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Stem Cell

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Stem Cell and Differentiation 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; 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.

Abell, A. N. and G. L. Johnson (2014). "Implications of Mesenchymal Cells in Cancer Stem Cell Populations: Relevance to EMT." Curr Pathobiol Rep **2**(1): 21-26.

The epithelial to mesenchymal transition (EMT) generates tumor cells having stem cell characteristics with phenotypes similar to cancer stem cells (CSCs). Evidence suggests CSCs are in an intermediate state of EMT expressing reduced levels of E-cadherin and exhibiting mesenchymal features including invasiveness associated with metastasis. These findings suggest mechanisms regulating EMT and stemness are closely integrated. Recent reports from multiple laboratories have identified novel mechanisms regulating EMT and stemness involving epigenetics, microenvironment, and dedifferentiation. Circulating tumor cells (CTCs) have also been shown to exhibit features of EMT, but it is unclear what fraction has CSCs properties. EMT characteristics of both CSCs and CTCs are associated with resistance to current clinical treatments, indicating therapies targeting the CSC in addition to the more differentiated tumor cells are required for durable responses. Thus, EMT characteristics of CTCs may prove useful biomarkers for effective therapies for many cancers.

Baghaban Eslaminejad, M. and E. Malakooty Poor (2014). "Mesenchymal stem cells as a potent cell source for articular cartilage regeneration." World J Stem Cells **6**(3): 344-354.

Since articular cartilage possesses only a weak capacity for repair, its regeneration potential is considered one of the most important challenges for orthopedic surgeons. The treatment options, such as marrow stimulation techniques, fail to induce a repair tissue with the same functional and mechanical properties of native hyaline cartilage. Osteochondral transplantation is considered an effective treatment option but is associated with some disadvantages, including donor-site morbidity, tissue supply limitation, unsuitable mechanical properties and thickness of the obtained tissue. Although autologous chondrocyte implantation results in reasonable repair, it requires a two-step surgical procedure. Moreover, chondrocytes expanded in culture gradually undergo dedifferentiation, so lose morphological features and specialized functions. In the search for alternative cells, scientists have found mesenchymal stem cells (MSCs) to be an appropriate cellular material for articular cartilage repair. These cells were originally isolated

from bone marrow samples and further investigations have revealed the presence of the cells in many other tissues. Furthermore, chondrogenic differentiation is an inherent property of MSCs noticed at the time of the cell discovery. MSCs are known to exhibit homing potential to the damaged site at which they differentiate into the tissue cells or secrete a wide spectrum of bioactive factors with regenerative properties. Moreover, these cells possess a considerable immunomodulatory potential that make them the general donor for therapeutic applications. All of these topics will be discussed in this review.

Bai, F., et al. (2014). "BRCA1 suppresses epithelial-to-mesenchymal transition and stem cell dedifferentiation during mammary and tumor development." Cancer Res **74**(21): 6161-6172.

BRCA1 mutation carriers are predisposed to developing basal-like breast cancers with high metastasis and poor prognosis. Yet, how BRCA1 suppresses formation of basal-like breast cancers is still obscure. Deletion of p18(Ink4c) (p18), an inhibitor of CDK4 and CDK6, functionally inactivates the RB pathway, stimulates mammary luminal stem cell (LSC) proliferation, and leads to spontaneous luminal tumor development. Alternately, germline mutation of Brca1 shifts the fate of luminal cells to cause luminal-to-basal mammary tumor transformation. Here, we report that disrupting Brca1 by either germline or epithelium-specific mutation in p18-deficient mice activates epithelial-to-mesenchymal transition (EMT) and induces dedifferentiation of LSCs, which associate closely with expansion of basal and cancer stem cells and formation of basal-like tumors. Mechanistically, BRCA1 bound to the TWIST promoter, suppressing its activity and inhibiting EMT in mammary tumor cells. In human luminal cancer cells, BRCA1 silencing was sufficient to activate TWIST and EMT and increase tumor formation. In parallel, TWIST expression and EMT features correlated inversely with BRCA1 expression in human breast cancers. Together, our findings showed that BRCA1 suppressed TWIST and EMT, inhibited LSC dedifferentiation, and repressed expansion of basal stem cells and basal-like tumors. Thus, our work offers the first genetic evidence that Brca1 directly suppresses EMT and LSC dedifferentiation during breast tumorigenesis.

Blick, T., et al. (2010). "Epithelial mesenchymal transition traits in human breast cancer cell lines parallel the CD44(hi/)CD24 (lo/-) stem cell phenotype in human breast cancer." J Mammary Gland Biol Neoplasia **15**(2): 235-252.

We review here the recently emerging relationship between epithelial-mesenchymal transition (EMT) and breast cancer stem cells (BCSC), and provide analyses of published data on human breast cancer cell lines, supporting their utility as a model for the EMT/BCSC state. Genome-wide transcriptional profiling of these cell lines has confirmed the existence of a subgroup with mesenchymal tendencies and enhanced invasive properties ('Basal B'/Mesenchymal), distinct from subgroups with either predominantly luminal ('Luminal') or mixed basal/luminal ('Basal A') features (Neve et al. Cancer Cell, 2006). A literature-derived EMT gene signature has shown specific enrichment within the Basal B subgroup of cell lines, consistent with their over-expression of various EMT transcriptional drivers. Basal B cell lines are found to resemble BCSC, being CD44(high)CD24(low). Moreover, gene products that distinguish Basal B from Basal A and Luminal cell lines (Basal B Discriminators) showed close concordance with those that define BCSC isolated from clinical material, as reported by Shipitsin et al. (Cancer Cell, 2007). CD24 mRNA levels varied across Basal B cell lines, correlating with other Basal B Discriminators. Many gene products correlating with CD24 status in Basal B cell lines were also differentially expressed in isolated BCSC. These findings confirm and extend the importance of the cellular product of the EMT with Basal B cell lines, and illustrate the value of analysing these cell lines for new leads that may improve breast cancer outcomes. Gene products specific to Basal B cell lines may serve as tools for the detection, quantification, and analysis of BCSC/EMT attributes.

Cournil-Henrionnet, C., et al. (2008). "Phenotypic analysis of cell surface markers and gene expression of human mesenchymal stem cells and chondrocytes during monolayer expansion." Biorheology **45**(3-4): 513-526.

Both chondrocytes and mensenchymal stem cells (MSCs) are the most used cell sources for cartilage tissue engineering. However, monolayer expansion to obtain sufficient cells leads to a rapid chondrocyte dedifferentiation and a subsequent ancillary reduced ability of MSCs to differentiate into chondrocytes, thus limiting their application in cartilage repair. The aim of this study was to investigate the influence of the monolayer expansion on the immunophenotype and the gene expression profile of both cell types, and to find the appropriate compromise between monolayer expansion and the remaining chondrogenic characteristics. To this end, human chondrocytes, isolated enzymatically from femoral head slice, and human MSCs, derived from bone marrow, were maintained in monolayer culture up to passage 5. The respective expressions of cell surface markers (CD34, CD45, CD73, CD90, CD105, CD166) and several chondrogenic-related genes for each passage (P0-P5) of those cells were then analyzed using flow cytometry and quantitative real-time PCR, respectively. Flow cytometry analyses showed that, during the monolayer expansion, some qualitative and

quantitative regulations occur for the expression of cell surface markers. A rapid increase in mRNA expression of type 1 collagen occurs whereas a significant decrease of type 2 collagen and Sox 9 was observed in chondrocytes through the successive passages. On the other hand, the expansion did not induced obvious change in MSCs gene expression. In conclusion, our results suggest that passage 1 might be the up-limit for chondrocytes in order to achieve their subsequent redifferentiation in 3D scaffold. Nevertheless, MSCs could be expanded in monolayer until passage 5 without loosing their undifferentiated phenotypes.

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

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

Foja, S., et al. (2013). "Hypoxia supports reprogramming of mesenchymal stromal cells via induction of embryonic stem cell-specific microRNA-302 cluster and pluripotency-associated genes." Cell Reprogram **15**(1): 68-79.

Pluripotency is characterized by specific transcription factors such as OCT4, NANOG, and SOX2, but also by pluripotency-associated microRNAs (miRs). Somatic cells can be reprogrammed by forced expression of these factors leading to induced pluripotent stem cells (iPSCs) with characteristics similar to embryonic stem cells (ESCs). However, current reprogramming strategies are commonly based on viral delivery of the pluripotency-associated factors, which affects the integrity of the genome and impedes the use of such cells in any clinical application. In an effort to establish nonviral, nonintegrating reprogramming strategies, we examined the influence of hypoxia on the expression of pluripotency-associated factors and the ESC-specific miR-302 cluster in primary and immortalized mesenchymal stromal cells (MSCs). The combination of hypoxia and fibroblast growth factor 2 (FGF2) treatments led to the induction of OCT4 and NANOG in an immortalized cell line L87 and primary MSCs, accompanied with increased doubling rates and decreased senescence. Most importantly, the endogenous ECS-specific cluster miR-302 was induced upon hypoxic culture and FGF2 supplementation. Hypoxia also improved reprogramming of MSCs via episomal expression of pluripotency factors. Thus, our data illustrate that hypoxia in combination with FGF2 supplementation efficiently facilitates reprogramming of MSCs.

Georgi, N., et al. (2014). "Mesenchymal stromal/stem cell-or chondrocyte-seeded microcarriers as building blocks for cartilage tissue engineering." Tissue Eng Part A **20**(17-18): 2513-2523.

In this study we have tested the use of mesenchymal stromal/stem cell (MSC)- or chondrocyte (hch)-laden microcarriers as building blocks for engineered cartilage tissue. MSCs and hchs expanded on microcarriers were used in chondrogenic coculture and compared with monoculture of MSCs or hchs. The use of cell-laden microcarriers as building blocks for cartilage tissue engineering led to a compact tissue formation with significant volume increase compared to the biomaterial-free approach. After 28 days of differentiation culture, formation of cartilaginous matrix in cocultures and chondrocyte monoculture approaches was observed. Coculture resulted in beneficial glycosaminoglycan deposition compared with monoculture of MSCs or chondrocytes attached to microcarriers. Further, the microcarrier-adhered coculture displayed increased levels of the differentiation marker ACAN and reduced levels of the dedifferentiation marker COL1A1. To our knowledge, this is the first article that successfully combines an innovative combination of cell expansion on microcarriers and the direct use of MSC- or hch-cell-laden microcarriers as building blocks in cartilage tissue engineering.

Goessler, U. R., et al. (2006). "In vitro analysis of integrin expression during chondrogenic differentiation of mesenchymal stem cells and chondrocytes upon dedifferentiation in cell culture." Int J Mol Med **17**(2): 301-307.

Tissue engineering represents a promising method for generating chondrogenic grafts for reconstructive surgery. In cultured chondrocytes, the

dedifferentiation of cells seems unavoidable for multiplication. Stem cells, however, displaying unlimited self-renewal and the capacity to differentiate towards chondrocytes, might be usable after further characterization. As the interactions between the extracellular matrix and the cellular compartment can alter the cellular behaviour, we investigated the expression of integrins using microarray analysis during chondrogenic differentiation of human mesenchymal stem cells (MSC) in comparison with de-differentiating human chondrocytes (HC) harvested during septoplasty. During chondrogenic differentiation of MSC, the fibronectin-receptor (Integrin beta1alpha5), fibronectin and the GPIIb/IIIa-receptor were downregulated. The components of the vitronectin-receptor (Integrin alphavbeta3) and CD47 were constantly expressed and ILK was downregulated. Vitronectin and osteopontin were not expressed by the cells. In HC, Integrin beta1alpha5 in conjunction with the ligand fibronectin were upregulated during dedifferentiation, Integrin alphavbeta3 as well as the GBIIb/IIIa-receptor were activated on day 21 but neither vitronectin nor osteopontin were expressed by the cells. The integrins, beta2, beta4, beta6, beta8 and alpha2, alpha4, alpha6, alpha7, alpha11, were not expressed at any time. ILK, CD47, and ICAP were activated with ongoing dedifferentiation. In conclusion, a candidate for signal-transmission is the fibronectin receptor (integrin alpha5beta1) in conjunction with its ligand fibronectin. Other receptors, e.g. for vitronectin and osteopontin (alphavbeta3), or their ligands do not seem to be involved in signal transmission for dedifferentiation. The GPIIb/IIIa-receptor might assist the process of dedifferentiation. Intracellularly, ILK, ICAP1 and CD47 might be involved in the transduction of integrin-dependent signals.

Goessler, U. R., et al. (2005). "In-vitro analysis of the expression of TGFbeta -superfamily-members during chondrogenic differentiation of mesenchymal stem cells and chondrocytes during dedifferentiation in cell culture." Cell Mol Biol Lett **10**(2): 345-362.

Traditional surgical methods for the reconstruction of cartilage defects rely on the transplantation of autologous and allogenous tissues. The disadvantages of these techniques are the limited availability of suitable tissues and the donor site morbidity of transplants. In addition, in cultured chondrocytes, the dedifferentiation of cells seems unavoidable during multiplication. In this study, we investigated the expression of distinct markers during the dedifferentiation of human chondrocytes (HC) and human mesenchymal stem cells (MSC) in cell culture using microarray technique, immunohistochemistry and RT-PCR. Transforming growth factor beta (TGFbeta) is a multifunctional peptide that plays play a crucial role in inducing and maintaining chondrogenic differentiation. In dedifferentiating chondrocytes, the gene for TGFbeta1 was constantly expressed, while the gene for TGFbeta2 was never expressed. The genes for TGFalpha, TGFbeta4 and TGFbetai were activated with ongoing dedifferentiation. TGFbeta-receptor 3 was constantly expressed, while the genes for the TGFbeta-receptors 1 and 2 were never expressed. Immunohistochemical staining for TGFbeta beta 3 revealed upregulation in the course of dedifferentiation. The genes for LTBP1 and LTBP2 were activated with ongoing dedifferentiation, whereas the gene for LTBP3 was constantly expressed, and negative results were obtained for the gene for LTBP4. The genes for LTBP1 and LTBP2 were activated with ongoing dedifferentiation. During chondrogenic differentiation, the MSCs constantly expressed TGFbeta1, beta2, beta3 and beta4. LTBP1, LTBP2 and TGFbeta-R3 were downregulated. In conclusion, TGFbeta3, TGFbeta4, TGFbetai, LTBP1 and LTBP2 may assist the process of dedifferentiation, while TGFbeta1 and beta2 might not be involved in this process. Of the TGFbeta-receptors, only type 3 might be involved in dedifferentiation.

Hoch, A. I., et al. (2016). "Cell-secreted matrices perpetuate the bone-forming phenotype of differentiated mesenchymal stem cells." Biomaterials **74**: 178-187.

Prior to transplantation, mesenchymal stem/stromal cells (MSCs) can be induced toward the osteoblastic phenotype using a cocktail of soluble supplements. However, there is little evidence of differentiated MSCs directly participating in bone formation, suggesting that MSCs may either die or revert in phenotype upon transplantation. Cell-secreted decellularized extracellular matrices (DMs) are a promising platform to confer bioactivity and direct cell fate through the presentation of a complex and physiologically relevant milieu. Therefore, we examined the capacity of biomimetic DMs to preserve the mineral-producing phenotype upon withdrawal of the induction stimulus. Regardless of induction duration, ranging up to 6 weeks, MSCs exhibited up to a 5-fold reduction in osteogenic markers within 24 h following stimulus withdrawal. We show that seeding osteogenically induced MSCs on DMs yields up to 2-fold more calcium deposition than tissue culture plastic, and this improvement is at least partially mediated by increasing actin cytoskeletal tension via the ROCK II pathway. MSCs on DMs also secreted 25% more vascular endothelial growth factor (VEGF), a crucial endogenous proangiogenic factor that is abrogated during MSC osteogenic differentiation. The deployment of DMs into a subcutaneous ectopic site enhanced the persistence of MSCs 5-fold, vessel density 3-fold, and bone formation 2-fold more than MSCs delivered without DMs. These results

underscore the need for deploying MSCs using biomaterial platforms such as DMs to preserve the in vitro-acquired mineral-producing phenotype and accelerate the process of bone repair.

Hu, C., et al. (2016). "Adipogenic placenta-derived mesenchymal stem cells are not lineage restricted by withdrawing extrinsic factors: developing a novel visual angle in stem cell biology." Cell Death Dis **7**: e2141.

Current evidence implies that differentiated bone marrow mesenchymal stem cells (BMMSCs) can act as progenitor cells and transdifferentiate across lineage boundaries. However, whether this unrestricted lineage has specificities depending on the stem cell type is unknown. Placental-derived mesenchymal stem cells (PDMSCs), an easily accessible and less invasive source, are extremely useful materials in current stem cell therapies. No studies have comprehensively analyzed the transition in morphology, surface antigens, metabolism and multilineage potency of differentiated PDMSCs after their dedifferentiation. In this study, we showed that after withdrawing extrinsic factors, adipogenic PDMSCs reverted to a primitive cell population and retained stem cell characteristics. The mitochondrial network during differentiation and dedifferentiation may serve as a marker of absent or acquired pluripotency in various stem cell models. The new population proliferated faster than unmanipulated PDMSCs and could be differentiated into adipocytes, osteocytes and hepatocytes. The cell adhesion molecules (CAMs) signaling pathway and extracellular matrix (ECM) components modulate cell behavior and enable the cells to proliferate or differentiate during the differentiation, dedifferentiation and redifferentiation processes in our study. These observations indicate that the dedifferentiated PDMSCs are distinguishable from the original PDMSCs and may serve as a novel source in stem cell biology and cell-based therapeutic strategies. Furthermore, whether PDMSCs differentiated into other lineages can be dedifferentiated to a primitive cell population needs to be investigated.

Ju, G. Q., et al. (2015). "Microvesicles derived from human umbilical cord mesenchymal stem cells facilitate tubular epithelial cell dedifferentiation and growth via hepatocyte growth factor induction." PLoS One **10**(3): e0121534.

During acute kidney injury (AKI), tubular cell dedifferentiation initiates cell regeneration; hepatocyte growth factor (HGF) is involved in modulating cell dedifferentiation. Mesenchymal stem cell (MSC)-derived microvesicles (MVs) deliver RNA into injured tubular cells and alter their gene expression, thus regenerating these cells. We boldly speculated that MVs might induce HGF synthesis via RNA transfer, thereby facilitating tubular cell dedifferentiation and regeneration. In a rat model of unilateral AKI, the administration of MVs promoted kidney recovery. One of the mechanisms of action is the acceleration of tubular cell dedifferentiation and growth. Both in vivo and in vitro, rat HGF expression in damaged rat tubular cells was greatly enhanced by MV treatment. In addition, human HGF mRNA present in MVs was delivered into rat tubular cells and translated into the HGF protein as another mechanism of HGF induction. RNase treatment abrogated all MV effects. In the in vitro experimental setting, the conditioned medium of MV-treated injured tubular cells, which contains a higher concentration of HGF, strongly stimulated cell dedifferentiation and growth, as well as Erk1/2 signaling activation. Intriguingly, these effects were completely abrogated by either c-Met inhibitor or MEK inhibitor, suggesting that HGF induction is a crucial contributor to the acceleration of cell dedifferentiation and growth. All these findings indicate that MV-induced HGF synthesis in damaged tubular cells via RNA transfer facilitates cell dedifferentiation and growth, which are important regenerative mechanisms.

Karlsson, C., et al. (2008). "Neither Notch1 expression nor cellular size correlate with mesenchymal stem cell properties of adult articular chondrocytes." Cells Tissues Organs **187**(4): 275-285.

BACKGROUND: Tissue repair is thought to be regulated by progenitor cells, which in other tissues are characterized by their Notch1 expression or small cellular size. Here we studied if these traits affect the chondrogenic potential and are markers for multipotent progenitor cell populations in adult articular cartilage. METHODS: Directly isolated articular chondrocytes were sorted with regard to their Notch1 expression or cellular size. Their colony forming efficiency (CFE) and their potential to differentiate towards adipogenic, osteogenic and chondrogenic lineages were investigated. The different sorted populations were also expanded in monolayer and analyzed in the same manner as the directly isolated cells. RESULTS: No differences in CFE or adipogenic, osteogenic and chondrogenic potentials were detected among the sorted populations. Expanded cells displayed a higher osteochondral potential than directly isolated cells. CONCLUSION: Cellular size or Notch1 expression is not per se a specific marker for mesenchymal progenitor cells in adult articular cartilage. Monolayer-expanded adult chondrocytes contain a larger mesenchymal progenitor cell-like population than directly isolated cells, highly likely as a result of dedifferentiation. If there are resident Notch1-positive cells or cells of a specific size in adult articular cartilage with functional features of progenitor cells, the population consists of only a very small number of cells.

Laschke, M. W., et al. (2014). "In vitro osteogenic differentiation of adipose-derived mesenchymal stem cell spheroids impairs their in vivo vascularization capacity inside implanted porous polyurethane scaffolds." Acta Biomater **10**(10): 4226-4235.

Undifferentiated adipose-derived mesenchymal stem cell (adMSC) spheroids are attractive vascularization units for tissue engineering. Their osteogenic differentiation further offers the possibility of directed generation of bone constructs. The aim of this study was to analyze how this differentiation affects their in vivo vascularization capacity. Green fluorescent protein (GFP)-positive adMSCs were isolated from C57BL/6-TgN(ACTB-EGFP)1Osb/J mice for the generation of undifferentiated and differentiated spheroids using the liquid overlay technique. Subsequently, polyurethane scaffolds were seeded with these spheroids and successful osteogenic differentiation was proven by von Kossa staining and high-resolution microtomography. The scaffolds were then implanted into dorsal skinfold chambers of C57BL/6 wild-type mice to analyze their vascularization and incorporation using intravital fluorescence microscopy, histology and immunohistochemistry. Scaffolds seeded with differentiated spheroids exhibited a markedly impaired vascularization. Immunohistochemical analyses revealed that this was caused by the lost ability of differentiated spheroids to form GFP-positive microvascular networks inside the scaffolds. This was associated with a reduced tissue incorporation of the implants. Moreover, they no longer exhibited a mineralized matrix after the 14day implantation period, indicating the dedifferentiation of the spheroids under the given in vivo conditions. These findings indicate that osteogenic differentiation of adMSC spheroids markedly impairs their vascularization capacity. Hence, it may be reasonable to combine adMSC spheroids of varying differentiation stages in scaffolds for bone tissue engineering to promote both vascularization and bone formation.

Lee, J., et al. (2017). "Fully Dedifferentiated Chondrocytes Expanded in Specific Mesenchymal Stem Cell Growth Medium with FGF2 Obtains Mesenchymal Stem Cell Phenotype In Vitro but Retains Chondrocyte Phenotype In Vivo." Cell Transplant **26**(10): 1673-1687.

Given recent progress in regenerative medicine, we need a means to expand chondrocytes in quantity without losing their regenerative capability. Although many reports have shown that growth factor supplementation can have beneficial effects, the use of growth factor-supplemented basal media has widespread effect on the characteristics of chondrocytes. Chondrocytes were in vitro cultured in the 2 most widely used chondrocyte growth media, conventional chondrocyte culture medium and mesenchymal stem cell (MSC) culture medium, both with and without fibroblast growth factor-2 (FGF2) supplementation. Their expansion rates, expressions of extracellular matrix-related factors, senescence, and differentiation potentials were examined in vitro and in vivo. Our results revealed that chondrocytes quickly dedifferentiated during expansion in all tested media, as assessed by the loss of type II collagen expression. The 2 basal media (chondrocyte culture medium vs. MSC culture medium) were associated with distinct differences in cell senescence. Consistent with the literature, FGF2 was associated with accelerated dedifferentiation during expansion culture and superior redifferentiation upon induction. However, chondrocytes expanded in FGF2-containing conventional chondrocyte culture medium showed MSC-like features, as indicated by their ability to direct ectopic bone formation and cartilage formation. In contrast, chondrocytes cultured in FGF2-supplemented MSC culture medium showed potent chondrogenesis and almost no bone formation. The present findings show that the chosen basal medium can exert profound effects on the characteristics and activity of in vitro-expanded chondrocytes and indicate that right growth factor/medium combination can help chondrocytes retain a high-level chondrogenic potential without undergoing hypertrophic transition.

Liu, L., et al. (2010). "Novel strategy to engineer trachea cartilage graft with marrow mesenchymal stem cell macroaggregate and hydrolyzable scaffold." Artif Organs **34**(5): 426-433.

Limited donor sites of cartilage and dedifferentiation of chondrocytes during expansion, low tissue reconstruction efficiency, and uncontrollable immune reactions to foreign materials are the main obstacles to overcome before cartilage tissue engineering can be widely used in the clinic. In the current study, we developed a novel strategy to fabricate tissue-engineered trachea cartilage grafts using marrow mesenchymal stem cell (MSC) macroaggregates and hydrolyzable scaffold of polylactic acid-polyglycolic acid copolymer (PLGA). Rabbit MSCs were continuously cultured to prepare macroaggregates in sheet form. The macroaggregates were studied for their potential for chondrogenesis. The macroaggregates were wrapped against the PLGA scaffold to make a tubular composite. The composites were incubated in spinner flasks for 4 weeks to fabricate trachea cartilage grafts. Histological observation and polymerase chain reaction array showed that MSC macroaggregates could obtain the optimal chondrogenic capacity under the induction of transforming growth factor-beta. Engineered trachea cartilage consisted of evenly spaced lacunae embedded in a matrix rich in proteoglycans. PLGA scaffold

degraded totally during in vitro incubation and the engineered cartilage graft was composed of autologous tissue. Based on this novel, MSC macroaggregate and hydrolyzable scaffold composite strategy, ready-to-implant autologous trachea cartilage grafts could be successfully fabricated. The strategy also had the advantages of high efficiency in cell seeding and tissue regeneration, and could possibly be used in future in vivo experiments.

Petrou, M., et al. (2013). "Mesenchymal stem cell chondrogenesis: composite growth factor-bioreactor synergism for human stem cell chondrogenesis." Regen Med **8**(2): 157-170.

BACKGROUND: Effective mesenchymal stem cell chondrogenesis can be accomplished by using a tailored mechanical-biochemical stimulus. To achieve this requires parallel suppression of hypertrophy and osteogenesis. MATERIALS & METHODS: We compared the effects of isolated bioreactor stimulation, isolated growth factor (TGF-beta1 or IGF-1) application and their combined stimulation on human bone marrow-derived mesenchymal stem cells cultured within 3D scaffolds. Free-swelling cell-matrix constructs underwent identical growth factor stimulation for control. RESULTS: Mechanical stimulation provoked stronger chondrogenic differentiation than free-swelling culture. Chondrogenesis by the addition of TGF-beta1 was enhanced compared with single physical stimulation. There were no such effects under the influence of IGF-1 alone. Composite application of multiaxial mechanical stimulation plus TGF-beta1 and IGF-1 not only triggered the strongest chondrogenesis overall, but also the strongest hypertrophy and osteogenesis. CONCLUSION: Bioreactor-induced chondrogenic differentiation of human mesenchymal stem cells can be effectively enhanced by growth factor addition, while the partially effective suppression of unwanted signs of endochondral ossification requires further scientific input.

Pikir, B. S., et al. (2012). "Reversin increase the plasticity of bone marrow-derived mesenchymal stem cell for generation of cardiomyocyte in vitro." Acta Med Indones **44**(1): 23-27.

AIM: to speed up transdifferentiation of bone marrow-derived stem cells into cardiomyocyte in vitro by inducing dedifferentiation of bone marrow-derived mesenchymal stem cell, before induction by 5-aza-2'-deoxycytidine into cardiomyocyte. METHODS: two-three months old 2.5 kg weight adult male New Zealanad Rabbits were anesthezied with ether, thigh bones were excised, and bone marrow cells were obtained by aspiration. RESULTS: in our experiments after 1 week of mesenchymal stem cell cultures, 20 nM reversin was given to induce dediferentiation and after 24 hours exposure with 9muM 5-aza-2-deoxycytidine, early phase of cardiomyocyte differentiation appeared as cultured cell were strongly positive for GATA-4 and weakly positive for MLC-2alpha, although beating cardiomyocyte has not yet appeared at the end of experiment. These experiments also showed a marked CD34+ and c-kit+ gene expression on RT-PCR examination. CONCLUSION: reversine increase plasticity of bone marrow-derived mesenchymal stem cell to generate cardiomyocyte after 5-aza-2'-deoxycytidine induction. CD34+ and c-kit+ may be a marker for cardiomyocyte progenitor cells.

Rubio, D., et al. (2008). "Human mesenchymal stem cell transformation is associated with a mesenchymal-epithelial transition." Exp Cell Res **314**(4): 691-698.

Carcinomas are widely thought to derive from epithelial cells with malignant progression often associated with an epithelial-mesenchymal transition (EMT). We have characterized tumors generated by spontaneously transformed human mesenchymal cells (TMC) previously obtained in our laboratory. Immunohistopathological analyses identified these tumors as poorly differentiated carcinomas, suggesting that a mesenchymal-epithelial transition (MET) was involved in the generation of TMC. This was corroborated by microarray and protein expression analysis that showed that almost all mesenchymal-related genes were severely repressed in these TMC. Interestingly, TMC also expressed embryonic antigens and were able to integrate into developing blastocysts with no signs of tumor formation, suggesting a dedifferentiation process was associated with the mesenchymal stem cell (MSC) transformation. These findings support the hypothesis that some carcinomas are derived from mesenchymal rather than from epithelial precursors.

Shakhbazau, A. V., et al. (2009). "Plasticity of human mesenchymal stem cell phenotype and expression profile under neurogenic conditions." Bull Exp Biol Med **147**(4): 513-516.

Human bone marrow MSC cultured in neurogenic medium containing EGF and FGFbeta demonstrated alteration of the phenotype and expression of neuronal precursor/early neuron markers nestin and NSE. Signals of expression of neuronal and oligodendroglial markers MAP-2, dm-20, and MBP were detected after prolongation of incubation in neurogenic medium to 2 weeks. Cells with neuronal morphology were immunopositive to early neuronal marker beta-III-tubulin. Replacement of neurogenic medium for alpha-MEM with 10% fetal calf serum induced reversion of the phenotype to that typical for human MSC. This indicates high plasticity of the phenotype and expression profile of neuronal markers in MSC cultured under neurogenic conditions or possibility of dedifferentiation of MSC reaching the stage of neuronal precursors/early neurons.

Song, L., et al. (2006). "Identification and functional analysis of candidate genes regulating mesenchymal stem cell self-renewal and multipotency." Stem Cells **24**(7): 1707-1718.

Adult human mesenchymal stem cells (hMSCs) possess multilineage differentiation potential, and differentiated hMSCs have recently been shown to have the ability to transdifferentiate into other lineages. However, the molecular signature of hMSCs is not well-known, and the mechanisms regulating their self-renewal, differentiation, and transdifferentiation are not completely understood. In this study, we demonstrate that fully differentiated hMSCs could dedifferentiate, a likely critical step for transdifferentiation. By comparing the global gene expression profiles of undifferentiated, differentiated, and dedifferentiation cells in three mesenchymal lineages (osteogenesis, chondrogenesis, and adipogenesis), we identified a number of "stemness" and "differentiation" genes that might be essential to maintain adult stem cell multipotency as well as to drive lineage-specific commitment. These genes include those that encode cell surface molecules, as well as components of signaling pathways. These genes may be valuable for developing methods to isolate, enrich, and purify homogeneous population of hMSCs and/or maintain and propagate hMSCs as well as guide or regulate their differentiation for gene and cell-based therapy. Using small interfering RNA gene inactivation, we demonstrate that five genes (actin filament-associated protein, frizzled 7, dickkopf 3, protein tyrosine phosphatase receptor F, and RAB3B) promote cell survival without altering cell proliferation, as well as exhibiting different effects on the commitment of hMSCs into multiple mesenchymal lineages.

Ullah, M., et al. (2013). "Transdifferentiation of mesenchymal stem cells-derived adipogenic-differentiated cells into osteogenic- or chondrogenic-differentiated cells proceeds via dedifferentiation and have a correlation with cell cycle arresting and driving genes." Differentiation **85**(3): 78-90.

It is generally accepted that after differentiation bone marrow mesenchymal stem cells (MSC) become lineage restricted and unipotent in an irreversible manner. However, current results imply that even terminally differentiated cells transdifferentiate across lineage boundaries and therefore act as a progenitor cells for other lineages. This leads to the questions that whether transdifferentiation occurs via direct cell-to-cell conversion or dedifferentiation to a progenitor cells and subsequent differentiation, and whether MSC potency decreases or increases during differentiation. To address these questions, MSC were differentiated into adipogenic lineage cells, followed by dedifferentiation. The process of dedifferentiation was also confirmed by single cell clonal analysis. Finally the dedifferentiated cells were used for adipogenesis, osteogenesis and chondrogenesis. Histology, FACS, qPCR and GeneChip analyses of undifferentiated MSC, adipogenic-differentiated and dedifferentiated cells were performed. Interestingly, gene profiling and bioinformatics demonstrated that upregulation (DHCR24, G0S2, MAP2K6, SESN3) and downregulation (DST, KAT2, MLL5, RB1, SMAD3, ZAK) of distinct genes have an association with cell cycle arrest in adipogenic-differentiated cells and perhaps narrow down the lineage potency. However, the upregulation (CCND1, CHEK, HGF, HMGA2, SMAD3) and downregulation (CCPG1, RASSF4, RGS2) of these genes have an association with cell cycle progression and maybe motivate dedifferentiation of adipogenic-differentiated cells. We found that dedifferentiated cells have a multilineage potency comparable to MSC, and also observed the associative role of proliferation genes with cell cycle arrest and progression. Concluded, our results indicate that transdifferentiation of adipogenic-differentiated cells into osteogenic- or chondrogenic-differentiated cells proceeds via dedifferentiation and correlates with cell cycle arresting and deriving genes. Regarding clinical use, the knowledge of potency and underlying mechanisms are prerequisites.

West, N. R., et al. (2014). "Oncostatin-M promotes phenotypic changes associated with mesenchymal and stem cell-like differentiation in breast cancer." Oncogene **33**(12): 1485-1494.

Cancer stem cell (CSC) biology and the epithelial-to-mesenchymal transition (EMT) are thought to be mechanistically linked and may be key components of cancer development and progression. However, stimuli that induce EMT and CSC-like features ('stemness') are poorly defined. We and others have shown that the inflammatory cytokine oncostatin-M (OSM) mediates phenotypic changes in breast cancer that are consistent with EMT and dedifferentiation, including enhanced migration and loss of hormone receptors. In this study, we have expanded on these prior observations to determine whether OSM is a cell-extrinsic driver of EMT and/or stemness. OSM stimulation of the luminal breast cancer cell lines MCF7 and T47D induced EMT features including loss of membranous E-cadherin and induction of snail and slug expression. OSM treatment markedly enhanced the formation of mammospheres (up to 20-fold, $P<0.001$), which displayed high expression of the pluripotency factor SOX2. The proportion of cells with a CD44(high)CD24(-/low) phenotype was similarly increased by OSM ($P<0.001$). OSM-induced mammosphere formation and CD44(high)CD24(-/low) induction was dependent on PI3K signalling. In silico analysis of human breast

tumours (from a publicly available data set, n=322) confirmed that co-expression of a PI3K transcriptional signature, but not MAPK or STAT3 signatures, was necessary to detect an association between OSMR and poor prognosis. Assessment of a second in silico data set (n=241 breast tumours) confirmed a significant relationship between OSMR, markers of EMT and CSCs, and chemotherapy resistance. Direct analysis of mRNA expression by RT-PCR in a third cohort (n=72 breast tumours) demonstrated that high expression of OSM is associated positively with indicators of EMT (SNAI1, P<0.001) and stemness (SOX2, P<0.05). Our data suggest for the first time that OSM may promote a clinically relevant EMT/CSC-like phenotype in human breast cancer via a PI3K-dependent mechanism.

Yang, Y., et al. (2018). "Mesenchymal stem cell-derived extracellular matrix enhances chondrogenic phenotype of and cartilage formation by encapsulated chondrocytes in vitro and in vivo." Acta Biomater **69**: 71-82.

Mesenchymal stem cell derived extracellular matrix (MSC-ECM) is a natural biomaterial with robust bioactivity and good biocompatibility, and has been studied as a scaffold for tissue engineering. In this investigation, we tested the applicability of using decellularized human bone marrow derived MSC-ECM (hBMSC-ECM) as a culture substrate for chondrocyte expansion in vitro, as well as a scaffold for chondrocyte-based cartilage repair. hBMSC-ECM deposited by hBMSCs cultured on tissue culture plastic (TCP) was harvested, and then subjected to a decellularization process to remove hBMSCs. Compared with chondrocytes grown on TCP, chondrocytes seeded onto hBMSC-ECM exhibited significantly increased proliferation rate, and maintained better chondrocytic phenotype than TCP group. After being expanded to the same cell number and placed in high-density micromass cultures, chondrocytes from the ECM group showed better chondrogenic differentiation profile than those from the TCP group. To test cartilage formation ability, composites of hBMSC-ECM impregnated with chondrocytes were subjected to brief trypsin treatment to allow cell-mediated contraction, and folded to form 3-dimensional chondrocyte-impregnated hBMSC-ECM (Cell/ECM constructs). Upon culture in vitro in chondrogenic medium for 21days, robust cartilage formation was observed in the Cell/ECM constructs. Similarly prepared Cell/ECM constructs were tested in vivo by subcutaneous implantation into SCID mice. Prominent cartilage formation was observed in the implanted Cell/ECM constructs 14days post-implantation, with higher sGAG deposition compared to controls consisting of chondrocyte cell sheets. Taken together, these findings demonstrate that hBMSC-ECM is a superior culture substrate for chondrocyte expansion and a bioactive matrix potentially applicable for cartilage regeneration in vivo. STATEMENT OF SIGNIFICANCE: Current cell-based treatments for focal cartilage defects face challenges, including chondrocyte dedifferentiation, need for xenogenic scaffolds, and suboptimal cartilage formation. We present here a novel technique that utilizes adult stem cell-derived extracellular matrix, as a culture substrate and/or encapsulation scaffold for human adult chondrocytes, for the repair of cartilage defects. Chondrocytes cultured in stem cell-derived matrix showed higher proliferation, better chondrocytic phenotype, and improved redifferentiation ability upon in vitro culture expansion. Most importantly, 3-dimensional constructs formed from chondrocytes folded within stem cell matrix manifested excellent cartilage formation both in vitro and in vivo. These findings demonstrate the suitability of stem cell-derived extracellular matrix as a culture substrate for chondrocyte expansion as well as a candidate bioactive matrix for cartilage regeneration.

Yu, W., et al. (2018). "Dissecting Molecular Mechanisms Underlying Pulmonary Vascular Smooth Muscle Cell Dedifferentiation in Pulmonary Hypertension: Role of Mutated Caveolin-1 (Cav1(F92A))-Bone Marrow Mesenchymal Stem Cells." Heart Lung Circ.

BACKGROUND: Pulmonary arterial hypertension (PAH) is characterised by remodelling in vascular smooth muscles, and switching from contractile (differentiated) to synthetic (dedifferentiated) phenotype. This study aimed to investigate the effect of a mutated caveolin-1 (Cav1(F92A)) gene from bone marrow mesenchymal stem cells (rBMSCs) on phenotypic switching in the smooth muscle cells during PAH. METHODS: Human pulmonary smooth muscle cells (HPASMCs) were treated with monocrotaline (MCT,1muM), and co-cultured with Cav1(F92A) gene modified rBMSCs (rBMSCs/Cav1(F92A)). The nitric oxide (NO) production, cell adhesion, cell viability and inflammatory cytokines expression in rBMSCs was measured to evaluate the survival rate of rBMSCs and the changes of inflammatory cytokines. The concentration of NO/cGMP (nitric oxide/Guanosine-3',5'-cyclic monophosphate), the tumour necrosis factor-alpha (TNF-alpha), transforming growth factor-beta1 (TGF-beta1) mRNA, the expression of contractile smooth muscle cells (SMCs) phenotype markers (thrombospondin-1 and Matrix Gla protein, MGP), the synthetic SMCs phenotype markers (H-caldesmon and smooth muscle gene SM22 alpha, SM22alpha), cell migration and the morphological changes in rBMSCs/Cav1(F92A) co-cultured HPASMCs were investigated. RESULTS: Cav1(F92A) increased NO concentration, cell adhesion, cell viability, anti-inflammatory cytokines interleukin-4

(IL-4), and interleukin-10 (IL-10), but decreased the inflammatory cytokines interleukin-1alpha (IL-1alpha), interferon-gamma (INF-gamma) and TNF-alpha expression in rBMSCs. rBMSCs/Cav1(F92A) activated the NO/cGMP, down-regulated TNF-alpha, TGF-beta1, thrombospondin-1 and MGP expression, up-regulated SM22alpha and H-caldesmon expression, restored cell morphology, and inhibited cell migration in MCT treated HPASMCs. CONCLUSIONS: rBMSCs/Cav1(F92A) inhibits switching from contractile to synthetic phenotype in HPASMCs. It also inhibits migration and promotes morphological restoration of these cells. rBMSCs/Cav1(F92A) may be used as a therapeutic modality for PAH.

Zhong, W., et al. (2013). "Mesenchymal stem cell and chondrocyte fates in a multishear microdevice are regulated by Yes-associated protein." Stem Cells Dev **22**(14): 2083-2093.

Mechanical cues exert considerable influence on the fates of stem cells and terminally differentiated chondrocytes. The elucidation of the interactions between cell fate and mechanical cues in nuclear mechanotransduction will provide new clues to modulate tissue homeostasis and regeneration. In this study, we used an integrated microfluidic perfusion device to simultaneously generate multiple-parameter fluid shear stresses to investigate the role of fluid flow stimuli in the regulation of Yes-associated protein (YAP) expression and the fates of mesenchymal stem cells (MSCs) and primary chondrocytes. YAP expression was regulated by the level of fluid flow stimulus in both MSCs and chondrocytes. An increase in the magnitude of stimulation enhanced the expression of YAP, ultimately resulting in an increase in osteogenesis and a decrease in adipogenesis for MSCs, and initiating dedifferentiation for chondrocytes. Cytochalasin D not only repressed nuclear YAP accumulation in the flow state, but also abrogated flow-induced effects on MSC differentiation and the chondrocyte phenotype, resulting in MSC adipogenesis and the maintenance of the chondrocyte phenotype. Our findings reveal the connection between YAP and MSC/chondrocyte fates in a fluid flow-induced mechanical microenvironment and provide new insights into the mechanisms by which mechanical cues regulate the fates of MSCs and chondrocytes.

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