activate the canonical Notch pathway and down-regulate Delta within their daughters, a process that programs these daughters to become enterocytes. ISCs that express little vesiculate Delta, or are genetically impaired in Notch signaling, specify their daughters to become enteroendocrine cells. Thus, ISCs control daughter cell fate by modulating Notch signaling over time. Our studies suggest that ISCs actively coordinate cell production with local tissue requirements by this mechanism.

Pierce, A., et al. (2002). "BCR-ABL alters the proliferation and differentiation response of multipotent hematopoietic cells to stem cell factor." Oncogene **21**(19): 3068-3075.

Chronic myeloid leukaemia (CML), a hematopoietic stem cell disorder is characterized by the expression of BCR-ABL. To investigate the effects of BCR-ABL on multipotent hematopoietic cells, a

temperature sensitive BCR-ABL tyrosine kinase was expressed in the cell line, FDCP-Mix. BCR-ABL mediated an increase in c-kit expression that correlated with an enhanced mitogenic response to SCF. This was not observed in the absence of Bcr-Abl kinase activity or presence of the BCR-ABL inhibitor STI571, which also inhibits c-kit. When cultured in a combination of SCF plus G-CSF the FDCP-Mix cells undergo neutrophilic differentiation over a 7-10 day period. When BCR-ABL was active there was a marked inhibition of cell maturation compared to control cells in which BCR-ABL was either inactive or not present. However, BCR-ABL did not block differentiation as the cells eventually undergo terminal maturation. These data argue that BCR-ABL is directly responsible for the enhanced response to SCF reported in CML progenitor cells. Furthermore, although the primary effect of STI571 is via direct inhibition of BCR-ABL, STI571 additionally reduces the enhanced response to SCF. Thus there are two sites of STI571 action of potential importance in Bcr-Abl expressing cells.

Radtke, S., et al. (2016). "The frequency of multipotent CD133(+)CD45RA(-)CD34(+) hematopoietic stem cells is not increased in fetal liver compared with adult stem cell sources." Exp Hematol **44**(6): 502-507.

The cell surface marker CD133 has been used to describe a revised model of adult human hematopoiesis, with hematopoietic stem cells and multipotent progenitors (HSCs/MPPs: CD133(+)CD45RA(-)CD34(+)) giving rise to lymphomyeloid-primed progenitors (LMPPs: CD133(+)CD45RA(+)CD34(+)) and erythromyeloid progenitors (EMPs: CD133(low)CD45RA(-)CD34(+)). Because adult and fetal hematopoietic stem and progenitor cells (HSPCs) differ in their gene expression profile, differentiation capabilities, and cell surface marker expression, we were interested in whether the reported segregation of lineage potentials in adult human hematopoiesis would also apply to human fetal liver. CD133 expression was easily detected in human fetal liver cells, and the defined hematopoietic subpopulations were similar to those found for adult HSPCs. Fetal HSPCs were enriched for EMPs and HSCs/MPPs, which were primed toward erythromyeloid differentiation. However, the frequency of multipotent CD133(+)CD45RA(-)CD34(+) HSPCs was much lower than previously reported and comparable to that of umbilical cord blood. We noted that engraftment in NSG (NOD scid gamma [NOD.Cg-Prkdc(scid) Il2rg(tm1Wjl)/SzJ]) mice was driven mostly by LMPPs, confirming recent findings that repopulation in mice is not a unique feature of multipotent HSCs/MPPs. Thus, our data challenge the general assumption that human fetal liver contains a greater percentage of multipotent HSCs/MPPs than any adult HSC source, and the mouse model may have to be re-evaluated with respect to the type of readout it provides.

Rajasingh, J., et al. (2008). "Cell-free embryonic stem cell extract-mediated derivation of multipotent stem cells from NIH3T3 fibroblasts for functional and anatomical ischemic tissue repair." Circ Res **102**(11): e107-117.

The oocyte-independent source for the generation of pluripotent stem cells is among the ultimate goals in regenerative medicine. We report that on exposure to mouse embryonic stem cell (mESC) extracts, reversibly permeabilized NIH3T3 cells undergo dedifferentiation followed by stimulus-induced redifferentiation into multiple lineage cell types. Genome-wide expression profiling revealed significant differences between NIH3T3 control and ESC extract-treated NIH3T3 cells including the reactivation of ESC-specific transcripts. Epigenetically, ESC extracts induced CpG demethylation of Oct4 promoter, hyperacetylation of histones 3 and 4, and decreased lysine 9 (K-9) dimethylation of histone 3. In mouse models of surgically induced hindlimb ischemia or acute myocardial infarction transplantation of reprogrammed NIH3T3 cells significantly improved postinjury physiological functions and showed anatomic evidence of engraftment and transdifferentiation into skeletal muscle, endothelial cell, and cardiomyocytes. These data provide evidence for the generation of functional multipotent stem-like cells from terminally differentiated somatic cells without the introduction of retroviral mediated transgenes or ESC fusion.

Rameshwar, P., et al. (2001). "The dynamics of bone marrow stromal cells in the proliferation of multipotent hematopoietic progenitors by substance P: an understanding of the effects of a neurotransmitter on the differentiating hematopoietic stem cell." J Neuroimmunol **121**(1-2): 22-31.

Communication within the hematopoietic-neuroendocrine-immune axis is partly mediated by neurotransmitters (e.g. substance P, SP) and cytokines. SP mediates neuromodulation partly through the stimulation of bone marrow (BM) progenitors. This study shows that SP, through the neurokinin-1 receptor, stimulates the proliferation of primitive hematopoietic progenitors: cobblestone-forming cells (CAFC, CD34+). This effect is optimal when macrophage is included within the fibroblast support. Indirect induction of IL-1 could be important in the proliferation of CAFC colonies by SP. Phenotypic and functional studies suggest that SP might directly interact with the CD34+/CD45(dim) population. These studies indicate that SP can initiate a cascade of biological responses in the BM stroma and stem cells to stimulate hematopoiesis.

Sart, S., et al. (2009). "Ear mesenchymal stem cells: an efficient adult multipotent cell population fit for rapid and scalable expansion." J Biotechnol **139**(4): 291-299.

Bone marrow mesenchymal stem cells (BM-MSCs) have the potential to be used for tissue engineering. Nevertheless, they exhibit a low growth rate that limits their availability. In this work we use an alternative model of MSCs from the outer ear (ear mesenchymal stem cells, E-MSCs). These cells bear the characteristics of progenitor cells because of their ability to be differentiated into the three lineages of chondrocytes, osteocytes and adipocytes. This model cell population had a threefold higher cell growth rate compared to BM-MSCs. This allowed rapid testing of the scalability in microcarrier culture using bead-to-bead transfer and also enabled their expansion in a 1-l bioreactor. The cells were able to maintain their potential for differentiation into the above three lineages. Therefore, E-MSCs appear to be an attractive model for assessing a number of bioengineering parameters that may affect the behavior of adult stem cells in culture.

Shinohara, T., et al. (1983). "Chronic myelomonocytic leukemia with a chromosome abnormality (46,XY,20q-) in all dividing myeloid cells: evidence for clonal origin in a multipotent stem cell common to granulocyte, monocyte, erythrocyte, and thrombocyte." Am J Hematol **15**(3): 289-293.

In a typical case of chronic myelomonocytic leukemia (CMML), a chromosome abnormality, 46,XY,20q-, was observed in all the dividing cells including up to 16-ploid cells in the bone marrow and the blood. As the mitotic figures could be easily seen not only in myelomonocytoid cells but also in erythroblasts in the bone marrow smear, it was concluded that all the cell lineages except lymphocytes had the abnormality. The present case will support the view that the leukemic process in CMML affects a multipotent stem cell rather than a granulocyte-monocyte committed stem cell.

Song, N., et al. (2014). "Multipotent mesenchymal stem cells from human subacromial bursa: potential for cell based tendon tissue engineering." Tissue Eng Part A **20**(1-2): 239-249.

Rotator cuff injuries are a common clinical problem either as a result of overuse or aging. Biological approaches to tendon repair that involve use of scaffolding materials or cell-based approaches are currently being investigated. The cell-based approaches are focused on applying multipotent mesenchymal stem cells (MSCs) mostly harvested from bone marrow. In the present study, we focused on characterizing cells harvested from tissues associated with rotator cuff tendons based on an assumption that these cells would be more appropriate for tendon repair. We isolated MSCs from bursa tissue associated with rotator cuff tendons and characterized them for multilineage differentiation in vitro and in vivo. Human bursa was obtained from patients undergoing rotator cuff surgery and cells within were isolated using collagenase and dispase digestion. The cells isolated from the tissues were characterized for osteoblastic, adipogenic, chondrogenic, and tenogenic differentiation in vitro and in vivo. The results showed that the cells isolated from bursa tissue exhibited MSCs characteristics as evidenced by the expression of putative cell surface markers attributed to MSCs. The cells exhibited high proliferative capacity and differentiated toward cells of mesenchymal lineages with high efficiency. Bursa-derived cells expressed markers of tenocytes when treated with bone morphogenetic protein-12 (BMP-12) and assumed aligned morphology in culture. Bursa cells pretreated with BMP-12 and seeded in ceramic scaffolds formed extensive bone, as well as tendon-like tissue in vivo. Bone formation was demonstrated by histological analysis and immunofluorescence for DMP-1 in tissue sections made from the scaffolds seeded with the cells. Tendon-like tissue formed in vivo consisted of parallel collagen fibres typical of tendon tissues. Bursa-derived cells also formed a fibrocartilagenous tissue in the ceramic scaffolds. Taken together, the results demonstrate a new source of MSCs with a high potential for application in tendon repair.

Stockl, S., et al. (2013). "Sox9 modulates cell survival and adipogenic differentiation of multipotent adult rat mesenchymal stem cells." J Cell Sci **126**(Pt 13): 2890-2902.

Sox9 is a key transcription factor in early chondrogenesis with distinct roles in differentiation processes and during embryonic development. Here, we report that Sox9 modulates cell survival and contributes to the commitment of mesenchymal stem cells (MSC) to adipogenic or osteogenic differentiation lineages. We found that the Sox9 activity level affects the expression of the key transcription factor in adipogenic differentiation, C/EBPbeta, and that cyclin D1 mediates the expression of the osteogenic marker osteocalcin in undifferentiated adult bone-marrow-derived rat MSC. Introducing a stable Sox9 knockdown into undifferentiated rat MSC resulted in a marked decrease in proliferation rate and an increase in apoptotic activity. This was linked to a profound upregulation of p21 and cyclin D1 gene and protein expression accompanied by an induction of caspase 3/7 activity and an inhibition of Bcl-2. We observed that Sox9 silencing provoked a delayed S-phase progression and an increased nuclear localization of p21. The protein stability of cyclin D1 was induced in the absence of Sox9 presumably as a function of altered p38 signalling. In addition, the major transcription factor for adipogenic differentiation, C/EBPbeta, was

repressed after silencing Sox9. The nearly complete absence of C/EBPbeta protein as a result of increased destabilization of the C/EBPbeta mRNA and the impact on osteocalcin gene expression and protein synthesis, suggests that a delicate balance of Sox9 level is not only imperative for proper chondrogenic differentiation of progenitor cells, but also affects the adipogenic and probably osteogenic differentiation pathways of MSC. Our results identified Sox9 as an important link between differentiation, proliferation and apoptosis in undifferentiated adult rat mesenchymal stem cells, emphasizing the importance of the delicate balance of a precisely regulated Sox9 activity in MSC not only for proper skeletal development during embryogenesis but probably also for successful repair and regeneration of tissues and organs in adults.

Szabo, P., et al. (2011). "Mouse 3T3 fibroblasts under the influence of fibroblasts isolated from stroma of human basal cell carcinoma acquire properties of multipotent stem cells." Biol Cell **103**(5): 233-248.

BACKGROUND INFORMATION: Multipotent mesenchymal stem cells can participate in the formation of a microenvironment stimulating the aggressive behaviour of cancer cells. Moreover, cells exhibiting pluripotent ESC (embryonic stem cell) markers (Nanog and Oct4) have been observed in many tumours. Here, we investigate the role of cancer-associated fibroblasts in the formation of stem cell supporting properties of tumour stroma. We test the influence of fibroblasts isolated from basal cell carcinoma on mouse 3T3 fibroblasts, focusing on the expression of stem cell markers and plasticity in vitro by means of microarrays, qRT-PCR (quantitative real-time PCR) and immunohistochemistry. RESULTS: We demonstrate the biological activity of the cancer stromal fibroblasts by influencing the 3T3 fibroblasts to express markers such as Oct4, Nanog and Sox2 and to show differentiation potential similar to mesenchymal stem cells. The role of growth factors such as IGF2 (insulin-like growth factor 2), FGF7 (fibroblast growth factor 7), LEP (leptin), NGF (nerve growth factor) and TGFbeta (transforming growth factor beta), produced by the stromal fibroblasts, is established to participate in their bioactivity. Uninduced 3T3 do not express the stem cell markers and show minimal differentiation potential. CONCLUSIONS: Our observations indicate the pro-stem cell activity of cancer-associated fibroblasts and underline the role of epithelial-mesenchymal interaction in tumour biology.

Taghon, T., et al. (2003). "Homeobox gene expression profile in human hematopoietic multipotent stem cells and T-cell progenitors: implications for human T-cell development." Leukemia **17**(6): 1157-1163.

Class I homeobox (HOX) genes comprise a large family of transcription factors that have been implicated in normal and malignant hematopoiesis. However, data on their expression or function during T-cell development is limited. Using degenerated RT-PCR and Affymetrix microarray analysis, we analyzed the expression pattern of this gene family in human multipotent stem cells from fetal liver (FL) and adult bone marrow (ABM), and in T-cell progenitors from child thymus. We show that FL and ABM stem cells are similar in terms of HOX gene expression, but significant differences were observed between these two cell types and child thymocytes. As the most immature thymocytes are derived from immigrated FL and ABM stem cells, this indicates a drastic change in HOX gene expression upon entry into the thymus. Further analysis of HOX-A7, HOX-A9, HOX-A10, and HOX-A11 expression with specific RT-PCR in all thymocyte differentiation stages showed a sequential loss of 3' region HOX-A cluster genes during intrathymic T-cell development and an unexpected expression of HOX-A11, previously not recognized to play a role in hematopoiesis. Also HOX-B3 and HOX-C4 were expressed throughout thymocyte development. Overall, these data provide novel evidence for an important role of certain HOX genes in human T-cell development.

Tavian, M., et al. (2001). "The human embryo, but not its yolk sac, generates lympho-myeloid stem cells: mapping multipotent hematopoietic cell fate in intraembryonic mesoderm." Immunity **15**(3): 487-495.

We have traced emerging hematopoietic cells along human early ontogeny by culturing embryonic tissue rudiments in the presence of stromal cells that promote myeloid and B cell differentiation, and by assaying T cell potential in the NOD-SCID mouse thymus. Hematogenous potential was present inside the embryo as early as day 19 of development in the absence of detectable CD34+ hematopoietic cells, and spanned both lymphoid and myeloid lineages from day 24 in the splanchnopleural mesoderm and derived aorta where CD34+ progenitors appear at day 27. By contrast, hematopoietic cells arising in the third week yolk sac, as well as their progeny at later stages, were restricted to myelopoiesis and therefore are unlikely to contribute to definitive hematopoiesis in man.

Tomita, Y., et al. (2005). "Cardiac neural crest cells contribute to the dormant multipotent stem cell in the mammalian heart." J Cell Biol **170**(7): 1135-1146.

Arodent cardiac side population cell fraction formed clonal spheroids in serum-free medium, which expressed nestin, Musashi-1, and multi-drug resistance transporter gene 1, markers of undifferentiated neural precursor cells. These markers were lost following differentiation, and were replaced by the expression of neuron-, glial-, smooth muscle cell-, or cardiomyocyte-

specific proteins. Cardiosphere-derived cells transplanted into chick embryos migrated to the truncus arteriosus and cardiac outflow tract and contributed to dorsal root ganglia, spinal nerves, and aortic smooth muscle cells. Lineage studies using double transgenic mice encoding protein 0-Cre/Floxed-EGFP revealed undifferentiated and differentiated neural crest-derived cells in the fetal myocardium. Undifferentiated cells expressed GATA-binding protein 4 and nestin, but not actinin, whereas the differentiated cells were identified as cardiomyocytes. These results suggest that cardiac neural crest-derived cells migrate into the heart, remain there as dormant multipotent stem cells-and under the right conditions-differentiate into cardiomyocytes and typical neural crest-derived cells, including neurons, glia, and smooth muscle.

Tuckett, A. Z., et al. (2014). "Image-guided intrathymic injection of multipotent stem cells supports lifelong T-cell immunity and facilitates targeted immunotherapy." Blood **123**(18): 2797-2805.

T-cell deficiency related to disease, medical treatment, or aging represents a major clinical challenge and is associated with significant morbidity and mortality in cancer and bone marrow transplantation recipients. This study describes several innovative and clinically relevant strategies to manipulate thymic function based on an interventional radiology technique for intrathymic injection of cells or drugs. We show that intrathymic injection of multipotent hematopoietic stem/progenitor cells into irradiated syngeneic or allogeneic young or aged recipients resulted in efficient and long-lasting generation of functional donor T cells. Persistence of intrathymic donor cells was associated with intrathymic presence of cells resembling long-term hematopoietic stem cells, suggesting a self-renewal capacity of the intrathymically injected cells. Furthermore, our approach enabled the induction of long-term antigen-specific T-cell-mediated antitumor immunity following intrathymic injection of progenitor cells harboring a transgenic T-cell receptor gene. The intrathymic injection of interleukin-7 prior to irradiation conferred radioprotection. In addition, thymopoiesis of aged mice improved with a single intrathymic administration of low-dose keratinocyte growth factor, an effect that was sustained even in the setting of radiation-induced injury. Taken together, we established a preclinical framework for the development of novel clinical protocols to establish lifelong antigen-specific T-cell immunity.

van de Ven, C., et al. (2007). "The potential of umbilical cord blood multipotent stem cells for nonhematopoietic tissue and cell regeneration." Exp Hematol **35**(12): 1753-1765.

Stem cells have been isolated from human embryos, fetal tissue, umbilical cord blood (UCB), and also from "adult" sources. Adult stem cells are found in many tissues of the body and are capable of maintaining, generating, and replacing terminally differentiated cells. A source of pluripotent stem cells has been recently identified in UCB that can also differentiate across tissue lineage boundaries into neural, cardiac, epithelial, hepatocytic, and dermal tissue. Thus, UCB may provide a future source of stem cells for tissue repair and regeneration. Its widespread availability makes UCB an attractive source for tissue regeneration. UCB-derived stem cells offer multiple advantages over adult stem cells, including their immaturity, which may play a significant role in reduced rejection after transplantation into a mismatched host and their ability to produce larger quantities of homogenous tissue or cells. While research with embryonic stem cells continues to generate considerable controversy, human umbilical stem cells provide an alternative cell source that has been more ethically acceptable and appears to have widespread public support. This review will summarize the in vitro and in vivo studies examining UCB stem cells and their potential use for therapeutic application for nonhematopoietic tissue and cell regeneration.

Veraitch, O., et al. (2017). "Induction of hair follicle dermal papilla cell properties in human induced pluripotent stem cell-derived multipotent LNGFR(+)THY-1(+) mesenchymal cells." Sci Rep **7**: 42777.

The dermal papilla (DP) is a specialised mesenchymal component of the hair follicle (HF) that plays key roles in HF morphogenesis and regeneration. Current technical difficulties in preparing trichogenic human DP cells could be overcome by the use of highly proliferative and plastic human induced pluripotent stem cells (hiPSCs). In this study, hiPSCs were differentiated into induced mesenchymal cells (iMCs) with a bone marrow stromal cell phenotype. A highly proliferative and plastic LNGFR(+)THY-1(+) subset of iMCs was subsequently programmed using retinoic acid and DP cell activating culture medium to acquire DP properties. The resultant cells (induced DP-substituting cells [iDPSCs]) exhibited up-regulated DP markers, interacted with human keratinocytes to up-regulate HF related genes, and when co-grafted with human keratinocytes in vivo gave rise to fibre structures with a hair cuticle-like coat resembling the hair shaft, as confirmed by scanning electron microscope analysis. Furthermore, iDPSCs responded to the clinically used hair growth reagent, minoxidil sulfate, to up-regulate DP genes, further supporting that they were capable of, at least in part, reproducing DP properties. Thus, LNGFR(+)THY-1(+) iMCs may provide material for HF bioengineering and drug screening for hair diseases.

Voog, J., et al. (2008). "Multipotent somatic stem cells contribute to the stem cell niche in the Drosophila testis." Nature **454**(7208): 1132-1136.

Adult stem cells reside in specialized microenvironments, or niches, that have an important role in regulating stem cell behaviour. Therefore, tight control of niche number, size and function is necessary to ensure the proper balance between stem cells and progenitor cells available for tissue homeostasis and wound repair. The stem cell niche in the Drosophila male gonad is located at the tip of the testis where germline and somatic stem cells surround the apical hub, a cluster of approximately 10-15 somatic cells that is required for stem cell self-renewal and maintenance. Here we show that somatic stem cells in the Drosophila testis contribute to both the apical hub and the somatic cyst cell lineage. The Drosophila orthologue of epithelial cadherin (DE-cadherin) is required for somatic stem cell maintenance and, consequently, the apical hub. Furthermore, our data indicate that the transcriptional repressor escargot regulates the ability of somatic cells to assume and/or maintain hub cell identity. These data highlight the dynamic relationship between stem cells and the niche and provide insight into genetic programmes that regulate niche size and function to support normal tissue homeostasis and organ regeneration throughout life.

Wang, L., et al. (2016). "[Efficacy and security of matched unrelated donor hematopoietic stem cell transplant with transfusion of multipotent mesenchymal cells in pediatric severe aplastic anemia]." Zhonghua Xue Ye Xue Za Zhi **37**(6): 453-457.

OBJECTIVE: To observe the efficacy of matched unrelated donor hematopoietic stem cell transplant (HSCT) with transfusion of multipotent mesenchymal cells (MSC) in pediatric severe aplastic anemia (SAA). METHODS: 19 children with SAA received matched unrelated donor HSCT with MSC, and the hematopoietic recovery and transplant-associated complications of these children were monitored. RESULTS: All patients achieved rapid hematopoietic reconstruction after HSCT, and the median durations to neutrophil and platelet recovery were 12 (9-21) days and 14 (8-24) days respectively, but delayed rejection occurred in one case four months after HSCT. 9 cases developed grade acute graft-versus-host (aGVHD), and one case grade aGVHD and diffuse chronic graft-versus-host. Cytomegalovirus viremias were observed in 15 patients. 2 cases developed hemorrhagic cystitis, 10 children experienced infections. All the children were alive during a median following-up time of 27(8-70) months, one of them developed LPD and received rituximab and chemotherapy, delayed rejection occurred in this patient four months after HSCT, Haplo-identical HSCT from his father as the donor was performed and achieved successful engraftment. CONCLUSION: The matched unrelated donor HSCT with MSC in pediatric SAA was safe and effective.

Wang, X., et al. (2013). "Periostin contributes to the acquisition of multipotent stem cell-like properties in human mammary epithelial cells and breast cancer cells." PLoS One **8**(8): e72962.

Periostin (POSTN), a recently characterised matricellular protein, is frequently dysregulated in various malignant cancers and promotes tumor metastatic growth. POSTN plays a critical role in the crosstalk between murine breast cancer stem cells (CSCs) and their niche to permit metastatic colonization. However, whether pro-metastatic capability of POSTN is associated with multipotent potentials of mesenchymal stem cells (MSCs) has not been documented. Here we demonstrate that POSTN promotes a stem cell-like trait and a mesenchymal phenotype in human mammary epithelial cells and breast cancer cells. Interestingly, ectopic overexpression of POSTN or recombinant POSTN treatment can induce human mammary epithelial cells and breast cancer cells differentiation into multiple cell lineages that recapitulate part of the multilineage differentiation potentials of MSCs. Moreover, POSTN is highly expressed in bone marrow-derived MSCs and their derived adipocytes, chondrocytes, and osteoblasts in vitro. Furthermore, POSTN promotes the growth of xenograft tumors in vivo. POSTN-overexpressing human mammary epithelial cells enhance breast tumor growth and metastasis. These data thus provide evidence of a new role for POSTN in mammary epithelial neoplasia and metastasis, suggesting that epithelial cancer cells might acquire CSC-like traits and a mesenchymal phenotype, as well as the multipotent potentials of MSCs to promote tumorigenesis and metastasis. Therefore, targeting POSTN and other extracellular matrix components of tumor microenvironment may help to develop new therapeutical strategies to inhibit tumor metastasis.

Weist, R., et al. (2018). "Differential Expression of Cholinergic System Components in Human Induced Pluripotent Stem Cells, Bone Marrow-Derived Multipotent Stromal Cells, and Induced Pluripotent Stem Cell-Derived Multipotent Stromal Cells." Stem Cells Dev **27**(3): 166-183.

The components of the cholinergic system are evolutionary very old and conserved molecules that are expressed in typical spatiotemporal patterns. They are involved in signaling in the nervous system, whereas their functions in nonneuronal tissues are hardly understood. Stem cells present an attractive cellular system to address functional issues. This study therefore compared human induced pluripotent stem cells (iPSCs; from cord blood endothelial cells),

mesenchymal stromal cells derived from iPSCs (iPSC-MSCs), and bone marrow-derived MSCs (BM-MSCs) from up to 33 different human donors with respect to gene expressions of components of the cholinergic system. The status of cells was identified and characterized by the detection of cell surface antigens using flow cytometry. Acetylcholinesterase expression in iPSCs declined during their differentiation into MSCs and was comparably low in BM-MSCs. Butyrylcholinesterase was present in iPSCs, increased upon transition from the three-dimensional embryoid body phase into monolayer culture, and declined upon further differentiation into iPSC-MSCs. In BM-MSCs a notable butyrylcholinesterase expression could be detected in only four donors, but was elusive in other patient-derived samples. Different nicotinic acetylcholine receptor subunits were preferentially expressed in iPSCs and during early differentiation into iPSC-MSCs, low expression was detected in iPS-MSCs and in BM-MSCs. The m2 and m3 variants of muscarinic acetylcholine receptors were detected in all stem cell populations. In BM-MSCs, these gene expressions varied between donors. Together, these data reveal the differential expression of cholinergic signaling system components in stem cells from specific sources and suggest the utility of our approach to establish informative biomarkers.

Yi, T., et al. (2016). "Single Cell Clones Purified from Human Parotid Glands Display Features of Multipotent Epitheliomesenchymal Stem Cells." Sci Rep **6**: 36303.

A better understanding of the biology of tissue-resident stem cell populations is essential to development of therapeutic strategies for regeneration of damaged tissue. Here, we describe the isolation of glandular stem cells (GSCs) from a small biopsy specimen from human parotid glands. Single colony-forming unit-derived clonal cells were isolated through a modified subfractionation culture method, and their stem cell properties were examined. The isolated clonal cells exhibited both epithelial and mesenchymal stem cell (MSC)-like features, including differentiation potential and marker expression. The cells transiently displayed salivary progenitor phenotypes during salivary epithelial differentiation, suggesting that they may be putative multipotent GSCs rather than progenitor cells. Both epithelial and mesenchymal-expressing putative GSCs, LGR5(+)CD90(+) cells, were found in vivo, mostly in inter-secretory units of human salivary glands. Following in vivo transplantation into irradiated salivary glands of mice, these cells were found to be engrafted around the secretory complexes, where they contributed to restoration of radiation-induced salivary hypofunction. These results showed that multipotent epitheliomesenchymal GSCs are present in glandular mesenchyme, and that isolation of homogenous GSC clones from human salivary glands may promote the precise understanding of biological function of bona fide GSCs, enabling their therapeutic application for salivary gland regeneration.

Zakaria, N., et al. (2015). "Human non-small cell lung cancer expresses putative cancer stem cell markers and exhibits the transcriptomic profile of multipotent cells." BMC Cancer **15**: 84.

BACKGROUND: Despite significant advances in staging and therapies, lung cancer remains a major cause of cancer-related lethality due to its high incidence and recurrence. Clearly, a novel approach is required to develop new therapies to treat this devastating disease. Recent evidence indicates that tumours contain a small population of cells known as cancer stem cells (CSCs) that are responsible for tumour maintenance, spreading and resistant to chemotherapy. The genetic composition of CSCs so far is not fully understood, but manipulation of the specific genes that maintain their integrity would be beneficial for developing strategies to combat cancer. Therefore, the goal of this study isto identify the transcriptomic composition and biological functions of CSCs from non-small cell lung cancer (NSCLC). METHODS: We isolated putative lung CSCs from lung adenocarcinoma cells (A549 and H2170) and normal stem cells from normal bronchial epithelial cells (PHBEC) on the basis of positive expression of stem cell surface markers (CD166, CD44, and EpCAM) using fluorescence-activated cell sorting. The isolated cells were then characterised for their self-renewal characteristics, differentiation capabilities, expression of stem cell transcription factor and in vivo tumouregenicity. The transcriptomic profiles of putative lung CSCs then were obtained using microarray analysis. Significantly regulated genes ($p < 0.05$, fold change (FC) > 2.0) in putative CSCs were identified and further analysed for their biological functions using the Database for Annotation, Visualization, and Integrated Discovery (DAVID). RESULTS: The putative lung CSCs phenotypes of CD166(+)/CD44(+) and CD166(+)/EpCAM(+) showed multipotent characteristics of stem cells, including the ability to differentiate into adipogenic and osteogenic cells, self-renewal, and expression of stem cell transcription factors such as Sox2 and Oct3/4. Moreover, the cells also shows the in vivo tumouregenicity characteristic when transplanted into nude mice. Microarray and bioinformatics data analyses revealed that the putative lung CSCs have molecular signatures of both normal and cancer stem cells and that the most prominent biological functions are associated with angiogenesis, migration, pro-apoptosis and anti-apoptosis, osteoblast differentiation, mesenchymal cell differentiation, and mesenchyme development. Additionally, self-renewal pathways such as the Wnt and hedgehog signalling

pathways, cancer pathways, and extracellular matrix (ECM)-receptor interaction pathways are significantly associated with the putative lung CSCs. CONCLUSION: This study revealed that isolated lung CSCs exhibit the characteristics of multipotent stem cells and that their genetic composition might be valuable for future gene and stem cells therapy for lung cancer.

Zemel'ko, V. I., et al. (2011). "[Multipotent mesenchymal stem cells of desquamated endometrium: isolation, characterization and use as feeder layer for maintenance of human embryonic stem cell lines]." Tsitologiia **53**(12): 919-929.

In this study, we characterize new multipotent human mesenchymal stem cell (MSC) lines derived from desquamated (shedding) endometrium in menstrual blood. The isolated endometrial MSC (eMSC) is an adhesive to plastic heterogeneous population composed mainly of endometrial glandular and stromal cells. The established cell lines meet the criteria of the International Society for Cellular Therapy for defining multipotent human MSC of any origin. The eMSCs have positive expression of CD73, CD90, CD105, CD13, CD29, CD44 markers and the absence of expression of the hematopoietic cell surface antigens CD19, CD34, CD45, CD117, CD130 and HLA-DR (class II). Multipotency of the established eMSC is confirmed by their ability to differentiate into other mesodermal cell types such as osteocytes and adipocytes. Besides, the isolated eMSC lines partially (over 50%) express the pluripotency marker SSEA-4, but do not express Oct-4. Immunofluorescent analysis of the derived cells revealed the expression of the neural precursor markers nestin and beta-III-tubulin. This suggests a neural predisposition of the established eMSC. These cells are characterized by high rate of cell proliferation (doubling time 22-23 h) and high cloning efficiency (about 60%). In vitro the eMSCs undergo more than 45 population doublings revealing normal karyotype without karyotipic abnormalilies. We demonstrate, that the mititotically inactivated eMSCs are perfect feeder cells for human embryonic stem cell lines (hESC) C612 and C910. The eMSC being a feeder culture maintain the pluripotent status of the hESC, which is revealed by the expression of Oct-4, alkaline phosphatase and SSEA-4. When co-culturing, hESC retain their morphology, proliferative rate for more than 40 passages and capability for spontaneous differentiation into embryoid bodies comprising the three embryonic germ layers. Thus, an easy and non-invasive extraction of the eMSC in menstrual blood, their multipotency and high proliferative activity in vitro without karyotypic abnormalities demonstrate the potential of use of these stem cells in regenerative medicine. Using the derived eMSCs as the feeder culture eliminates the risks associated with animal cells while transferring hESC to clinical setting.

Zeng, L., et al. (2015). "Isolation of lung multipotent stem cells using a novel microfluidic magnetic activated cell sorting system." Cell Biol Int **39**(11): 1348-1353.

In recent years, more and more research has shown that the lung is an organ of regenerative potential, with several types of stem/progenitor cells undergoing proliferation and differentiation after lung injury and participating the injury repair process. Mouse lung multipotent stem cells (MLSCs) have extensive self-renewal ability in culture and could differentiate into endothelial and lung epithelial (alveolar epithelial type 1, 2, and Clara) cells in vitro. But the research of MLSCs was limited due to its rarity. In this study, we introduced a novel microfluidic magnetic activated cell sorting system in the isolation of MLSCs. The sorted MLSCs had better viability and purity. They were identified by colony formation efficiency and differentiation ability and they have self-renewal and differentiation capacities, highlighting their stem cell properties.

Zhao, L., et al. (2009). "Comparison of multipotent differentiation potentials of murine primary bone marrow stromal cells and mesenchymal stem cell line C3H10T1/2." Calcif Tissue Int **84**(1): 56-64.

Murine C3H10T1/2 cells have many features of mesenchymal stem cells (MSCs). Whether or not the multipotent differentiation capability of C3H10T1/2 cells is comparable to that of primary bone marrow-derived MSCs (BM-MSCs) was investigated in this study. For in vitro osteogenic differentiation, both BM-MSCs and C3H10T1/2 cells differentiated to osteoblastic cell lineage and showed positive staining for alkaline phosphatase (ALP) and increased mRNA expression of Runx2, Col1alphaI, and osteocalcin. C3H10T1/2 cells and BM-MSCs induced similar amounts of bone formation in the biomaterials. Under chondrogenic induction in the presence of TGF-beta1, cell pellets of both BM-MSCs and C3H10T1/2 cells formed cartilage-like tissues with cartilage matrix components including proteoglycan, type II collagen, and aggrecan. However, C3H10T1/2 cells presented lower adipogenic differentiation potential, with only about 10% C3H10T1/2 cells (but about 70% of BM-MSCs) being committed to adipogenesis. In this study we confirmed that C3H10T1/2 cells coimplanted with osteoconductive scaffolds can form bone spontaneously in vivo and that C3H10T1/2 cells have a basal level of osteocalcin expression, suggesting that they may be a good alternative source of primary BM-MSCs for investigating osteogenic and chondrogenic differentiation in bone or cartilage tissue engineering studies. Caution is needed when using C3H10T1/2

cells for adipogenic studies as they appear to have lower adipogenic potential than BM-MSCs.

Zhao, Y., et al. (2012). "Reversal of type 1 diabetes via islet beta cell regeneration following immune modulation by cord blood-derived multipotent stem cells." BMC Med **10**: 3.

BACKGROUND: Inability to control autoimmunity is the primary barrier to developing a cure for type 1 diabetes (T1D). Evidence that human cord blood-derived multipotent stem cells (CB-SCs) can control autoimmune responses by altering regulatory T cells (Tregs) and human islet beta cell-specific T cell clones offers promise for a new approach to overcome the autoimmunity underlying T1D. METHODS: We developed a procedure for Stem Cell Educator therapy in which a patient's blood is circulated through a closed-loop system that separates lymphocytes from the whole blood and briefly co-cultures them with adherent CB-SCs before returning them to the patient's circulation. In an open-label, phase1/phase 2 study, patients (n=15) with T1D received one treatment with the Stem Cell Educator. Median age was 29 years (range: 15 to 41), and median diabetic history was 8 years (range: 1 to 21). RESULTS: Stem Cell Educator therapy was well tolerated in all participants with minimal pain from two venipunctures and no adverse events. Stem Cell Educator therapy can markedly improve C-peptide levels, reduce the median glycated hemoglobin A1C (HbA1C) values, and decrease the median daily dose of insulin in patients with some residual beta cell function (n=6) and patients with no residual pancreatic islet beta cell function (n=6). Treatment also produced an increase in basal and glucose-stimulated C-peptide levels through 40 weeks. However, participants in the Control Group (n=3) did not exhibit significant change at any follow-up. Individuals who received Stem Cell Educator therapy exhibited increased expression of co-stimulating molecules (specifically, CD28 and ICOS), increases in the number of CD4+CD25+Foxp3+ Tregs, and restoration of Th1/Th2/Th3 cytokine balance. CONCLUSIONS: Stem Cell Educator therapy is safe, and in individuals with moderate or severe T1D, a single treatment produces lasting improvement in metabolic control. Initial results indicate Stem Cell Educator therapy reverses autoimmunity and promotes regeneration of islet beta cells. Successful immune modulation by CB-SCs and the resulting clinical improvement in patient status may have important implications for other autoimmune and inflammation-related diseases without the safety and ethical concerns associated with conventional stem cell-based approaches. TRIAL REGISTRATION: ClinicalTrials.gov number, NCT01350219.

Zhao, Y., et al. (2013). "Targeting insulin resistance in type 2 diabetes via immune modulation of cord blood-derived multipotent stem cells (CB-SCs) in stem cell educator therapy: phase I/II clinical trial." BMC Med **11**: 160.

BACKGROUND: The prevalence of type 2 diabetes (T2D) is increasing worldwide and creating a significant burden on health systems, highlighting the need for the development of innovative therapeutic approaches to overcome immune dysfunction, which is likely a key factor in the development of insulin resistance in T2D. It suggests that immune modulation may be a useful tool in treating the disease. METHODS: In an open-label, phase 1/phase 2 study, patients (N=36) with long-standing T2D were divided into three groups (Group A, oral medications, n=18; Group B, oral medications+insulin injections, n=11; Group C having impaired beta-cell function with oral medications+insulin injections, n=7). All patients received one treatment with the Stem Cell Educator therapy in which a patient's blood is circulated through a closed-loop system that separates mononuclear cells from the whole blood, briefly co-cultures them with adherent cord blood-derived multipotent stem cells (CB-SCs), and returns the educated autologous cells to the patient's circulation. RESULTS: Clinical findings indicate that T2D patients achieve improved metabolic control and reduced inflammation markers after receiving Stem Cell Educator therapy. Median glycated hemoglobin (HbA1C) in Group A and B was significantly reduced from 8.61%+/-1.12 at baseline to 7.25%+/-0.58 at 12 weeks (P=2.62E-06), and 7.33%+/-1.02 at one year post-treatment (P=0.0002). Homeostasis model assessment (HOMA) of insulin resistance (HOMA-IR) demonstrated that insulin sensitivity was improved post-treatment. Notably, the islet beta-cell function in Group C subjects was markedly recovered, as demonstrated by the restoration of C-peptide levels. Mechanistic studies revealed that Stem Cell Educator therapy reverses immune dysfunctions through immune modulation on monocytes and balancing Th1/Th2/Th3 cytokine production. CONCLUSIONS: Clinical data from the current phase 1/phase 2 study demonstrate that Stem Cell Educator therapy is a safe approach that produces lasting improvement in metabolic control for individuals with moderate or severe T2D who receive a single treatment. In addition, this approach does not appear to have the safety and ethical concerns associated with conventional stem cell-based approaches. TRIAL REGISTRATION: ClinicalTrials.gov number, NCT01415726.

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