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

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

Stem Cell

MARSLAND PRESS
Multidisciplinary Academic Journal Publisher

Stem Cell Research Literatures (3)

Mark Herbert, PhD

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

Abstract: Stem cells are derived from embryonic and non-embryonic tissues. Most stem cell studies are for animal stem cells and plants have also stem cell. Stem cells were discovered in 1981 from early mouse embryos. Stem cells have the potential to develop into all different cell types in the living body. Stem cell is a body repair system. When a stem cell divides it can be still a stem cell or become adult cell, such as a brain cell. Stem cells are unspecialized cells and can renew themselves by cell division, and stem cells can also differentiate to adult cells with special functions. Stem cells replace the old cells and repair the damaged tissues. Embryonic stem cells can become all cell types of the body because they are pluripotent. Adult stem cells are thought to be limited to differentiating into different cell types of their tissue of origin. This article introduces recent research reports as references in the related studies.

[Dr. Mark Herbert. **Stem Cell Research Literatures (3).** Stem Cell. 2024;15(1):36-50] ISSN: 1945-4570 (print); ISSN: 1945-4732 (online). http://www.sciencepub.net/stem. 3. doi:10.7537/marsscj150124.03.

Key words: stem cell; life; research; literature

Introduction

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

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

Ahmadyan, S., et al. (2018). "The osmolyte type affects cartilage associated pathologic marker expression during in vitro mesenchymal stem cell chondrogenesis under hypertonic conditions." Cell Mol Biol (Noisy-le-grand) **64**(3): 56-61.

Stem cells' fate during in vitro differentiation is influenced by biophysicochemical cues. Osmotic stress has proved to enhance chondrocyte marker expression, however its potent negative impacts had never been surveyed. We questioned whether specific osmotic conditions, regarding the osmolyte agent, could benefit chondrogenesis while dampening undesired concomitant hypertrophy and inflammatory responses. To examine the potential side effects of hypertonicity, we assessed cell proliferation as well as chondrogenic and hypertrophic marker expression of human Adipose Derived-MSC after a two week induction in chondrogenic media with either NaCl or Sorbitol, as the osmolyte agent to reach a +100 mOsm hypertonic condition. Calcium deposition and TNF-alpha secretion as markers associated with hypertrophy and inflammation were then assayed. While both hyperosmotic conditions upregulated chondrogenic markers, sorbitol had a nearly three times higher chondro-promotive effect and a lesser hypertrophic effect compared to NaCl. Also, a significantly lesser calcium deposition was observed in sorbitol hypertonic group. NaCl showed an anti-proinflammatory effect while sorbitol had no effect on inflammatory markers. The ossification potential and cartilage associated pathologic markers were affected differentially by the type of the osmolyte. Thus, a vigilant application of the osmotic agent is inevitable in order to avoid or reduce undesired hypertrophic and inflammatory phenotype acquisition by MSC during chondrogenic differentiation. Our findings are a step towards developing a more reliable chondrogenic regimen using external hypertonic cues for MSC chondrogenesis with potential applications in chondral lesions cell therapy.

Bertolo, A., et al. (2015). "In vitro cell motility as a potential mesenchymal stem cell marker for multipotency." Stem Cells Transl Med **4**(1): 84-90.

Mesenchymal stem cells (MSCs) are expected to have a fundamental role in future cell-based therapies because of their high proliferative ability, multilineage potential, and immunomodulatory properties. Autologous transplantations have the "elephant in the room" problem of wide donor variability, reflected by variability in MSC quality and characteristics, leading to uncertain outcomes in the use of these cells. We propose life imaging as a tool to characterize populations of human MSCs. Bone marrow MSCs from various donors and in vitro passages were evaluated for their in vitro motility, and the distances were correlated to the adipogenic, chondrogenic, and osteogenic differentiation potentials and the levels of senescence and cell size. Using life-image measuring of track lengths of 70 cells per population for a period of 24 hours, we observed that slow-moving cells had the higher proportion of senescent cells compared with fast ones. Larger cells moved less than smaller ones, and spindle-shaped cells had an average speed. Both fast cells and slow cells were characterized by a low differentiation potential, and average-moving cells were more effective in undergoing all three lineage differentiations. Furthermore, heterogeneity in single cell motility within a population correlated with the average-moving cells, and fast- and slow-moving cells tended toward homogeneity (i.e., a monotonous moving pattern). In conclusion, in vitro cell motility might be a useful tool to quickly characterize and distinguish the MSC population's differentiation potential before additional use.

Bierlein De la Rosa, M., et al. (2017). "Transdifferentiation of brain-derived neurotrophic factor (BDNF)-secreting mesenchymal stem cells significantly enhance BDNF secretion and Schwann cell marker proteins." J Biosci Bioeng **124**(5): 572-582.

The use of genetically modified mesenchymal stem cells (MSCs) is a rapidly growing area of research targeting delivery of therapeutic factors for neuro-repair. Cells can be programmed to hypersecrete various growth/trophic factors such as brain-derived neurotrophic factor (BDNF), glial cell line-derived neurotrophic factor (GDNF), and nerve growth factor (NGF) to promote regenerative neurite outgrowth. In addition to genetic modifications, MSCs can be subjected to transdifferentiation protocols to generate neural cell types to physically and biologically support nerve regeneration. In this study, we have taken a novel approach by combining these two unique strategies and evaluated the impact of transdifferentiating genetically modified MSCs into a Schwann cell-like phenotype. After 8 days in transdifferentiation media, approximately 30-50% of transdifferentiated BDNF-secreting cells immunolabeled for Schwann cell markers such as S100beta, S100, and p75(NTR). An enhancement was observed 20 days after inducing transdifferentiation with minimal decreases in expression levels. BDNF production was quantified by ELISA, and its biological activity tested via the PC12-TrkB cell assay. Importantly, the bioactivity of secreted BDNF was verified by the increased neurite outgrowth of PC12-TrkB cells. These findings demonstrate that not only is BDNF actively secreted by the transdifferentiated BDNF-MSCs, but also that it has the capacity to promote neurite sprouting and regeneration. Given the fact that BDNF production remained stable for over 20 days, we believe that these cells have the capacity to produce sustainable, effective, BDNF concentrations over prolonged time periods and should be tested within an in vivo system for future experiments.

Boozarpour, S., et al. (2016). "Glial cell derived neurotrophic factor induces spermatogonial stem cell marker genes in chicken mesenchymal stem cells." Tissue Cell **48**(3): 235-241.

Mesenchymal stem cells (MSCs) are known with the potential of multi-lineage differentiation. Advances in differentiation technology have also resulted in the conversion of MSCs to other kinds of stem cells. MSCs are considered as a suitable source of cells for biotechnology purposes because they are abundant, easily accessible and well characterized cells. Nowadays small molecules are introduced as novel and efficient factors to differentiate stem cells. In this work, we examined the potential of glial cell derived neurotrophic factor (GDNF) for differentiating chicken MSCs toward spermatogonial stem cells. MSCs were isolated and characterized from chicken and cultured under treatment with all-trans retinoic acid (RA) or glial cell derived neurotrophic factor. Expression analysis of specific genes after 7days of RA treatment, as examined by RT-PCR, proved positive for some germ cell markers such as CVH, STRA8, PLZF and

some genes involved in spermatogonial stem cell maintenance like BCL6b and c-KIT. On the other hand, GDNF could additionally induce expression of POU5F1, and NANOG as well as other genes which were induced after RA treatment. These data illustrated that GDNF is relatively more effective in diverting chicken MSCs towards Spermatogonial stem cell -like cells in chickens and suggests GDNF as a new agent to obtain transgenic poultry, nevertheless, exploitability of these cells should be verified by more experiments.

Chung, T., et al. (2016). "Dihydropyrimidine Dehydrogenase Is a Prognostic Marker for Mesenchymal Stem Cell-Mediated Cytosine Deaminase Gene and 5-Fluorocytosine Prodrug Therapy for the Treatment of Recurrent Gliomas." Theranostics **6**(10): 1477-1490.

We investigated a therapeutic strategy for recurrent malignant gliomas using mesenchymal stem cells (MSC), expressing cytosine deaminase (CD), and prodrug 5-Fluorocytosine (5-FC) as a more specific and less toxic option. MSCs are emerging as a novel cell therapeutic agent with a cancer-targeting property, and CD is considered a promising enzyme in cancer gene therapy which can convert non-toxic 5-FC to toxic 5-Fluorouracil (5-FU). Therefore, use of prodrug 5-FC can minimize normal cell toxicity. Analyses of microarrays revealed that targeting DNA damage and its repair is a selectable option for gliomas after the standard chemo/radio-therapy. 5-FU is the most frequently used anti-cancer drug, which induces DNA breaks. Because dihydropyrimidine dehydrogenase (DPD) was reported to be involved in 5-FU metabolism to block DNA damage, we compared the survival rate with 5-FU treatment and the level of DPD expression in 15 different glioma cell lines. DPD-deficient cells showed higher sensitivity to 5-FU, and the regulation of DPD level by either siRNA or overexpression was directly related to the 5-FU sensitivity. For MSC/CD with 5-FC therapy, DPD-deficient cells such as U87MG, GBM28, and GBM37 showed higher sensitivity compared to DPD-high U373 cells. Effective inhibition of tumor growth was also observed in an orthotopic mouse model using DPD- deficient U87MG, indicating that DPD gene expression is indeed closely related to the efficacy of MSC/CD-mediated 5-FC therapy. Our results suggested that DPD can be used as a biomarker for selecting glioma patients who may possibly benefit from this therapy.

Da, C., et al. (2017). "Effects of irradiation on radioresistance, HOTAIR and epithelial-mesenchymal transition/cancer stem cell marker expression in esophageal squamous cell carcinoma." Oncol Lett **13**(4): 2751-2757.

Radiotherapy is a common therapeutic strategy used to treat esophageal squamous cell carcinoma (ESCC). However, tumor cells often develop radioresistance, thereby reducing treatment efficacy. Here, we aimed to identify the mechanisms through which ESCC cells develop radioresistance and identify associated biomarkers. Eca109 cells were exposed to repeated radiation at 2 Gy/fraction for a total dose of 60 Gy (Eca109R60/2Gy cells). MTT and colony formation assays were performed to measure cell proliferation and compare the radiation biology parameters of Eca109 and Eca109R60/2Gy cells. Cell cycle distributions and apoptosis were assessed by flow cytometry. Reverse transcription-quantitative polymerase chain reaction and western blotting were employed to analyze the expression of HOX transcript antisense RNA (HOTAIR), in addition to biomarkers of the epithelial-mesenchymal transition (EMT) and cancer stem cells (CSCs). Eca109R60/2Gy cells exhibited increased cell proliferation and clone formation, with significantly higher radiobiological parameters compared with the parental Eca109 cells. The Eca109R60/2Gy cells also exhibited significantly decreased accumulation in G2 phase and increased accumulation in S phase. Additionally, the apoptosis rate was significantly lower in Eca109R60/2Gy cells than in parental Eca109 cells. Finally, HOTAIR expression levels and SNAI1 and beta-catenin mRNA and protein expression levels were significantly higher, whereas E-cadherin levels were significantly lower in Eca109R60/2Gy cells than in Eca109 cells. Therefore, our findings demonstrated that radioresistance was affected by the expression of HOTAIR and biomarkers of the EMT and CSCs.

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

STATEMENT OF THE PROBLEM: Stem cells are considered as new implement for tissue regeneration. Several niches in adult human body are colonized by multipotent stem cells but access to these potential reservoirs is often limited. Although human dental pulp stem cells isolated from healthy teeth have been extensively characterized, it is still unknown whether stem cells also exist in reactive lesions of oral cavity such as pyogenic granuloma and peripheral ossifying fibroma which are deliberated as inflammatory proliferation of different cell families. PURPOSE: The aim of this study was to explore for clues to see whether pyogenic granuloma or peripheral ossifying fibroma contain dental mesenchymal stem cell (DMSC). MATERIALS AND METHOD: Four pyogenic granuloma and four peripheral ossifying fibroma specimens were collected by excisional biopsy and preserved in PBS-EDTA at -86 degrees C. Then we cut them in 5microm diameter using Cryostat. Having been rinsed with PBS, the samples were stained with a primary mouse anti-human STRO-1 monoclonal IgM antibody. Afterward, a secondary goat anti-mouse IgM-FITC antibody was applied to detect STRO-1+ cells as probable stem cells by immunofluorescence technique. RESULTS: Immunofluorescence microscopy revealed presence of STRO-1+ cells in these lesions, particularly localized on perivascular zone. The negative control group was not glowing. CONCLUSION: Based on these results, it was found that reactive lesions of pyogenic granuloma and peripheral ossifying fibroma have STRO-1 positive cells, which raises the possibility that these cells may be DMSCs.

Dickinson, S. C., et al. (2017). "The Wnt5a Receptor, Receptor Tyrosine Kinase-Like Orphan Receptor 2, Is a Predictive Cell Surface Marker of Human Mesenchymal Stem Cells with an Enhanced Capacity for Chondrogenic Differentiation." Stem Cells **35**(11): 2280-2291.

Multipotent mesenchymal stem cells (MSCs) have enormous potential in tissue engineering and regenerative medicine. However, until now, their development for clinical use has been severely limited as they are a mixed population of cells with varying capacities for lineage differentiation and tissue formation. Here, we identify receptor tyrosine kinase-like orphan receptor 2 (ROR2) as a cell surface marker expressed by those MSCs with an enhanced capacity for cartilage formation. We generated clonal human MSC populations with varying capacities for chondrogenesis. ROR2 was identified through screening for upregulated genes in the most chondrogenic clones. When isolated from uncloned populations, ROR2+ve MSCs were significantly more chondrogenic than either ROR2-ve or unfractionated MSCs. In a sheep cartilage-repair model, they produced significantly more defect filling with no loss of cartilage quality compared with controls. ROR2+ve MSCs/perivascular cells were present in developing human cartilage, adult bone marrow, and adipose tissue. Their frequency in bone marrow was significantly lower in patients with osteoarthritis (OA) than in controls. However, after isolation of these cells and their initial expansion in vitro, there was greater ROR2 expression in the population derived from OA patients compared with controls. Furthermore, osteoarthritis-derived MSCs were better able to form cartilage than MSCs from control patients in a tissue engineering assay. We conclude that MSCs expressing high levels of ROR2 provide a defined population capable of predictably enhanced cartilage production. Stem Cells 2017;35:2280-2291.

Djouad, F., et al. (2014). "Promyelocytic leukemia zinc-finger induction signs mesenchymal stem cell commitment: identification of a key marker for stemness maintenance?" Stem Cell Res Ther **5**(1): 27.

INTRODUCTION: Mesenchymal stem cells (MSCs) are an attractive cell source for cartilage and bone tissue engineering given their ability to differentiate into chondrocytes and osteoblasts. However, the common origin of these two specialized cell types raised the question about the identification of regulatory pathways determining the differentiation fate of MSCs into chondrocyte or osteoblast. METHODS: Chondrogenesis, osteoblastogenesis, and adipogenesis of human and mouse MSC were induced by using specific inductive culture conditions. Expression of promyelocytic leukemia zinc-finger (PLZF) or differentiation markers in MSCs was determined by RT-qPCR. PLZF-expressing MSC were implanted in a mouse osteochondral defect model and the neotissue was analyzed by routine histology and microcomputed tomography. RESULTS: We found out that PLZF is not expressed in MSCs and its expression at early stages of MSC

differentiation is the mark of their commitment toward the three main lineages. PLZF acts as an upstream regulator of both Sox9 and Runx2, and its overexpression in MSC enhances chondrogenesis and osteogenesis while it inhibits adipogenesis. In vivo, implantation of PLZF-expressing MSC in mice with full-thickness osteochondral defects resulted in the formation of a reparative tissue resembling cartilage and bone. CONCLUSIONS: Our findings demonstrate that absence of PLZF is required for stemness maintenance and its expression is an early event at the onset of MSC commitment during the differentiation processes of the three main lineages.

Farahani, R. M. and M. Xaymardan (2015). "Platelet-Derived Growth Factor Receptor Alpha as a Marker of Mesenchymal Stem Cells in Development and Stem Cell Biology." Stem Cells Int **2015**: 362753.

Three decades on, the mesenchymal stem cells (MSCs) have been intensively researched on the bench top and used clinically. However, ambiguity still exists in regard to their anatomical locations, identities, functions, and extent of their differentiative abilities. One of the major impediments in the quest of the MSC research has been lack of appropriate in vivo markers. In recent years, this obstacle has been resolved to some degree as PDGFRalpha emerges as an important mesenchymal stem cell marker. Accumulating lines of evidence are showing that the PDGFRalpha (+) cells reside in the perivascular locations of many adult interstitium and fulfil the classic concepts of MSCs in vitro and in vivo. PDGFRalpha has long been recognised for its roles in the mesoderm formation and connective tissue development during the embryogenesis. Current review describes the lines of evidence regarding the role of PDGFRalpha in morphogenesis and differentiation and its implications for MSC biology.

Guan, X., et al. (2014). "Evaluation of CD24 as a marker to rapidly define the mesenchymal stem cell phenotype and its differentiation in human nucleus pulposus." Chin Med J (Engl) **127**(8): 1474-1481.

BACKGROUND: Recent studies have indicated that human nucleus pulposus contain mesenchymal stem cells (NP-MSCs). However, the immunophenotypic variation of NP-MSCs in vitro was unclear. The present study was conducted to address the immunophenotypic variation of mesenchymal stem cells in nucleus pulposus under continuous proliferation in vitro and show the difference between mesenchymal stem cells and nucleus pulposus cell. METHODS: Tissue samples were obtained from thoracolumbar burst fracture patients and degenerative disc disease patients who underwent discectomy and fusion procedures. Flow cytometric and laser scanning confocal microscope (LSCM) were used to detect the variation of mesenchymal stem cells in nucleus pulposus which were expressing CD105 and CD24 in condition with or without transforming growth factor beta1 (TGF-beta1). RESULTS: More than 90% of the analyzed primary cells of mesenchymal stem cells in nucleus pulposus fulfilled the general immunophenotyping criteria for MSCs, such as CD44, CD105 and CD29, but the marker of mature NP cells characterized as CD24 was negative. In continuous cultures, the proportion of mesenchymal stem cells which were expressing CD44, CD105 and CD29 in nucleus pulposus gradually decreased. The mesenchymal stem cells in nucleus pulposus cells were positive for CD105 and CD29, with slight positivity for CD44. The CD24 expression gradually increased in proliferation. Biparametric flow cytometry and laser scanning confocal microscopy confirmed the presence of cells which were expressing CD105 and CD24 independently, and only a small part of cells expressed both CD105 and CD24 simultaneously. TGF-beta1 could stimulate mesenchymal stem cells in nucleus pulposus to express CD24. CONCLUSIONS: Non-degenerative and degenerative NP contains mesechymal stem cells. The variation of CD24 can be used as a marker to identify the NP-MSCs differentiation into NP-like cells.

Hirvonen, T., et al. (2013). "Production of a recombinant antibody specific for i blood group antigen, a mesenchymal stem cell marker." Biores Open Access **2**(5): 336-345.

Multipotent mesenchymal stem/stromal cells (MSCs) offer great promise for future regenerative and anti-inflammatory therapies. Panels of functional and phenotypical markers are currently used in characterization of different therapeutic stem cell populations from various sources. The i antigen (linear poly-N-acetyllactosamine) from the Ii blood group system has been suggested as a marker

for MSCs derived from umbilical cord blood (UCB). However, there are currently no commercially available antibodies recognizing the i antigen. In the present study, we describe the use of antibody phage display technology to produce recombinant antibodies recognizing a structure from the surface of mesenchymal stem cells. We constructed IgM phage display libraries from the lymphocytes of a donor with an elevated serum anti-i titer. Antibody phage display technology is not dependent on immunization and thus allows the generation of antibodies against poorly immunogenic molecules, such as carbohydrates. Agglutination assays utilizing i antigen-positive red blood cells (RBCs) from UCB revealed six promising single-chain variable fragment (scFv) antibodies, three of which recognized epitopes from the surface of UCB-MSCs in flow cytometric assays. The amino acid sequence of the VH gene segment of B12.2 scFv was highly similar to the VH4.21 gene segment required to encode anti-i specificities. Further characterization of binding properties revealed that the binding of B12.2 hyperphage was inhibited by soluble linear lactosamine oligosaccharide. Based on these findings, we suggest that the B12.2 scFv we have generated is a prominent anti-i antibody that recognizes i antigen on the surface of both UCB-MSCs and RBCs. This binder can thus be utilized in UCB-MSC detection and isolation as well as in blood group serology.

Ishimine, H., et al. (2013). "N-Cadherin is a prospective cell surface marker of human mesenchymal stem cells that have high ability for cardiomyocyte differentiation." Biochem Biophys Res Commun **438**(4): 753-759.

Mesenchymal stem cells (MSCs) are among the most promising sources of stem cells for regenerative medicine. However, the range of their differentiation ability is very limited. In this study, we explored prospective cell surface markers of human MSCs that readily differentiate into cardiomyocytes. When the cardiomyogenic differentiation potential and the expression of cell surface markers involved in heart development were analyzed using various immortalized human MSC lines, the MSCs with high expression of N-cadherin showed a higher probability of differentiation into beating cardiomyocytes. The differentiated cardiomyocytes expressed terminally differentiated cardiomyocyte-specific markers such as alpha-actinin, cardiac troponin T, and connexin-43. A similar correlation was observed with primary human MSCs derived from bone marrow and adipose tissue. Moreover, N-cadherin-positive MSCs isolated with N-cadherin antibody-conjugated magnetic beads showed an apparently higher ability to differentiate into cardiomyocytes than the N-cadherin-negative population. Quantitative polymerase chain reaction analyses demonstrated that the N-cadherin-positive population expressed significantly elevated levels of cardiomyogenic progenitor-specific transcription factors, including Nkx2.5, Hand1, and GATA4 mRNAs. Our results suggest that N-cadherin is a novel prospective cell surface marker of human MSCs that show a better ability for cardiomyocyte differentiation.

Ishimura, D., et al. (2008). "Differentiation of adipose-derived stromal vascular fraction culture cells into chondrocytes using the method of cell sorting with a mesenchymal stem cell marker." Tohoku J Exp Med **216**(2): 149-156.

The incidence of arthritic diseases is rapidly increasing in most advanced countries. Articular cartilage, which is the most important tissue in the joint, consists of chondrocytes and abundant extracellular matrix, including aggrecan, and shows poor self-repair. We studied the potential of stem cells in mouse subcutaneous adipose tissue as a source of cells to regenerate cartilage tissue. Analysis of adipose-derived stromal vascular fraction culture cells (ADSVFs) using mesenchymal stem cell markers showed that CD90-positive cells accounted for 93.8%, CD105-positive cells for 68.5%, and p75 neurotrophin receptor (p75NTR, CD271)-positive cells for 36.1%. These results indicate that cells positive for mesenchymal stem cell markers are present in ADSVFs. The CD105-positive or -negative cells were isolated from ADSVFs by magnetic cell separation (MACS), and the efficiency of differentiation into chondrocytes was compared with using three methods of pellet method, gel-coating method, and gel-embedding sheet method. Using the CD105-positive cells and the gel-embedding sheet method, aggrecan mRNA was detected about three times higher than pellet and gel-coating methods. The above data suggest that ADSVFs could be differentiated into chondrocyte-like cells in the gel-embedding sheet method and could be useful in

regenerative medicine to treat cartilage defects or cartilage degenerative disease. The use of cells sorted by mesenchymal stem cell markers from adipose tissue would gain position in the repair of cartilage tissue.

Li, Z., et al. (2013). "Effect of cell culture using chitosan membranes on stemness marker genes in mesenchymal stem cells." Mol Med Rep **7**(6): 1945-1949.

Mesenchymal stem cell (MSC) therapy is a promising treatment for diseases of the nervous system. However, MSCs often lose their stemness and homing abilities when cultured in conventional twodimensional (2D) systems. Consequently, it is important to explore novel culture methods for MSC-based therapies in clinical practice. To investigate the effect of a cell culture using chitosan membranes on MSCs, the morphology of MSCs cultured using chitosan membranes was observed and the expression of stemness marker genes was analyzed. We demonstrated that MSCs cultured using chitosan membranes form spheroids. Additionally, the expression of stemness marker genes, including Oct4, Sox2 and Nanog, increased significantly when MSCs were cultured using chitosan membranes compared with 2D culture systems. Finally, MSCs cultured using chitosan membranes were found to have an increased potential to differentiate into nerve cells and chrondrocytes. In conclusion, we demonstrated that MSCs cultured on chitosan membranes maintain their stemness and homing abilities. This finding may be further investigated for the development of novel cell-based therapies for diseases involving neuron-like cells and chondrogenesis.

Lin, G., et al. (2011). "Tissue distribution of mesenchymal stem cell marker Stro-1." Stem Cells Dev **20**(10): 1747-1752.

Stro-1 is the best-known mesenchymal stem cell marker. However, despite its bone marrow origin, its localization in bone marrow has never been demonstrated. By immunofluorescence staining, we show here that approximately 0.74% of nucleated bone marrow cells expressed Stro-1. We also found that approximately 8.7% of CD34-expressing cells expressed Stro-1, and more than 20% of Stro-1-expressing cells did not express CD34. In adipose tissue Stro-1 expression was identified in the endothelium of arterioles and capillaries. Stro-1 was also localized in the endothelium of some but not all adipose tissue veins. Endothelial expression of Stro-1 was also identified in blood vessels in penis and in leg muscles, but not in other tested tissues. In these other tissues, Stro-1 was scantly expressed near but not in blood vessels. These variable and endothelial expression patterns of Stro-1 point to a need to re-examine published data that relied on Stro-1 as a mesenchymal stem cell marker.

Madsen, S. D., et al. (2017). "Decoy TRAIL receptor CD264: a cell surface marker of cellular aging for human bone marrow-derived mesenchymal stem cells." Stem Cell Res Ther **8**(1): 201.

BACKGROUND: Mesenchymal stem cells (MSCs) are a mixture of progenitors that are heterogeneous in their regenerative potential. Development of MSC therapies with consistent efficacy is hindered by the absence of an immunophenotype of MSC heterogeneity. This study evaluates decoy TRAIL receptor CD264 as potentially the first surface marker to detect cellular aging in heterogeneous MSC cultures. METHODS: CD264 surface expression, regenerative potential, and metrics of cellular aging were assessed in vitro for marrow MSCs from 12 donors ages 20-60 years old. Male and female donors were age matched. Expression of CD264 was compared with that of p16, p21, and p53 during serial passage of MSCs. RESULTS: When CD264(+) cell content was 20% to 35%, MSC cultures from young (ages 20-40 years) and older (ages 45-60 years) donors proliferated rapidly and differentiated extensively. Older donor MSCs containing < 35% CD264(+) cells had a small size and negligible senescence despite the donor's advanced chronological age. Above the 35% threshold, CD264 expression inversely correlated with proliferation and differentiation potential. When CD264(+) cell content was 75%, MSCs were enlarged and mostly senescent with severely compromised regenerative potential. There was no correlation of the older donors' chronological age to either CD264(+) cell content or the regenerative potential of the donor MSCs. CD264 was upregulated after p53 and had a similar expression profile to that of p21 during serial passage of MSCs. No sex-linked differences were detected in this study. CONCLUSIONS: These results suggest that CD264 is a surface marker of cellular age for MSCs, not the chronological age of the MSC

donor. CD264 is first upregulated in MSCs at an intermediate stage of cellular aging and remains upregulated as aging progresses towards senescence. The strong inverse correlation of CD264(+) cell content to the regenerative potential of MSCs has possible application to assess the therapeutic potential of patient MSCs, standardize the composition and efficacy of MSC therapies, and facilitate aging research on MSCs.

Mercati, F., et al. (2009). "Expression of mesenchymal stem cell marker CD90 on dermal sheath cells of the anagen hair follicle in canine species." Eur J Histochem **53**(3): 159-166.

The dermal sheath (DS) of the hair follicle is comprised by fibroblast-like cells and extends along the follicular epithelium, from the bulb up to the infundibulum. From this structure, cells with stem characteristics were isolated: they have a mesenchymal origin and express CD90 protein, a typical marker of mesenchymal stem cells. It is not yet really clear in which region of hair follicle these cells are located but some experimental evidence suggests that dermal stem cells are localized prevalently in the lower part of the anagen hair follicle. As there are no data available regarding DS stem cells in dog species, we carried out a morphological analysis of the hair follicle DS and performed both an immunohistochemical and an immunocytochemical investigation to identify CD90+ cells. We immunohistochemically evidenced a clear and abundant positivity to CD90 protein in the DS cells located in the lower part of anagen hair follicle. The positive cells showed a typical fibroblast-like morphology. They were flat and elongated and inserted among bundles of collagen fibres. The whole structure formed a close and continuous sleeve around the anagen hair follicle. Our immunocytochemical study allowed us to localize CD90 protein at the cytoplasmic membrane level.

Mercati, F., et al. (2009). "Expression of mesenchymal stem cell marker CD90 on dermal sheath cells of the anagen hair follicle in canine species." Eur J Histochem **53**(3): e19.

The dermal sheath (DS) of the hair follicle is comprised by fibroblast-like cells and extends along the follicular epithelium, from the bulb up to the infundibulum. From this structure, cells with stem characteristics were isolated: they have a mesenchymal origin and express CD90 protein, a typical marker of mesenchymal stem cells. It is not yet really clear in which region of hair follicle these cells are located but some experimental evidence suggests that dermal stem cells are localized prevalently in the lower part of the anagen hair follicle. As there are no data available regarding DS stem cells in dog species, we carried out a morphological analysis of the hair follicle DS and performed both an immunohistochemical and an immunocytochemical investigation to identify CD90(+) cells. We immunohistochemically evidenced a clear and abundant positivity to CD90 protein in the DS cells located in the lower part of anagen hair follicle. The positive cells showed a typical fibroblast-like morphology. They were flat and elongated and inserted among bundles of collagen fibres.The whole structure formed a close and continuous sleeve around the anagen hair follicle. Our immunocytochemical study allowed us to localize CD90 protein at the cytoplasmic membrane level.

Nam, K. H., et al. (2017). "Predictive value for lymph node metastasis of epithelial-mesenchymal transition and cancer stem cell marker expression in early gastric cancer." Pathol Res Pract **213**(9): 1221-1226.

BACKGROUND: Minimally invasive therapies, including endoscopic mucosal resection or sentinel node navigation surgery, have been widely applied in early gastric cancer because of their benefits in promoting patient quality of life. However, lymph node dissection is beyond the capability of endoscopic therapy, and in sentinel node navigation surgery, the potential for skip metastasis is not negligible. Therefore, the possibility of lymph node metastasis is the most important factor to consider when deciding whether to apply the minimally invasive therapies. In the present study, the significance of epithelial mesenchymal transition and stem cell marker expression in lymph node metastasis in early gastric cancer was investigated. METHODS: We evaluated the significance of the expression of 5 epithelial mesenchymal transition-related markers (E-cadherin, MMP7, S100A, Snail-1, and HGF) and 6 stem cell markers (ALDH1, SOX2, CD24, CD44, CD54, and CD133) in 119 early gastric cancer specimens using immunohistochemistry. Because protein expression is heterogeneous in gastric cancer, we analyzed the expression of these markers

in two selected regions (one each at the superficial zone and the deep invasive front). RESULTS: Expression of E-cadherin, MMP7, HGF, and CD133 at the deep invasive front was associated with the absence of lymph node metastasis (P=0.013, 0.018, <0.001, and 0.026, respectively). Presence of diffuse-type component, lymphatic invasion, and lack of expression of HGF and CD133 at the deep invasive front were independent predictive markers of lymph node metastasis (P=0.019, <0.001, 0.015, and 0.047, respectively). CONCLUSIONS: Lymph node metastasis is strongly associated with expression status of HGF and CD133 at the deep invasive front, suggesting the usefulness of these proteins as independent predictive markers of lymph node metastasis in early gastric cancer.

Naylor, A. J., et al. (2012). "The mesenchymal stem cell marker CD248 (endosialin) is a negative regulator of bone formation in mice." Arthritis Rheum **64**(10): 3334-3343.

OBJECTIVE: CD248 (tumor endothelial marker 1/endosialin) is found on stromal cells and is highly expressed during malignancy and inflammation. Studies have shown a reduction in inflammatory arthritis in CD248-knockout (CD248(-/-)) mice. The aim of the present study was to investigate the functional effect of genetic deletion of CD248 on bone mass. METHODS: Western blotting, polymerase chain reaction, and immunofluorescence were used to investigate the expression of CD248 in humans and mice. Micro-computed tomography and the 3-point bending test were used to measure bone parameters and mechanical properties of the tibiae of 10-week-old wild-type (WT) or CD248(-/-) mice. Human and mouse primary osteoblasts were cultured in medium containing 10 mM beta-glycerophosphate and 50 mug/ml ascorbic acid to induce mineralization, and then treated with platelet-derived growth factor BB (PDGF-BB). The mineral apposition rate in vivo was calculated by identifying newly formed bone via calcein labeling. RESULTS: Expression of CD248 was seen in human and mouse osteoblasts, but not osteoclasts. CD248(-/-) mouse tibiae had higher bone mass and superior mechanical properties (increased load required to cause fracture) compared to WT mice. Primary osteoblasts from CD248(-/-) mice induced increased mineralization in vitro and produced increased bone over 7 days in vivo. There was no decrease in bone mineralization and no increase in proliferation of osteoblasts in response to stimulation with PDGF-BB, which could be attributed to a defect in PDGF signal transduction in the CD248(-/-) mice. CONCLUSION: There is an unmet clinical need to address rheumatoid arthritis-associated bone loss. Genetic deletion of CD248 in mice results in high bone mass due to increased osteoblast-mediated bone formation, suggesting that targeting CD248 in rheumatoid arthritis may have the effect of increasing bone mass in addition to the previously reported effect of reducing inflammation.

Ning, H., et al. (2011). "Mesenchymal stem cell marker Stro-1 is a 75 kd endothelial antigen." Biochem Biophys Res Commun **413**(2): 353-357.

Stro-1 is the best-known mesenchymal stem cell (MSC) marker. However, previous studies have observed its expression in the endothelium. In the present study we performed immunofluorescence (IF) staining for Stro-1, using endothelial marker vWF as reference. In the liver, both proteins were expressed in the endothelium of the central veins and hepatic sinusoids. In the lung, both were expressed in the endothelium of pulmonary blood vessels, but while vWF was absent in the alveolar capillaries, Stro-1 was present. In the kidney, both were expressed in the endothelium of renal arterial branches, but while vWF was strongly expressed in the glomeruli, Stro-1 only scantly. IF staining in cultured endothelial cells also showed extensive overlaps between Stro-1 and vWF. Western blot analysis with Stro-1 antibody detected a single protein band of 75 kd in endothelial cells but not smooth muscle cells, fibroblasts, or B cells. Cancer cell lines PC3, DU145, MCF7, and K562 were also positive. Adipose-derived stem cells (ADSCs) expressed higher levels of Stro-1 when cultured beyond the first passage or when induced to differentiate into endothelial cells. These data, together with previous studies, indicate that Stro-1 is intrinsically an endothelial antigen, and its expression in MSC is probably an induced event.

Ning, X., et al. (2018). "Ectopic expression of miR-147 inhibits stem cell marker and epithelial-mesenchymal transition (EMT)-related protein expression in colon cancer cells." Oncol Res.

Colon cancer is one of the most common cancers in the world. Epithelial-to-mesenchymal transition (EMT) is a crucial step in tumor progression and also involves in the acquisition of stem cell-like properties. Some miRNAs have been shown to function as either tumor suppressors or oncogenes in colon cancer. Here, we investigated the role of miR-147 in the regulation of stem cell-like traits of colon cancer cells. We observed that miR-147 was down-regulated in several colon cancer cell lines and overexpressed miR-147 decreased the expression of cancer stem cell (CSC) markers OCT4, SOX2 and NANOG in colon cancer cells (HCT116, SW480). Besides that, overexpressed miR-147 inhibited EMT by increasing the expression of epithelial markers Ecadherin and alpha-catenin while decreasing the expression of mesenchymal markers fibronectin and vimentin. Moreover, activation of EMT by TGF-beta1 treatment counteracted the inhibitive effect of miR-147 on the expression of CSC markers OCT4, SOX2 and NANOG significantly, supporting that overexpressed miR-147 inhibited stem cell-like traits by suppressing EMT in colon cancer. In addition, we found that overexpressed miR-147 down-regulated the expression of beta-Catenin, c-myc and Survivin which were related to Wnt/beta-Catenin pathway. Moreover, treatment with Wnt/beta-Catenin pathway activator Licl in miR-147 mimic transfected cells attenuated the inhibitive effect of miR-147 mimic on EMT and stem cell-like traits of colon cancer cells, indicating that ectopic expression of miR-147 inhibited stem cell-like traits in colon cancer cells through suppressing EMT via the Wnt/beta-Catenin pathway. In summary, our present study highlighted the crucial role of miR-147 in the inhibition of stem cell-like traits of colon cancer cells and indicated that miR-147 could be a promising therapeutic target for colon cancer treatment.

Park, J. Y., et al. (2013). "Comparative analysis of mesenchymal stem cell surface marker expression for human dental mesenchymal stem cells." Regen Med **8**(4): 453-466.

AIM: Human dental mesenchymal stem cells (hDMSCs) have been isolated from extracted human teeth and proven to have different proliferation and differentiation abilities among the subtypes. Despite increasing interest in the clinical use of hDMSCs, a well-defined specific marker has been absent for these stem cells. In this study, a comparative analysis with known mesenchymal stem cell surface markers such as STRO-1, CD90, CD146, CD34 and TfR (CD71) was performed. MATERIALS & METHODS: Four subtypes of the hDMSCs were obtained and cultured. The hDMSCs were processed by flow cytometric analysis, fluorescence immunocytostaining for in vitro study and in situ immunohistochemical staining for in vivo study. RESULTS & CONCLUSION: The previously known positive and negative MSC markers, such as STRO-1, CD90, CD146 and CD34 showed comparative expression profiles of hDMSC subtypes. TfR was highly positive in hDMSCs compared with the control cells; therefore, TfR was suggested as a new marker for hDMSCs in this study.

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

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

SSEA-4, whereas heart MSCs express Oct4, Nanog, SOX2 and SSEA-4. Our results also indicate that human adult mesenchymal stem cells preserve tissue-specific differences under in vitro culture conditions during early passages, as shown by distinct germ layer and embryonic stem cell marker expression patterns. Studies are now needed to determine the functional role of embryonic stem cell markers Oct4, Nanog and SOX2 in adult human MSCs.

Schinke, C., et al. (2018). "The Pattern of Mesenchymal Stem Cell Expression Is an Independent Marker of Outcome in Multiple Myeloma." Clin Cancer Res **24**(12): 2913-2919.

Purpose: Mesenchymal stem cells (MSC) are an essential component of the bone marrow microenvironment and have shown to support cancer evolution in multiple myeloma. Despite the increasing evidence that multiple myeloma MSCs differ from their healthy counterparts, little knowledge exists as to whether MSCs independently influence disease outcome. The aim of this study was to determine the importance of MSCs in disease progression and outcome in multiple myeloma.Experimental Design: To determine the impact of MSCs on multiple myeloma outcome in an in vivo system, we first identified genes from cultured MSCs that were specific to MSC expression and were not or minimally expressed in plasma cells (PC) or other cells present in bone marrow aspirates. We then applied this MSC gene signature to whole bone marrow biopsies of multiple myeloma patients compared with healthy controls and determined MSC expression scores specific to multiple myeloma and predictive of outcome.Results: We show that multiple myeloma MSC gene expression signatures can differentiate multiple myeloma from monoclonal gammopathy and smoldering multiple myeloma (SMM) as well as from healthy controls and treated multiple myeloma patients who have achieved a complete remission. We identified a prognostic gene score based on three MSC specific genes, COL4A1, NPR3 and ITGBL1, that was able to predict progression-free survival in multiple myeloma patients and progression into multiple myeloma from SMM.Conclusions: Our findings show that progression of multiple myeloma and of SMM into multiple myeloma does not rely solely on intrinsic PC factors, but is independently affected by the biology of the surrounding microenvironment. Clin Cancer Res; 24(12); 2913-9. (c)2018 AACR.

Sullivan, K. E., et al. (2017). "The stem cell/cancer stem cell marker ALDH1A3 regulates the expression of the survival factor tissue transglutaminase, in mesenchymal glioma stem cells." Oncotarget **8**(14): 22325-22343.

Tissue transglutaminase (tTG), a dual-function enzyme with GTP-binding and acyltransferase activities, has been implicated in the survival and chemotherapy resistance of aggressive cancer cells and cancer stem cells, including glioma stem cells (GSCs). Using a model system comprising two distinct subtypes of GSCs referred to as proneural (PN) and mesenchymal (MES), we find that the phenotypically aggressive and radiation therapy-resistant MES GSCs exclusively express tTG relative to PN GSCs. As such, the self-renewal, proliferation, and survival of these cells was sensitive to treatment with tTG inhibitors, with a benefit being observed when combined with the standard of care for high grade gliomas (i.e. radiation or temozolomide). Efforts to understand the molecular drivers of tTG expression in MES GSCs revealed an unexpected link between tTG and a common marker for stem cells and cancer stem cells, Aldehyde dehydrogenase 1A3 (ALDH1A3). ALDH1A3, as well as other members of the ALDH1 subfamily, can function in cells as a retinaldehyde dehydrogenase to generate retinoic acid (RA) from retinal. We show that the enzymatic activity of ALDH1A3 and its product, RA, are necessary for the observed expression of tTG in MES GSCs. Additionally, the ectopic expression of ALDH1A3 in PN GSCs is sufficient to induce the expression of tTG in these cells, further demonstrating a causal link between ALDH1A3 and tTG. Together, these findings ascribe a novel function for ALDH1A3 in an aggressive GSC phenotype via the up-regulation of tTG, and suggest the potential for a similar role by ALDH1 family members across cancer types.

Vanella, L., et al. (2011). "Crosstalk between EET and HO-1 downregulates Bach1 and adipogenic marker expression in mesenchymal stem cell derived adipocytes." Prostaglandins Other Lipid Mediat **96**(1-4): 54-62.

Epoxygenase activity and synthesis of epoxyeicosatrienoic acids (EETs) have emerged as important modulators of obesity

and diabetes. We examined the effect of the EET-agonist 12-(3-hexylureido)dodec-8(2) enoic acid on mesenchymal stem cell (MSC) derived adipocytes proliferation and differentiation. MSCs expressed substantial levels of EETs and inhibition of soluble epoxide hydrolase (sEH) increased the level of EETs and decreased adipogenesis. EET agonist treatment increased HO-1 expression by inhibiting a negative regulator of HO-1 expression, Bach-1. EET treatment also increased betacatenin and pACC levels while decreasing PPARgamma C/EBPalpha and fatty acid synthase levels. These changes were manifested by a decrease in the number of large inflammatory adipocytes, TNFalpha, IFNgamma and IL-1alpha, but an increase in small adipocytes and in adiponectin levels. In summary, EET agonist treatment inhibits adipogenesis and decreases the levels of inflammatory cytokines suggesting the potential action of EETs as intracellular lipid signaling modulators of adipogenesis and adiponectin.

Wirths, S., et al. (2013). "Shared cell surface marker expression in mesenchymal stem cells and adult sarcomas." Stem Cells Transl Med **2**(1): 53-60.

Advanced adult soft-tissue sarcomas (STSs) are rare tumors with a dismal prognosis and limited systemic treatment options. STSs may originate from mesenchymal stem cells (MSCs); the latter have mainly been isolated from adult bone marrow as plastic-adherent cells with differentiation capacity into mesenchymal tissues. Recently, a panel of antibodies has been established that allows for the prospective isolation of primary MSCs with high selectivity. Similar to cancer stem cells in other malignancies, sarcoma stem cells may bear immunophenotypic similarity with the corresponding precursor, that is, MSCs. We therefore set out to establish the expression pattern of MSC markers in sarcoma cell lines and primary tumor samples by flow cytometry. In addition, fibroblasts from different sources were examined. The results document a significant amount of MSC markers shared by sarcoma cells. The expression pattern includes uniformly expressed markers, as well as MSC markers that only stained subpopulations of sarcoma cells. Expression of W5C5, W8B2 (tissue nonspecific alkaline phosphatase [TNAP]), CD344 (frizzled-4), and CD271 marked subpopulations displaying increased proliferation potential. Moreover, CD271+ cells displayed in vitro doxorubicin resistance and an increased capacity to form spheres under serum-free conditions. Interestingly, another set of antigens, including the bona fide progenitor cell markers CD117 and CD133, were not expressed. Comparative expression patterns of novel MSC markers in sarcoma cells, as well as fibroblasts and MSCs, are presented. Our data suggest a hierarchical cytoarchitecture of the most common adult type sarcomas and introduce W5C5, TNAP, CD344, and CD271 as potential sarcoma progenitor cell markers.

Xu, G. F., et al. (2014). "Combined epithelial-mesenchymal transition with cancer stem cell-like marker as predictors of recurrence after radical resection for gastric cancer." World J Surg Oncol **12**: 368.

BACKGROUND: The aim of the study was to identify the incidence and the predictors of recurrence after curative resection and the clinical significance of epithelial-mesenchymal transition (EMT) and stem cell-like phenotypes in gastric cancer. METHODS: In a total of 1,463 patients that underwent curative resection for gastric cancer between January 2001 and January 2008 at Drum Tower Hospital, 402 (27.5%) experienced recurrence. They were divided into early recurrence (within two years) and late recurrence (more than two years). The clinicopathological characteristics, including five EMT-related proteins (Snail-1, ZEB-1, E-cadherin, vimentin, and beta-catenin) and the gastric cancer stem cell markers CD44 and CD54, therapeutic modalities, survival time after recurrence, and recurrence patterns were compared between the two groups. RESULTS: Loss of E-cadherin expression and aberrant expression of vimentin and the known gastric cancer stem cell maker CD44 were significantly associated with aggressive clinicopathologic features. Multivariate analysis showed that stage III gastric cancer patients with early recurrence had larger tumors and more lymph node metastasis, coupled with aberrant expression EMT and cancer stem cell marker, than patients with late recurrence. Early recurrence was associated with more distant metastasis than late recurrence and patients tended to die within two years of recurrence. CONCLUSIONS: Combined EMT with cancer stem cell-like marker is a predictor of

recurrence after radical resection for gastric cancer. Advanced TNM stage was associated with early cancer death after recurrence.

Yoon, S. J., et al. (2016). "Tumor Mesenchymal Stem-Like Cell as a Prognostic Marker in Primary Glioblastoma." Stem Cells Int **2016**: 6756983.

The isolation from brain tumors of tumor mesenchymal stem-like cells (tMSLCs) suggests that these cells play a role in creating a microenvironment for tumor initiation and progression. The clinical characteristics of patients with primary glioblastoma (pGBM) positive for tMSLCs have not been determined. This study analyzed samples from 82 patients with pGBM who had undergone tumor removal, pathological diagnosis, and isolation of tMSLC from April 2009 to October 2014. Survival, extent of resection, molecular markers, and tMSLC culture results were statistically evaluated. Median overall survival was 18.6 months, 15.0 months in tMSLC-positive patients and 29.5 months in tMSLC-negative patients (P = 0.014). Multivariate cox regression model showed isolation of tMSLC (OR = 2.5, 95% CI = 1.1~5.6, P = 0.021) showed poor outcome while larger extent of resection (OR = 0.5, 95% CI = 0.2~0.8, P = 0.011) has association with better outcome. The presence of tMSLCs isolated from the specimen of pGBM is associated with the survival of patient.

Yuan, Z., et al. (2017). "NRF2 overexpression in mesenchymal stem cells induces stem-cell marker expression and enhances osteoblastic differentiation." Biochem Biophys Res Commun **491**(1): 228-235.

Hypoxic environment has been suggested in stem cell culturing as their physiologic niche requires oxygen tension to maintain stemness. The administration of cobalt chloride (CoCl2) was widely applied in mimicking hypoxia for its economic advantages and convenience. We confirmed that CoCl2 could maintain stemness and promote the osteogenesis capacity of MSCs. However, CoCl2 could induce the apoptosis and hinder the proliferation of MSCs. To find out a potential method maintaining their stemness without threatening their survival, we analyzed the database of Gene Expression Omnibus (GEO) and proposed that NRF2 (nuclear factor erythroid-derived 2-like 2) might be the potential target. We found that knocking down NRF2 expression in MSCs impaired the expression of stem cell markers and the osteogenesis process even under hypoxic environment, but with NRF2 overexpression, the proliferation of MSCs was increased with significantly reduced rate of apoptosis. Therefore, our findings suggested that overexpressing NRF2 could be a potential method for maintaining stemness and preventing apoptosis in MSCs under oxidative stress.

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

References

[1]. Baidu. http://www.baidu.com. 2019.
[2]. Cancer Biology. http://www.cancerbio.net. 2019.
[3]. Google. http://www.google.com. 2019.
[4]. Journal of American Science. http://www.jofamericanscience.org. 2019.
[5]. Life Science Journal. http://www.lifesciencesite.com. 2019.
[6]. Ma H, Chen G. Stem cell. The Journal of American Science 2005;1(2):90-92. doi:10.7537/marsjas010205.14. http://www.jofamericanscience.org/journals/am-sci/0102/14-mahongbao.pdf.
[7]. Ma H, Cherng S. Eternal Life and Stem Cell. Nature and Science. 2007;5(1):81-96. doi:10.7537/marsnsj050107.10. http://www.sciencepub.net/nature/0501/10-0247-mahongbao-eternal-ns.pdf.
[8]. Ma H, Cherng S. Nature of Life. Life Science Journal 2005;2(1):7-15. doi:10.7537/marslsj020105.03. http://www.lifesciencesite.com/lsj/life0201/life-0201-03.pdf.
[9]. Ma H, Yang Y. Turritopsis nutricula. Nature and Science 2010;8(2):15-20. doi:10.7537/marsnsj080210.03. http://www.sciencepub.net/nature/ns0802/03_1279_hongbao_turritopsis_ns0802_15_20.pdf.
[10]. Ma H. The Nature of Time and Space. Nature and science 2003;1(1):1-11. doi:10.7537/marsnsj010103.01. http://www.sciencepub.net/nature/0101/01-ma.pdf.
[11]. Marsland Press. http://www.sciencepub.net. 2019; http://www.sciencepub.org. 2019.
[12]. National Center for Biotechnology Information, U.S. National Library of Medicine. http://www.ncbi.nlm.nih.gov/pubmed. 2019.
[13]. Nature and Science. http://www.sciencepub.net/nature. 2019.

[14]. Stem Cell. http://www.sciencepub.net/stem. 2019.
[15]. Wikipedia. The free encyclopedia. http://en.wikipedia.org. 2019.
[16]. Ahmadyan, S., et al. (2018). "The osmolyte type affects cartilage associated pathologic marker expression during in vitro mesenchymal stem cell chondrogenesis under hypertonic conditions." Cell Mol Biol (Noisy-le-grand) **64**(3): 56-61.
[17]. Bertolo, A., et al. (2015). "In vitro cell motility as a potential mesenchymal stem cell marker for multipotency." Stem Cells Transl Med **4**(1): 84-90.
[18]. Bierlein De la Rosa, M., et al. (2017). "Transdifferentiation of brain-derived neurotrophic factor (BDNF)-secreting mesenchymal stem cells significantly enhance BDNF secretion and Schwann cell marker proteins." J Biosci Bioeng **124**(5): 572-582.
[19]. Boozarpour, S., et al. (2016). "Glial cell derived neurotrophic factor induces spermatogonial stem cell marker genes in chicken mesenchymal stem cells." Tissue Cell **48**(3): 235-241.
[20]. Chung, T., et al. (2016). "Dihydropyrimidine Dehydrogenase Is a Prognostic Marker for Mesenchymal Stem Cell-Mediated Cytosine Deaminase Gene and 5-Fluorocytosine Prodrug Therapy for the Treatment of Recurrent Gliomas." Theranostics **6**(10): 1477-1490.
[21]. Da, C., et al. (2017). "Effects of irradiation on radioresistance, HOTAIR and epithelial-mesenchymal transition/cancer stem cell marker expression in esophageal squamous cell carcinoma." Oncol Lett **13**(4): 2751-2757.
[22]. Dehghani Nazhvani, A., et al. (2015). "Identification of Mesenchymal Stem Cell Marker STRO-1 in Oral Reactive Lesions by Immunofluorescence Method." J Dent (Shiraz) **16**(3 Suppl): 246-250.
[23]. Dickinson, S. C., et al. (2017). "The Wnt5a Receptor, Receptor Tyrosine Kinase-Like Orphan Receptor 2, Is a Predictive Cell Surface Marker of Human Mesenchymal Stem Cells with an Enhanced Capacity for Chondrogenic Differentiation." Stem Cells **35**(11): 2280-2291.
[24]. Djouad, F., et al. (2014). "Promyelocytic leukemia zinc-finger induction signs mesenchymal stem cell commitment: identification of a key marker for stemness maintenance?" Stem Cell Res Ther **5**(1): 27.
[25]. Farahani, R. M. and M. Xaymardan (2015). "Platelet-Derived Growth Factor Receptor Alpha as a Marker of Mesenchymal Stem Cells in Development and Stem Cell Biology." Stem Cells Int **2015**: 362753.
[26]. Guan, X., et al. (2014). "Evaluation of CD24 as a marker to rapidly define the mesenchymal stem cell phenotype and its differentiation in human nucleus pulposus." Chin Med J (Engl) **127**(8): 1474-1481.
[27]. Hirvonen, T., et al. (2013). "Production of a recombinant antibody specific for i blood group antigen, a mesenchymal stem cell marker." Biores Open Access **2**(5): 336-345.
[28]. Ishimine, H., et al. (2013). "N-Cadherin is a prospective cell surface marker of human mesenchymal stem cells that have high ability for cardiomyocyte differentiation." Biochem Biophys Res Commun **438**(4): 753-759.
[29]. Ishimura, D., et al. (2008). "Differentiation of adipose-derived stromal vascular fraction culture cells into chondrocytes using the method of cell sorting with a mesenchymal stem cell marker." Tohoku J Exp Med **216**(2): 149-156.
[30]. Li, Z., et al. (2013). "Effect of cell culture using chitosan membranes on stemness marker genes in mesenchymal stem cells." Mol Med Rep **7**(6): 1945-1949.
[31]. Lin, G., et al. (2011). "Tissue distribution of mesenchymal stem cell marker Stro-1." Stem Cells Dev **20**(10): 1747-1752.
[32]. Madsen, S. D., et al. (2017). "Decoy TRAIL receptor CD264: a cell surface marker of cellular aging for human bone marrow-derived mesenchymal stem cells." Stem Cell Res Ther **8**(1): 201.
[33]. Mercati, F., et al. (2009). "Expression of mesenchymal stem cell marker CD90 on dermal sheath cells of the anagen hair follicle in canine species." Eur J Histochem **53**(3): 159-166.
[34]. Mercati, F., et al. (2009). "Expression of mesenchymal stem cell marker CD90 on dermal sheath cells of the anagen hair follicle in canine species." Eur J Histochem **53**(3): e19.
[35]. Nam, K. H., et al. (2017). "Predictive value for lymph node metastasis of epithelial-mesenchymal transition and cancer stem cell marker expression in early gastric cancer." Pathol Res Pract **213**(9): 1221-1226.
[36]. Naylor, A. J., et al. (2012). "The mesenchymal stem cell marker CD248 (endosialin) is a negative regulator of bone formation in mice." Arthritis Rheum **64**(10): 3334-3343.
[37]. Ning, H., et al. (2011). "Mesenchymal stem cell marker Stro-1 is a 75 kd endothelial antigen." Biochem Biophys Res Commun **413**(2): 353-357.
[38]. Ning, X., et al. (2018). "Ectopic expression of miR-147 inhibits stem cell marker and epithelial-mesenchymal transition (EMT)-

related protein expression in colon cancer cells." Oncol Res.
[39]. Park, J. Y., et al. (2013). "Comparative analysis of mesenchymal stem cell surface marker expression for human dental mesenchymal stem cells." Regen Med **8**(4): 453-466.
[40]. Riekstina, U., et al. (2009). "Embryonic stem cell marker expression pattern in human mesenchymal stem cells derived from bone marrow, adipose tissue, heart and dermis." Stem Cell Rev **5**(4): 378-386.
[41]. Schinke, C., et al. (2018). "The Pattern of Mesenchymal Stem Cell Expression Is an Independent Marker of Outcome in Multiple Myeloma." Clin Cancer Res **24**(12): 2913-2919.
[42]. Sullivan, K. E., et al. (2017). "The stem cell/cancer stem cell marker ALDH1A3 regulates the expression of the survival factor tissue transglutaminase, in mesenchymal glioma stem cells." Oncotarget **8**(14): 22325-22343.
[43]. Vanella, L., et al. (2011). "Crosstalk between EET and HO-1 downregulates Bach1 and adipogenic marker expression in mesenchymal stem cell derived adipocytes." Prostaglandins Other Lipid Mediat **96**(1-4): 54-62.
[44]. Wirths, S., et al. (2013). "Shared cell surface marker expression in mesenchymal stem cells and adult sarcomas." Stem Cells Transl Med **2**(1): 53-60.
[45]. Xu, G. F., et al. (2014). "Combined epithelial-mesenchymal transition with cancer stem cell-like marker as predictors of recurrence after radical resection for gastric cancer." World J Surg Oncol **12**: 368.
[46]. Yoon, S. J., et al. (2016). "Tumor Mesenchymal Stem-Like Cell as a Prognostic Marker in Primary Glioblastoma." Stem Cells Int **2016**: 6756983.
[47]. Yuan, Z., et al. (2017). "NRF2 overexpression in mesenchymal stem cells induces stem-cell marker expression and enhances osteoblastic differentiation." Biochem Biophys Res Commun **491**(1): 228-235.

2/12/2024