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Stem Cell

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Stem Cell Unipotent 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; unipotent 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.

Unipotent cells can produce only one cell type, their own,[5] but have the property of self-renewal, which distinguishes them from non-stem cells (e.g. progenitor cells, which cannot self-renew).

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

Archacka, K., et al. (2013). "[Are satellite cells stem cells?]." Postepy Biochem **59**(2): 205-218.

Satellite cells, localized in the niche between the membrane of muscle fiber and basal lamina that surrounds it, serve as a source of myoblasts that are necessary for both growth and regeneration of skeletal muscle. Apart from their ability to convert into myoblasts, satellite cells are also able to self-renew, thus, they meet requirements for tissue specific, unipotent stem cells. Recently conducted research revealed that population of satellite cells is heterogeneous. The article summarizes current information on biology and characteristics of satellite cells, and also describes models concerning mechanisms of self-renewal and differentiation of satellite cells. Experiments regarding in vitro differentiation of satellite cells into other cell types are also discussed. Moreover, other population of stem cells localized in the muscle are described in this review.

Blanpain, C., et al. (2007). "Epithelial stem cells: turning over new leaves." Cell **128**(3): 445-458.

Most epithelial tissues self-renew throughout adult life due to the presence of multipotent stem cells and/or unipotent progenitor cells. Epithelial stem cells are specified during development and are controlled by epithelial-mesenchymal interactions. Despite morphological and functional differences among epithelia, common signaling pathways appear to control epithelial stem cell maintenance, activation, lineage determination, and differentiation. Additionally, deregulation of these pathways can lead to human disorders including cancer. Understanding epithelial stem cell biology has major clinical implications for the diagnosis, prevention, and treatment of human diseases, as well as for regenerative medicine.

Bose, B. and P. S. Shenoy (2016). "Aging induced loss of stemness with concomitant gain of myogenic properties of a pure population of CD34(+)/CD45(-) muscle derived stem cells." Int J Biochem Cell Biol **70**: 1-12.

Aging is accompanied by the functional decline of cells, tissues, and organs, as well as, a

striking increase in susceptibility to a wide range of diseases. Within a tissue, both differentiated cells and adult stem cells are susceptible to intrinsic and extrinsic changes while aging. Muscle derived stem cells (MDSCs) are tissue specific stem cells which have been studied well for their multipotential nature. Although there are reports relating to diminished function and regenerative capacity of aged MDSCs as compared to their young counterparts, not much has been reported relating to the concomitant gain in unipotent nature of aged MDSCs. In this study, we report an inverse correlation between aging and expression of adult/mesenchymal stem cell markers and a direct correlation between aging and myogenecity in MDSCs. Aged MDSCs were able to generate a greater number of dystrophin positive myofibres, as compared to, the young MDSCs when transplanted in muscle of dystrophic mice. Our data, therefore, suggests that aging stress adds to the decline in stem cell characteristics with a concomitant increase in unipotency, in terms of, myogenecity of MDSCs. This study, hence, also opens the possibilities of using unipotent aged MDSCs as potential candidates for transplantation in patients with muscular dystrophies.

Bozdag, S. C., et al. (2018). "Adult Stem Cells and Medicine." Adv Exp Med Biol **1079**: 17-36.

Stem cells can be either totipotent, pluripotent, multipotent or unipotent. Totipotent cells have the capability to produce all cell types of the developing organism, including both embryonic and extraembryonic tissues. The Hematopoietic Stem Cells (HSC) are the first defined adult stem cells (ASC) that give rise to all blood cells and immune system. Use of HSCs for treatment of hematologic malignancies, which is also called bone marrow (BM) transplantation or peripheral blood stem cells (PBSC) transplantation is the pioneer of cellular therapy and translational research. However, stem cell research field is developing so fast that, innovative approaches using HSCs for treatment of refractory diseases are growing rapidly. Hematopoietic stem cell transplantation (HSCT) has been widely used to achieve cure in different hematological diseases. Applications include the treatment of marrow failure syndromes, leukemia, lymphoma, multiple myeloma (MM), certain inherited blood disorders, autoimmune diseases and as an enzyme replacement in metabolic disorders. Innovative approaches such as haploidentical stem cell transplantation, new monoclonal antibodies and immunotherapies as well as Chimeric Antigen Receptor T-cell (CAR-T cell) therapies are on the way as promising treatment options especially for patients with refractory hematologic malignancies and even in solid tumors. However, there are still some challenges remaining before some of these therapies are translated into clinical application. In this paper, HSCs including its properties, niches, clinical usage and its contribution to modern medicine today and in the future will be discussed.

Can, A. (2008). "A Concise Review on the Classification and Nomenclature of Stem Cells." Turk J Haematol **25**(2): 57-59.

Stem cell biology and regenerative medicine is a relatively young field. However, in recent years there has been a tremendous interest in stem cells possibly due to their therapeutic potential in disease states. As a classical definition, a stem cell is an undifferentiated cell that can produce daughter cells that can either remain a stem cell in a process called self-renew notal, or commit to a specific cell type via the initiation of a differentiation pathway leading to the production of mature progeny cells. Despite this acknowledged definition, the classification of stem cells has been a perplexing notion that may often raise misconception even among stem cell biologists. Therefore, the aim of this brief review is to give a conceptual approach to classifying the stem cells beginning from the early morula stage totipotent embryonic stem cells to the unipotent tissue-resident adult stem cells, also called tissue-specific stem cells.

Carrelha, J., et al. (2018). "Hierarchically related lineage-restricted fates of multipotent haematopoietic stem cells." Nature **554**(7690): 106-111.

Rare multipotent haematopoietic stem cells (HSCs) in adult bone marrow with extensive self-renewal potential can efficiently replenish all myeloid and lymphoid blood cells, securing long-term multilineage reconstitution after physiological and clinical challenges such as chemotherapy and haematopoietic transplantations. HSC transplantation remains the only curative treatment for many haematological malignancies, but inefficient blood-lineage replenishment remains a major cause of morbidity and mortality. Single-cell transplantation has uncovered considerable heterogeneity among reconstituting HSCs, a finding that is supported by studies of unperturbed haematopoiesis and may reflect different propensities for lineage-fate decisions by distinct myeloid-, lymphoid- and platelet-biased HSCs. Other studies suggested that such lineage bias might reflect generation of unipotent or oligopotent self-renewing progenitors within the phenotypic HSC compartment, and implicated uncoupling of the defining HSC properties of self-renewal and multipotency. Here we use highly sensitive tracking of progenitors and mature cells of the megakaryocyte/platelet, erythroid, myeloid and B and T cell lineages, produced from singly transplanted HSCs, to reveal a highly organized, predictable and

stable framework for lineage-restricted fates of long-term self-renewing HSCs. Most notably, a distinct class of HSCs adopts a fate towards effective and stable replenishment of a megakaryocyte/platelet-lineage tree but not of other blood cell lineages, despite sustained multipotency. No HSCs contribute exclusively to any other single blood-cell lineage. Single multipotent HSCs can also fully restrict towards simultaneous replenishment of megakaryocyte, erythroid and myeloid lineages without executing their sustained lymphoid lineage potential. Genetic lineage-tracing analysis also provides evidence for an important role of platelet-biased HSCs in unperturbed adult haematopoiesis. These findings uncover a limited repertoire of distinct HSC subsets, defined by a predictable and hierarchical propensity to adopt a fate towards replenishment of a restricted set of blood lineages, before loss of self-renewal and multipotency.

Case, J., et al. (2008). "In vitro clonal analysis of murine pluripotent stem cells isolated from skeletal muscle and adipose stromal cells." Exp Hematol **36**(2): 224-234.

OBJECTIVE: Possible clinical utility of pluripotent stem cells (PSCs) with multilineage differentiation capacity depends on their ability to adapt to tissue-specific differentiation conditions. Previous data from our laboratory suggest that putative PSCs exhibiting an immunophenotype of CD45(-)Sca-1+CD117(-)CD90+ can be isolated from multiple tissues. In the present study, the clonal in vitro differentiation potential of two isolates of PSCs was examined. MATERIALS AND METHODS: Clonal analysis of the differentiation potential of skeletal muscle- (SM) and adipose stromal cell (ASC)-derived PSCs into myogenic, adipogenic, and neurogenic cells was investigated by expanding single PSCs prior to specification under three separate differentiation conditions. RESULTS: Differentiation of SM- and ASC-derived PSCs into myotubes, adipocytes, and neuronal-like cells was evident in clonal cultures promoting differentiation along these lineages. A total of 2.0%, 1.0%, and 0.33% of SM-derived clones demonstrated unipotent, bipotent, and tripotent differentiation, respectively, into combinations of myocytes, adipocytes, and neuronal cells. As a percentage of SM-derived PSCs, tripotent clones comprised 0.016% of total muscle cells. Similar results were obtained with ASC-derived PSCs, suggesting phenotypic and functional similarities between PSCs from both tissues. Following differentiation of single PSCs into three lineages, a clear and complete commitment to tissue-specific gene expression accompanied by inactivation of lineage-unrelated genes could not be demonstrated in several SM- and ASC-derived clones. CONCLUSIONS: These data demonstrate that phenotypically defined PSCs remain functionally heterogeneous at the single-cell level and illustrate that morphologic lineage commitment may be independent of exclusive expression and/or loss of associated lineage specific genes.

Case, J., et al. (2005). "Clonal multilineage differentiation of murine common pluripotent stem cells isolated from skeletal muscle and adipose stromal cells." Ann N Y Acad Sci **1044**: 183-200.

Pluripotent stem cells (PSCs) with transdifferentiation capacity may provide useful therapeutic modalities in the areas of cellular restoration and regenerative medicine. The utility of PSCs depends on their ability to respond to different stimuli and to adapt to tissue-specific differentiation conditions. Given that a number of cells possessing characteristics of PSCs have been identified and isolated from several adult murine tissues, we hypothesized that a common PSC may exist in multiple murine tissues and that these cells may either reside permanently in specific sites or continue to circulate and colonize tissues as needed. Previous data from our laboratory suggest that PSCs exhibiting an immunophenotype of CD45(-)Sca-1(+)c-kit(-)Thy-1(+) can be isolated from multiple murine tissues and may represent putative common PSCs (CoPSCs). To investigate whether the multiple tissue differentiation potential observed with these cells resulted from the presence of different tissue-restricted progenitors within CD45(-)Sca-1(+)c-kit(-)Thy-1(+) cells or was the product of clonal differentiation of CoPSCs, clonality studies were performed. Single skeletal muscle (SM)-derived CoPSCs were expanded for 10 days, and progeny cells were split into three culture conditions designed to stimulate myogenic, adipogenic, and neurogenic differentiation. Analysis of 600 clones indicated that 2.16%, 0.83%, and 0.33% of the total number of plated single cells were capable of unipotent, bipotent, and tripotent differentiation, respectively, into combinations of myocytes, adipocytes, and neuronal cells. Given that SM-derived CoPSCs represent 4.78% of the total cells analyzed, tripotent CoPSCs made up 0.016% of the total muscle cells. Similar results were obtained in clonal analyses using adipose stromal cell (ASC)-derived CoPSCs, suggesting that both SM- and ASC-derived CoPSCs may be phenotypically and functionally identical. Taken together, these data demonstrate that a common PSC can be identified in different murine tissues and suggest that a small fraction of these cells are capable of clonal differentiation into multiple cell types.

Chen, Z., et al. (2015). "Plasticity of male germline stem cells and their applications in reproductive and regenerative medicine." Asian J Androl **17**(3): 367-372.

Spermatogonial stem cells (SSCs), also known as male germline stem cells, are a small subpopulation of type A spermatogonia with the potential of self-renewal to maintain stem cell pool and differentiation into spermatids in mammalian testis. SSCs are previously regarded as the unipotent stem cells since they can only give rise to sperm within the seminiferous tubules. However, this concept has recently been challenged because numerous studies have demonstrated that SSCs cultured with growth factors can acquire pluripotency to become embryonic stem-like cells. The in vivo and in vitro studies from peers and us have clearly revealed that SSCs can directly transdifferentiate into morphologic, phenotypic, and functional cells of other lineages. Direct conversion to the cells of other tissues has important significance for regenerative medicine. SSCs from azoospermia patients could be induced to differentiate into spermatids with fertilization and developmental potentials. As such, SSCs could have significant applications in both reproductive and regenerative medicine due to their unique and great potentials. In this review, we address the important plasticity of SSCs, with focuses on their self-renewal, differentiation, dedifferentiation, transdifferentiation, and translational medicine studies.

Choi, N. Y., et al. (2014). "A novel feeder-free culture system for expansion of mouse spermatogonial stem cells." Mol Cells **37**(6): 473-479.

Spermatogonial stem cells (SSCs, also called germline stem cells) are self-renewing unipotent stem cells that produce differentiating germ cells in the testis. SSCs can be isolated from the testis and cultured in vitro for long-term periods in the presence of feeder cells (often mouse embryonic fibroblasts). However, the maintenance of SSC feeder culture systems is tedious because preparation of feeder cells is needed at each subculture. In this study, we developed a Matrigel-based feeder-free culture system for long-term propagation of SSCs. Although several in vitro SSC culture systems without feeder cells have been previously described, our Matrigel-based feeder-free culture system is time- and cost- effective, and preserves self-renewability of SSCs. In addition, the growth rate of SSCs cultured using our newly developed system is equivalent to that in feeder cultures. We confirmed that the feeder-free cultured SSCs expressed germ cell markers both at the mRNA and protein levels. Furthermore, the functionality of feeder-free cultured SSCs was confirmed by their transplantation into germ cell-depleted mice. These results suggest that our newly developed feeder-free culture system provides a simple approach to maintaining SSCs in vitro and studying the basic biology of SSCs, including determination of their fate.

Clarke, L. and D. van der Kooy (2011). "The adult mouse dentate gyrus contains populations of committed progenitor cells that are distinct from subependymal zone neural stem cells." Stem Cells **29**(9): 1448-1458.

There is currently a debate as to whether or not a neural stem cell (NSC) exists in the adult mammalian hippocampus. Clonal colony-forming assays allow single cells to cells to be evaluated for stem cell properties: self-renewal and multipotentiality. In these in vitro assays, single cells from the subependymal zone (SEZ) of the adult lateral ventricle yield large colonies which self-renew and are multipotential, while single cells from the adult dentate gyrus (DG) produce small, unipotent, and nonself-renewing colonies. We find that multipotential and long-term self-renewing colonies can be isolated only from the early embryonic hippocampus, before the formation of the DG. No movement of progenitors from the postnatal SEZ to the newly forming DG subgranular zone is detected and adult DG colonies in vitro originate from the embryonic hippocampal primordium. These data support a model where embryonic hippocampal NSCs change their properties as the organism ages. When adult DG spheres are cocultured with embryonic brain slices, self-renewal (but not multipotentiality) is restored and maintained for several passages off of slices. Adult clonal DG spheres grown on embryonic brain slices or transplanted into brains of neonatal mice do not give rise to neurons. Neurons arise from separate, small clones that are approximately 10 times more frequent than sphere colonies in vitro and may be responsible for maintaining neurogenesis in the adult in vivo. We propose that there are separate glial and neuronal clones in the adult hippocampus, with glial progenitors being the most proliferative in culture.

Corbineau, S., et al. (2017). "Spermatogonial stem cells and progenitors are refractory to reprogramming to pluripotency by the transcription factors Oct3/4, c-Myc, Sox2 and Klf4." Oncotarget **8**(6): 10050-10063.

The male germinal lineage, which is defined as unipotent, produces sperm through spermatogenesis. However, embryonic primordial germ cells and postnatal spermatogonial stem cells (SSCs) can change their fate and convert to pluripotency in culture when they are not controlled by the testicular microenvironment. The mechanisms underlying these reprogramming processes are poorly understood. Testicular germ cell tumors, including teratoma, share some molecular characteristics with pluripotent cells, suggesting that cancer could result from an abnormal differentiation of primordial germ cells or from an abnormal conversion of SCCs to pluripotency in the testis. Here, we investigated whether the somatic

reprogramming factors Oct3/4, Sox2, Klf4 and c-Myc (OSKM) could play a role in SSCs reprogramming and induce pluripotency using a doxycycline-inducible transgenic Col1a1-4F2A-OSKM mouse model. We showed that, in contrast to somatic cells, SSCs from adult mice are resistant to this reprogramming strategy, even in combination with small molecules, hypoxia, or p53 deficiency, which were previously described to favour the conversion of somatic cells to pluripotency. This finding suggests that adult SSCs have developed specific mechanisms to repress reprogramming by OSKM factors, contributing to circumvent testicular cancer initiation events.

Costamagna, D., et al. (2015). "Adult Stem Cells and Skeletal Muscle Regeneration." Curr Gene Ther **15**(4): 348-363.

Satellite cells are unipotent stem cells involved in muscle regeneration. However, the skeletal muscle microenvironment exerts a dominant influence over stem cell function. The cell intrinsic complexity of the skeletal muscle niche located within the connective tissue between fibers includes motor neurons, tendons, blood vessels, immune response mediators and interstitial cells. All these cell types modulate the trafficking of stimuli responsible of muscle fiber regeneration. In addition, several stem cell types have been discovered in skeletal muscle tissue, mainly located in the interstitium. The majority of these stem cells appears to directly contribute to myogenic differentiation, although some of them are mainly implicated in paracrine effects. This review focuses on adult stem cells, which have been used for therapeutic purposes, mainly in animal models of chronic muscle degeneration. Emerging literature identifies other myogenic progenitors generated from pluripotent stem cells as potential candidates for the treatment of skeletal muscle degeneration. However, adult stem cells still represent the gold standard for future comparative studies.

De Chiara, L., et al. (2014). "Renal cells from spermatogonial germline stem cells protect against kidney injury." J Am Soc Nephrol **25**(2): 316-328.

Spermatogonial stem cells reside in specific niches within seminiferous tubules and continuously generate differentiating daughter cells for production of spermatozoa. Although spermatogonial stem cells are unipotent, these cells are able to spontaneously convert to germline cell-derived pluripotent stem cells (GPSCs) in vitro. GPSCs have many properties of embryonic stem cells and are highly plastic, but their therapeutic potential in tissue regeneration has not been fully explored. Using a novel renal epithelial differentiation protocol, we obtained GPSC-derived tubular-like cells (GTCs) that were functional in vitro, as demonstrated through transepithelial electrical resistance analysis. In mice, GTCs injected after ischemic renal injury homed to the renal parenchyma, and GTC-treated mice showed reduced renal oxidative stress, tubular apoptosis, and cortical damage and upregulated tubular expression of the antioxidant enzyme hemeoxygenase-1. Six weeks after ischemic injury, kidneys of GTC-treated mice had less fibrosis and inflammatory infiltrate than kidneys of vehicle-treated mice. In conclusion, we show that GPSCs can be differentiated into functionally active renal tubular-like cells that therapeutically prevent chronic ischemic damage in vivo, introducing the potential utility of GPSCs in regenerative cell therapy.

de Kretser, D. (2007). "Totipotent, pluripotent or unipotent stem cells: a complex regulatory enigma and fascinating biology." J Law Med **15**(2): 212-218.

The search for sources of human stem cells has become a controversial topic from an ethical point of view primarily as it has required the destruction of human embryos. The development of alternative techniques that enable the generation of pluripotent stem cells from adult cells has opened new avenues of research but the generation of such cells has again been controversial since it requires the use of human eggs, using a technique called somatic cell nuclear transfer. Since the cells so generated have a very small potential to generate an "embryo" and since the production of the cell lines requires destruction of that "embryo", a further ethical issue arises. This article discusses these issues and suggests a framework that may assist their consideration. Finally, the article reviews some recent developments that have the potential to remove the need for the use of eggs or embryos in the generation of stem cell lines and highlights the danger of developing legislation on only our current knowledge.

Dulak, J., et al. (2015). "Adult stem cells: hopes and hypes of regenerative medicine." Acta Biochim Pol **62**(3): 329-337.

Stem cells are self-renewing cells that can differentiate into specialized cell type(s). Pluripotent stem cells, i.e. embryonic stem cells (ESC) or induced pluripotent stem cells (iPSC) differentiate into cells of all three embryonic lineages. Multipotent stem cells, like hematopoietic stem cells (HSC), can develop into multiple specialized cells in a specific tissue. Unipotent cells differentiate only into one cell type, like e.g. satellite cells of skeletal muscle. There are many examples of successful clinical applications of stem cells. Over million patients worldwide have benefited from bone marrow transplantations performed for treatment of leukemias, anemias or immunodeficiencies. Skin stem cells are used to heal severe burns, while limbal stem cells can regenerate the

damaged cornea. Pluripotent stem cells, especially the patient-specific iPSC, have a tremendous therapeutic potential, but their clinical application will require overcoming numerous drawbacks. Therefore, the use of adult stem cells, which are multipotent or unipotent, can be at present a more achievable strategy. Noteworthy, some studies ascribed particular adult stem cells as pluripotent. However, despite efforts, the postulated pluripotency of such events like "spore-like cells", "very small embryonic-like stem cells" or "multipotent adult progenitor cells" have not been confirmed in stringent independent studies. Also plasticity of the bone marrow-derived cells which were suggested to differentiate e.g. into cardiomyocytes, has not been positively verified, and their therapeutic effect, if observed, results rather from the paracrine activity. Here we discuss the examples of recent studies on adult stem cells in the light of current understanding of stem cell biology.

Dziedzic, K., et al. (2014). "Kidney stem cells in development, regeneration and cancer." Semin Cell Dev Biol **36**: 57-65.

The generation of nephrons during development depends on differentiation via a mesenchymal to epithelial transition (MET) of self-renewing, tissue-specific stem cells confined to a specific anatomic niche of the nephrogenic cortex. These cells may transform to generate oncogenic stem cells and drive pediatric renal cancer. Once nephron epithelia are formed the view of post-MET tissue renal growth and maintenance by adult tissue-specific epithelial stem cells becomes controversial. Recently, genetic lineage tracing that followed clonal evolution of single kidney cells showed that the need for new cells is constantly driven by fate-restricted unipotent clonal expansions in varying kidney segments arguing against a multipotent adult stem cell model. Lineage-restriction was similarly maintained in kidney organoids grown in culture. Importantly, kidney cells in which Wnt was activated were traced to give significant clonal progeny indicating a clonogenic hierarchy. In vivo nephron epithelia may be endowed with the capacity akin to that of unipotent epithelial stem/progenitor such that under specific stimuli can clonally expand/self renew by local proliferation of mature differentiated cells. Finding ways to ex vivo preserve and expand the observed in vivo kidney-forming capacity inherent to both the fetal and adult kidneys is crucial for taking renal regenerative medicine forward. Some of the strategies used to achieve this are sorting human fetal nephron stem/progenitor cells, growing adult nephrospheres or reprogramming differentiated kidney cells toward expandable renal progenitors.

Elias, S., et al. (2017). "Long-lived unipotent Blimp1-positive luminal stem cells drive mammary gland organogenesis throughout adult life." Nat Commun **8**(1): 1714.

The hierarchical relationships between various stem and progenitor cell subpopulations driving mammary gland morphogenesis and homoeostasis are poorly understood. Conditional inactivation experiments previously demonstrated that expression of the zinc finger transcriptional repressor Blimp1/PRDM1 is essential for the establishment of epithelial cell polarity and functional maturation of alveolar cells. Here we exploit a Prdm1.CreERT2-LacZ reporter allele for lineage tracing experiments. Blimp1 expression marks a rare subpopulation of unipotent luminal stem cells that initially appear in the embryonic mammary gland at around E17.5 coincident with the segregation of the luminal and basal compartments. Fate mapping at multiple time points in combination with whole-mount confocal imaging revealed these long-lived unipotent luminal stem cells survive consecutive involutions and retain their identity throughout adult life. Blimp1(+) luminal stem cells give rise to Blimp1(-) progeny that are invariably Elf5(+)ERalpha(-)PR(-). Thus, Blimp1 expression defines a mammary stem cell subpopulation with unique functional characteristics.

Fortunel, N., et al. (2000). "Release from quiescence of primitive human hematopoietic stem/progenitor cells by blocking their cell-surface TGF-beta type II receptor in a short-term in vitro assay." Stem Cells **18**(2): 102-111.

Genetic alterations of the signaling cascade of transforming growth factor-beta (TGF-beta) are often associated with neoplastic transformation of primitive cells. This demonstrates the key role for this pleiotropic factor in the control of quiescence and cell proliferation in vivo. In the high proliferative potential-quiescent cell (HPP-Q) in vitro assay, the use of TGF-beta1 blocking antibodies (anti-TGF-beta1) allows the detection within two to three weeks of primitive hematopoietic cells called HPP-Q, which otherwise would not grow. However, the possibility of triggering cell proliferation by blocking the cell-surface TGF-beta receptors has not been investigated until now. We have tested here the efficiency of a blocking antibody against TGF-betaRII (anti-TGF-betaRII) on CD34(+)CD38(-) hematopoietic cells, a subpopulation enriched in primitive stem/progenitor cells, and compared its effect with that of anti-TGF-beta1. About twice as many HPP colony-forming cells were detected in the presence of anti-TGF-beta1 or anti-TGF-betaRII, compared to the control ($p < 0.02$). Moreover, anti-TGF-betaRII was as efficient as anti-TGF-beta1 for activating multipotent HPP-granulocyte erythroid

macrophage megakaryocyte and HPP-Mix, bipotent HPP-granulocyte-macrophage (GM) and unipotent HPP-G, HPP-M and HPP-BFU-E. We therefore propose the use of anti-TGF-betaRII to release primitive cells from quiescence in the HPP-Q assay. This strategy could be extended to nonhematopoietic tissues, as TGF-beta1 may be a pleiotropic regulator of somatic stem cell quiescence.

Funayama, N. (2013). "The stem cell system in demosponges: suggested involvement of two types of cells: archeocytes (active stem cells) and choanocytes (food-entrapping flagellated cells)." Dev Genes Evol **223**(1-2): 23-38.

Major questions about stem cell systems include what type(s) of stem cells are involved (unipotent/totipotent/pluripotent/multipotent stem cells) and how the self-renewal and differentiation of stem cells are regulated. Sponges, the sister group of all other animals and probably the earliest branching multicellular lineage of extant animals, are thought to possess totipotent stem cells. This review introduces what is known about the stem cells in sponges based on histological studies and also on recent molecular biological studies that have started to reveal the molecular and cellular mechanisms of the stem cell system in sponges (mainly in demosponges). The currently proposed model of the stem cell system in demosponges is described, and the possible applicability of this model to other classes of sponges is discussed. Finally, a possible scenario of the evolution of stem cells, including how migrating stem cells arose in the urmetazoan (the last common ancestor of metazoans) and the evolutionary origin of germ line cells in the urbilaterian (the last common ancestor of bilaterians), are discussed.

Guettier, C. (2005). "[Which stem cells for adult liver?]." Ann Pathol **25**(1): 33-44.

While hepatocytes can be considered conceptually as unipotent stem cells, the presence of true stem or progenitor cells within adult livers has been largely debated. It is now accepted that the atypical ductular reaction observed in livers with sub-massive hepatitis represents the proliferation of hepatic progenitor cells similar to rat oval cells and able to differentiate towards the biliary and the hepatocytic lineage through intermediate progeny. In the normal liver, the identification of progenitor cells with a panel of markers including c-kit, CD34, Ov6, CK7, CK19, chromogranine A, CD56 remains difficult because these cells are very few and most of the markers are not specific. These progenitor cells could be located either within the canals of Hering or in periductular situation or both. Mechanisms leading to the activation and the proliferation of hepatic progenitor cells are still largely unknown: they involve growth factors as the stem cell factor, ligand of c-kit, cytokines, chemokines as SDF1 a and vagal or sympathetic innervation. Other potential stem cells for liver could be hematopoietic stem cells from bone marrow. First publications have showed that hematopoietic stem cells were able to differentiate into hepatocytes and cholangiocytes and to yield high level engraftment of injured livers. However it appears now that this phenomenon is minimal or even absent in physiological and usual pathological conditions. It does occur in extreme experimental conditions either by true transdifferentiation or cell fusion. The shared property of stem cells and tumor cells to proliferate endlessly, rises the question of the potential role of progenitor cells in liver carcinogenesis. In a number of animal models of hepatocarcinogenesis, tumors originate from oval cells. The identification of progenitor cells close to murine oval cells in the human liver raises the hypothesis of a potential role of these cells in the development of human liver tumors. Liver progenitor cells have been identified morphologically and phenotypically in dysplastic foci of cirrhotic livers and hepatocellular adenomas. More generally speaking, typical hepatocellular carcinomas and cholangiocarcinomas are at the two ends of a spectrum which includes transitional-type tumors intermediate between hepatocellular carcinoma and cholangiocarcinoma and combined hepato-cellular cholangiocarcinoma; these intermediate and combined types can be more easily explained as deriving from progenitor cells. Despite the difficulties, the doubts and the potential dangers, new experimental modalities to obtain efficient repopulation of the liver from bone marrow stem cells are currently under study: exogenous administration of cytokines and chemokines involved in cell homing and differentiation or development of selective pressure strategies. Other cell types as intra-hepatic progenitor cells, bone marrow multipotent adult progenitor cells (MAPCs) or fetal hepatocytes could be alternative sources for liver cell therapy. Thus, progressing knowledge about stem cells in adult liver would allow to better understand mechanisms of hepatic homeostasia and regeneration and would open the way to cell-based therapy for liver diseases.

Guilak, F., et al. (2006). "Clonal analysis of the differentiation potential of human adipose-derived adult stem cells." J Cell Physiol **206**(1): 229-237.

Pools of human adipose-derived adult stem (hADAS) cells can exhibit multiple differentiated phenotypes under appropriate in vitro culture conditions. Because adipose tissue is abundant and easily accessible, hADAS cells offer a promising source of cells for tissue engineering and other cell-based therapies. However, it is unclear whether

individual hADAS cells can give rise to multiple differentiated phenotypes or whether each phenotype arises from a subset of committed progenitor cells that exists within a heterogeneous population. The goal of this study was to test the hypothesis that single hADAS are multipotent at a clonal level. hADAS cells were isolated from liposuction waste, and ring cloning was performed to select cells derived from a single progenitor cell. Forty-five clones were expanded through four passages and then induced for adipogenesis, osteogenesis, chondrogenesis, and neurogenesis using lineage-specific differentiation media. Quantitative differentiation criteria for each lineage were determined using histological and biochemical analyses. Eighty one percent of the hADAS cell clones differentiated into at least one of the lineages. In addition, 52% of the hADAS cell clones differentiated into two or more of the lineages. More clones expressed phenotypes of osteoblasts (48%), chondrocytes (43%), and neuron-like cells (52%) than of adipocytes (12%), possibly due to the loss of adipogenic ability after repeated subcultures. The findings are consistent with the hypothesis that hADAS cells are a type of multipotent adult stem cell and not solely a mixed population of unipotent progenitor cells. However, it is important to exercise caution in interpreting these results until they are validated using functional in vivo assays.

Hamazaki, Y., et al. (2016). "Medullary thymic epithelial stem cells: role in thymic epithelial cell maintenance and thymic involution." Immunol Rev **271**(1): 38-55.

The thymus consists of two distinct anatomical regions, the cortex and the medulla; medullary thymic epithelial cells (mTECs) play a crucial role in establishing central T-cell tolerance for self-antigens. Although the understanding of mTEC development in thymic organogenesis as well as the regulation of their differentiation and maturation has improved, the mechanisms of postnatal maintenance remain poorly understood. This issue has a central importance in immune homeostasis and physiological thymic involution as well as autoimmune disorders in various clinicopathological settings. Recently, several reports have demonstrated the existence of TEC stem or progenitor cells in the postnatal thymus, which are either bipotent or unipotent. We identified stem cells specified for mTEC-lineage that are generated in the thymic ontogeny and may sustain mTEC regeneration and lifelong central T-cell self-tolerance. This finding suggested that the thymic medulla is maintained autonomously by its own stem cells. Although several issues, including the relationship with other putative TEC stem/progenitors, remain unclear, further examination of mTEC stem cells (mTECSCs) and their regulatory mechanisms may contribute to the understanding of postnatal immune homeostasis. Possible relationships between decline of mTECSC activity and early thymic involution as well as various autoimmune disorders are discussed.

Hammerick, K. E., et al. (2011). "Elastic properties of induced pluripotent stem cells." Tissue Eng Part A **17**(3-4): 495-502.

The recent technique of transducing key transcription factors into unipotent cells (fibroblasts) to generate pluripotent stem cells (induced pluripotent stem cells [iPSCs]) has significantly changed the stem cell field. These cells have great promise for many clinical applications, including that of regenerative medicine. Our findings show that iPSCs can be derived from human adipose-derived stromal cells (hASCs), a notable advancement in the clinical applicability of these cells. To investigate differences between two iPS cell lines (fibroblast-iPSC and hASC-iPSC), and also the gold standard human embryonic stem cell, we looked at cell stiffness as a possible indicator of cell differentiation-potential differences. We used atomic force microscopy as a tool to determine stem cell stiffness, and hence differences in material properties between cells. Human fibroblast and hASC stiffness was also ascertained for comparison. Interestingly, cells exhibited a noticeable difference in stiffness. From least to most stiff, the order of cell stiffness was as follows: hASC-iPSC, human embryonic stem cell, fibroblast-iPSC, fibroblasts, and, lastly, as the stiffest cell, hASC. In comparing hASC-iPSCs to their origin cell, the hASC, the reprogrammed cell is significantly less stiff, indicating that greater differentiation potentials may correlate with a lower cellular modulus. The stiffness differences are not dependent on cell culture density; hence, material differences between cells cannot be attributed solely to cell-cell constraints. The change in mechanical properties of the cells in response to reprogramming offers insight into how the cell interacts with its environment and might lend clues to how to efficiently reprogram cell populations as well as how to maintain their pluripotent state.

Ito, K. (2018). "[Metabolic regulation for cell fate decision of hematopoietic stem cells]." Rinsho Ketsueki **59**(7): 909-914.

Stem cells are self-renewing, either multipotent or unipotent, and they offer opportunities for stem cell-based therapies in the clinical setting. The mechanism underlying the division patterns of hematopoietic stem cells (HSCs) is one of the most fundamental biological questions. However, to date, analyses of individual HSC cell fate decisions have been restricted by the heterogeneity of available HSC-enriched fractions and the technical challenges of

imaging HSC fate. Comprehensive research accompanied with genetic models, metabolomics analyses, and single-cell approaches have highlighted the critical contributions of metabolic control to HSC homeostasis. Consequently, the roles of mitochondrial metabolism in the HSC division symmetry have become a central focus of the current research. Nevertheless, we are only beginning to comprehend the metabolic requirements of stemness. This review summarizes the recent advances in our understanding of the intriguing relationship between mitochondrial metabolism and HSC fate decisions. In addition, this study highlights our recent findings regarding the contributions of the mitochondrial quality control by autophagy to HSC division balance. Elucidation of the metabolic cues governing HSC fate decisions should lead to new techniques of metabolic manipulation, which can shift the division balance of HSCs and offer effective targets in strategies against leukemia and will, thus, be of high clinical importance.

Jensen, U. B., et al. (2013). "Isolation and characterization of cutaneous epithelial stem cells." Methods Mol Biol **989**: 61-69.

During homeostasis, adult mammalian skin turnover is maintained by a number of multipotent and -unipotent epithelial progenitors located either in the epidermis, hair follicle, or sebaceous gland. Recent work has illustrated that these various progenitor populations reside in regionalized niches and are phenotypically distinct from one another. This degree of heterogeneity within the progenitor cell landscape in the cutaneous epithelium complicates our ability to target, purify, and manipulate cutaneous epithelial stem cell subpopulations in adult skin. The techniques outlined in this chapter describe basic procedures for the isolation and purification of murine epithelial progenitors and assessing their capacity for ex vivo propagation.

Kawamoto, H., et al. (1997). "Direct evidence for the commitment of hematopoietic stem cells to T, B and myeloid lineages in murine fetal liver." Int Immunol **9**(7): 1011-1019.

We established an experimental system in vitro to examine the developmental capacity of individual hematopoietic progenitors to generate T, B and myeloid (M) cells. By using this system we analyzed the process of lineage commitment of hematopoietic progenitors in murine fetal liver (FL). It is known that small numbers of B and M cells, in addition to T cells, are generated in a co-culture of hematopoietic progenitors and a deoxyguanosine-treated fetal thymus (FT) lobe. We tried to enhance the growth of B and M cells by the addition of IL-7, IL-3 and stem cell factor into the co-culture. This cytokine-supplemented FT organ culture was used to examine the developmental capacity of individual hematopoietic progenitors in FL. Single cells of lineage marker (Lin)-c-kit+Sca-1+ (Sca-1+) and Lin-c-kit+Sca-1-(Sca-1-) populations from the FL harvested at day 12 of gestation were cultured for 10 days, and the phenotypes of cells generated in each lobe were analyzed with a flow cytometer. All progenitors in the Sca-1-population were shown to be committed to generate only T, B or M cells. On the other hand, multipotent progenitors, which are capable of generating T, B and M cells, as well as unipotent progenitors committed to the T, B or M lineage were found in the Sca-1+ population. Bipotent progenitors generating M and T cells and those generating M and B cells were also found in the Sca-1+ population, which probably represent progenitors in the process of commitment. However, no bipotent progenitors generating T and B cells were detected.

Ko, K., et al. (2010). "Conversion of adult mouse unipotent germline stem cells into pluripotent stem cells." Nat Protoc **5**(5): 921-928.

Germline stem cells (GSCs), often called spermatogonial stem cells, are unipotent stem cells that can give rise only to gametes. Under defined culture conditions, unipotent GSCs can be converted into pluripotent stem cells, termed as germline-derived pluripotent stem (gPS) cells. gPS cells can be differentiated into cells forming all three germ layers and germ cells. In this study, we describe a simple and robust protocol for the derivation of GSCs from adult mouse testis and the rapid and reproducible conversion of GSCs into gPS cells. Under our defined culture conditions, GSCs can be converted into gPS cells in approximately 1 month. The initial number of plated GSCs and the culture time are two conditions that are critical for the successful conversion of GSCs into gPS cells. gPS cells are similar to embryonic stem cells, as judged by molecular and cellular properties and its development potential. Thus, generation of gPS cells holds potential for tissue regenerative medicine.

Ko, K., et al. (2009). "Induction of pluripotency in adult unipotent germline stem cells." Cell Stem Cell **5**(1): 87-96.

Mouse and human stem cells with features similar to those of embryonic stem cells have been derived from testicular cells. Although pluripotent stem cells have been obtained from defined germline stem cells (GSCs) of mouse neonatal testis, only multipotent stem cells have been obtained so far from defined cells of mouse adult testis. In this study we describe a robust and reproducible protocol for obtaining germline-derived pluripotent stem (gPS) cells from adult unipotent GSCs. Pluripotency of gPS cells was

confirmed by in vitro and in vivo differentiation, including germ cell contribution and transmission. As determined by clonal analyses, gPS cells indeed originate from unipotent GSCs. We propose that the conversion process requires a GSC culture microenvironment that depends on the initial number of plated GSCs and the length of culture time.

Koniukhov, B. V. (1991). "[Genetic control over the determination and proliferation of melanocyte stem cells in mammals]." Ontogenez **22**(2): 167-175.

Data obtained in mutant mouse strains provide evidence for multilocus control of determination and proliferation of melanocyte stem cells. Mice are known to have five loci (mi, Sp, s, Ls, Dom) controlling melanoblast determination. Locus mi is expressed in pluripotent cells of the neural crest from which melanocyte and neuron clones are formed; it is also expressed in a strain of ectomesenchyme cells. Loci Sp, s, ls and Dom are expressed somewhat later, probably during one of the last quantal cell cycles leading to the determination of unipotent melanocyte stem cells. Mutant genes of these loci impair the development of pigment cells as well as of ganglial neurons. Three loci (W, vs, Sl) control the proliferation of melanocyte stem cells. Mutations of locus W present in a single copy inhibit the proliferative activity of melanoblasts, whereas when present at the double dose they completely block their proliferation. Locus Sl is not expressed in melanocytes but acts in another cell system, which is very important for the proliferation of melanocyte stem cells. Mutant genes Ga, si and vit decrease the lifespan of stem cells for epidermal melanocytes.

Krebsbach, P. H. and L. G. Villa-Diaz (2017). "The Role of Integrin alpha6 (CD49f) in Stem Cells: More than a Conserved Biomarker." Stem Cells Dev **26**(15): 1090-1099.

Stem cells have the capacity for self-renewal and differentiation into specialized cells that form and repopulated all tissues and organs, from conception to adult life. Depending on their capacity for differentiation, stem cells are classified as totipotent (ie, zygote), pluripotent (ie, embryonic stem cells), multipotent (ie, neuronal stem cells, hematopoietic stem cells, epithelial stem cells, etc.), and unipotent (ie, spermatogonial stem cells). Adult or tissue-specific stem cells reside in specific niches located in, or nearby, their organ or tissue of origin. There, they have microenvironmental support to remain quiescent, to proliferate as undifferentiated cells (self-renewal), and to differentiate into progenitors or terminally differentiated cells that migrate from the niche to perform specialized functions. The presence of proteins at the cell surface is often used to identify, classify, and isolate stem cells. Among the diverse groups of cell surface proteins used for these purposes, integrin alpha6, also known as CD49f, may be the only biomarker commonly found in more than 30 different populations of stem cells, including some cancer stem cells. This broad expression among stem cell populations indicates that integrin alpha6 may play an important and conserved role in stem cell biology, which is reaffirmed by recent demonstrations of its role maintaining self-renewal of pluripotent stem cells and breast and glioblastoma cancer stem cells. Therefore, this review intends to highlight and synthesize new findings on the importance of integrin alpha6 in stem cell biology.

Lee, H. J., et al. (2016). "Epigenetic alteration of imprinted genes during neural differentiation of germline-derived pluripotent stem cells." Epigenetics **11**(3): 177-183.

Spermatogonial stem cells (SSCs), which are unipotent stem cells in the testes that give rise to sperm, can be converted into germline-derived pluripotent stem (gPS) by self-induction. The androgenetic imprinting pattern of SSCs is maintained even after their reprogramming into gPS cells. In this study, we used an in vitro neural differentiation model to investigate whether the imprinting patterns are maintained or altered during differentiation. The androgenetic patterns of H19, Snrpn, and Mest were maintained even after differentiation of gPS cells into NSCs (gPS-NSCs), whereas the fully unmethylated status of Ndn in SSCs was altered to somatic patterns in gPS cells and gPS-NSCs. Thus, our study demonstrates epigenetic alteration of genomic imprinting during the induction of pluripotency in SSCs and neural differentiation, suggesting that gPS-NSCs can be a useful model to study the roles of imprinted genes in brain development and human neurodevelopmental disorders.

Lee, S. W., et al. (2018). "Self-Reprogramming of Spermatogonial Stem Cells into Pluripotent Stem Cells without Microenvironment of Feeder Cells." Mol Cells **41**(7): 631-638.

Spermatogonial stem cells (SSCs) derived from mouse testis are unipotent in regard of spermatogenesis. Our previous study demonstrated that SSCs can be fully reprogrammed into pluripotent stem cells, so called germline-derived pluripotent stem cells (gPS cells), on feeder cells (mouse embryonic fibroblasts), which supports SSC proliferation and induction of pluripotency. Because of an uncontrollable microenvironment caused by interactions with feeder cells, feeder-based SSC reprogramming is not suitable for elucidation of the self-reprogramming mechanism by which SSCs are converted into pluripotent stem

cells. Recently, we have established a Matrigel-based SSC expansion culture system that allows long-term SSC proliferation without mouse embryonic fibroblast support. In this study, we developed a new feeder-free SSC self-reprogramming protocol based on the Matrigel-based culture system. The gPS cells generated using a feeder-free reprogramming system showed pluripotency at the molecular and cellular levels. The differentiation potential of gPS cells was confirmed in vitro and in vivo. Our study shows for the first time that the induction of SSC pluripotency can be achieved without feeder cells. The newly developed feeder-free self-reprogramming system could be a useful tool to reveal the mechanism by which unipotent cells are self-reprogrammed into pluripotent stem cells.

Leung, Y., et al. (2013). "Label retaining cells (LRCs) with myoepithelial characteristic from the proximal acinar region define stem cells in the sweat gland." PLoS One **8**(9): e74174.

Slow cycling is a common feature shared among several stem cells (SCs) identified in adult tissues including hair follicle and cornea. Recently, existence of unipotent SCs in basal and lumenal layers of sweat gland (SG) has been described and label retaining cells (LRCs) have also been localized in SGs; however, whether these LRCs possess SCs characteristic has not been investigated further. Here, we used a H2BGFP LRCs system for in vivo detection of infrequently dividing cells. This system allowed us to specifically localize and isolate SCs with label-retention and myoepithelial characteristics restricted to the SG proximal acinar region. Using an alternative genetic approach, we demonstrated that SG LRCs expressed keratin 15 (K15) in the acinar region and lineage tracing determined that K15 labeled cells contributed long term to the SG structure but not to epidermal homeostasis. Surprisingly, wound healing experiments did not activate proximal acinar SG cells to participate in epidermal healing. Instead, predominantly non-LRCs in the SG duct actively divided, whereas the majority of SG LRCs remained quiescent. However, when we further challenged the system under more favorable isolated wound healing conditions, we were able to trigger normally quiescent acinar LRCs to trans-differentiate into the epidermis and adopt its long term fate. In addition, dissociated SG cells were able to regenerate SGs and, surprisingly, hair follicles demonstrating their in vivo plasticity. By determining the gene expression profile of isolated SG LRCs and non-LRCs in vivo, we identified several Bone Morphogenetic Protein (BMP) pathway genes to be up-regulated and confirmed a functional requirement for BMP receptor 1A (BMPR1A)-mediated signaling in SG formation. Our data highlight the existence of SG stem cells (SGSCs) and their primary importance in SG homeostasis. It also emphasizes SGSCs as an alternative source of cells in wound healing and their plasticity for regenerating different skin appendages.

Lilja, A. M., et al. (2018). "Clonal analysis of Notch1-expressing cells reveals the existence of unipotent stem cells that retain long-term plasticity in the embryonic mammary gland." Nat Cell Biol **20**(6): 677-687.

Recent lineage tracing studies have revealed that mammary gland homeostasis relies on unipotent stem cells. However, whether and when lineage restriction occurs during embryonic mammary development, and which signals orchestrate cell fate specification, remain unknown. Using a combination of in vivo clonal analysis with whole mount immunofluorescence and mathematical modelling of clonal dynamics, we found that embryonic multipotent mammary cells become lineage-restricted surprisingly early in development, with evidence for unipotency as early as E12.5 and no statistically discernable bipotency after E15.5. To gain insights into the mechanisms governing the switch from multipotency to unipotency, we used gain-of-function Notch1 mice and demonstrated that Notch activation cell autonomously dictates luminal cell fate specification to both embryonic and basally committed mammary cells. These functional studies have important implications for understanding the signals underlying cell plasticity and serve to clarify how reactivation of embryonic programs in adult cells can lead to cancer.

Lim, J. J., et al. (2013). "In vitro culture-induced pluripotency of human spermatogonial stem cells." Biomed Res Int **2013**: 143028.

Unipotent spermatogonial stem cells (SSCs) can be transformed into ESC-like cells that exhibit pluripotency in vitro. However, except for mouse models, their characterization and their origins have remained controversies in other models including humans. This controversy has arisen primarily from the lack of the direct induction of ESC-like cells from well-characterized SSCs. Thus, the aim of the present study was to find and characterize pluripotent human SSCs in in vitro cultures of characterized SSCs. Human testicular tissues were dissociated and plated onto gelatin/laminin-coated dishes to isolate SSCs. In the presence of growth factors SSCs formed multicellular clumps after 2-4 weeks of culture. At passages 1 and 5, the clumps were dissociated and were then analyzed using markers of pluripotent cells. The number of SSEA-4-positive cells was extremely low but increased gradually up to ~ 10% in the SSC clumps during culture. Most of the SSEA-4-negative cells expressed markers for SSCs, and some cells coexpressed markers of both pluripotent and germ cells. The pluripotent

cells formed embryoid bodies and teratomas that contained derivatives of the three germ layers in SCID mice. These results suggest that the pluripotent cells present within the clumps were derived directly from SSCs during in vitro culture.

Liu, Y., et al. (2016). "Epigenetic profiles signify cell fate plasticity in unipotent spermatogonial stem and progenitor cells." Nat Commun **7**: 11275.

Spermatogonial stem and progenitor cells (SSCs) generate adult male gametes. During in vitro expansion, these unipotent murine cells spontaneously convert to multipotent adult spermatogonial-derived stem cells (MASCs). Here we investigate this conversion process through integrative transcriptomic and epigenomic analyses. We find in SSCs that promoters essential to maintenance and differentiation of embryonic stem cells (ESCs) are enriched with histone H3-lysine4 and -lysine 27 trimethylations. These bivalent modifications are maintained at most somatic promoters after conversion, bestowing MASCs an ESC-like promoter chromatin. At enhancers, the core pluripotency circuitry is activated partially in SSCs and completely in MASCs, concomitant with loss of germ cell-specific gene expression and initiation of embryonic-like programs. Furthermore, SSCs in vitro maintain the epigenomic characteristics of germ cells in vivo. Our observations suggest that SSCs encode innate plasticity through the epigenome and that both conversion of promoter chromatin states and activation of cell type-specific enhancers are prominent features of reprogramming.

Marchionni, C., et al. (2009). "Angiogenic potential of human dental pulp stromal (stem) cells." Int J Immunopathol Pharmacol **22**(3): 699-706.

Dental pulp is a heterogeneous microenviroment where unipotent progenitor and pluripotent mesenchymal stem cells cohabit. In this study we investigated whether human dental pulp stromal (stem) cells (DP-SCs) committed to the angiogenic fate. DP-SCs showed the specific mesenchymal immunophenotypical profile positive for CD29, CD44, CD73, CD105, CD166 and negative for CD14, CD34, CD45, in accordance with that reported for bone marrow-derived SCs. The Oct-4 expression in DP-SCs, evaluated through RT-PCR analysis, increased in relation with the number of the passages in cell culture and decreased after angiogenic induction. In agreement with their multipotency, DP-SCs differentiated toward osteogenic and adipogenic commitments. In angiogenic experiments, differentiation of DP-SCs, through vascular endothelial growth factor (VEGF) induction, was evaluated by in vitro matrigel assay and by cytometric analysis. Accordingly, endothelial-specific markers like Flt-1 and KDR were basally expressed and they increased after exposure to VEGF together with the occurrence of ICAM-1 and von Willebrand factor positive cells. In addition, VEGF-induced DP-SCs maintained endothelial cell-like features when cultured in a 3-D fibrin mesh, displaying focal organization into capillary-like structures. The DP-SC angiogenic potential may prove a remarkable tool for novel approaches to developing tissue-engineered vascular grafts which are useful when vascularization of ischemic tissues is required.

Mariano, E. D., et al. (2015). "Adult stem cells in neural repair: Current options, limitations and perspectives." World J Stem Cells **7**(2): 477-482.

Stem cells represent a promising step for the future of regenerative medicine. As they are able to differentiate into any cell type, tissue or organ, these cells are great candidates for treatments against the worst diseases that defy doctors and researchers around the world. Stem cells can be divided into three main groups: (1) embryonic stem cells; (2) fetal stem cells; and (3) adult stem cells. In terms of their capacity for proliferation, stem cells are also classified as totipotent, pluripotent or multipotent. Adult stem cells, also known as somatic cells, are found in various regions of the adult organism, such as bone marrow, skin, eyes, viscera and brain. They can differentiate into unipotent cells of the residing tissue, generally for the purpose of repair. These cells represent an excellent choice in regenerative medicine, every patient can be a donor of adult stem cells to provide a more customized and efficient therapy against various diseases, in other words, they allow the opportunity of autologous transplantation. But in order to start clinical trials and achieve great results, we need to understand how these cells interact with the host tissue, how they can manipulate or be manipulated by the microenvironment where they will be transplanted and for how long they can maintain their multipotent state to provide a full regeneration.

Menzel-Severing, J., et al. (2012). "[Limbal stem cells and their niche: implications for bioengineered tissue constructs]." Klin Monbl Augenheilkd **229**(12): 1191-1197.

Regeneration and repair of corneal epithelium rely on a reservoir of unipotent progenitor cells, which is situated within the basal epithelial layer at the corneoscleral limbus. If these cells are lost, corneal surface integrity is disturbed, which may lead to a painful loss of vision. Since the late 1990s cultivated grafts of limbal epithelium are being used therapeutically. Limbal epithelial cells are obtained from the fellow eye or from an allogeneic donor, propagated in culture on different types of carriers, and

subsequently transplanted. This process entails removal of progenitor cells from their natural environment. However, surrounding cells and extracellular matrix are widely believed to provide important stimuli for stem cell maintenance and for correct differentiation. Therefore, new approaches aim at providing this so-called stem cell niche ex vivo and following transplantation. Niche factors can also drive transdifferentiation of alternative progenitor cell types towards a corneal phenotype. This permits the use of autologous cells in cases of bilateral limbal stem cell insufficiency. Several biosynthetic substrates have been devised for culture, transdifferentiation and transplantation of donor cells. This work intends to provide an overview of constructs that are currently available and to some extent clinically employed. In addition, a summary is given of novel concepts which aim at integrating putative niche factors into the stem cell carriers to replicate the stem cell niche.

Mise, N., et al. (2008). "Differences and similarities in the developmental status of embryo-derived stem cells and primordial germ cells revealed by global expression profiling." Genes Cells **13**(8): 863-877.

Embryonic germ-line cells are unipotent cells that give rise to either sperm or oocytes. However, pluripotent stem cells can be derived from primordial germ cells (PGCs) or spermatogonia, suggesting that germ-line cells retain a capacity for pluripotency. Here, we made genome-wide comparisons of the gene expression profiles of freshly isolated PGCs, in vitro-formed PGCs (iPGCs), and other stem cell lines, including embryonic stem cells (ESCs), embryonic germ cells (EGCs) and germ-line stem (GS) cells. Comparing PGC with ESC, 382 genes/transcripts were significantly up-regulated in ESC, while 188 were elevated in PGC. This suggests that PGCs possess transcription program distinct from that of ESC, although both share expression of many pluripotency-associated genes. Our micro-array analysis showed that the analyzed samples could be classified into two groups: one consisting of all the ESCs and most of EGCs, and the other containing PGC samples, iPGC, one type of female EGC and GS cells. We then identified "signature" genes for the two groups, and used them to characterize GS cells, EGC, and iPGCs, and revealed developmental status of each cell type. The relationships between PGCs and stem cells derived from embryos or germ cells are discussed in light of these findings.

Nagamatsu, G., et al. (2012). "Tracing the conversion process from primordial germ cells to pluripotent stem cells in mice." Biol Reprod **86**(6): 182.

To understand mechanisms underlying acquisition of pluripotency, it is critical to identify cells that can be converted to pluripotent stem cells. For this purpose, we focused on unipotent primordial germ cells (PGCs), which can be reprogrammed into pluripotent embryonic germ (EG) cells under defined conditions. Treatment of PGCs with combinations of signaling inhibitors, including inhibitors of MAP2K (MEK), GSK3B (GSK-3beta), and TGFB (TGFbeta) type 1 receptors, induced cells to enter a pluripotent state at a high frequency (12.1%) by Day 10 of culture. When we employed fluorescence-activated cell sorting to monitor conversion of candidate cells to a pluripotent state, we observed a cell cycle shift to S phase, indicating enrichment of pluripotent cells, during the early phase of EG formation. Transcriptome analysis revealed that PGCs retained expression of some pluripotent stem cell-associated genes, such as Pou5f1 and Sox2, during EG cell formation. On the other hand, PGCs lost their germ lineage characteristics and acquired expression of pluripotent stem cell markers, such as Klf4 and Eras. The overall gene expression profiles revealed by this system provide novel insight into how pluripotency is acquired in germ-committed cells.

Nagamatsu, G. and T. Suda (2013). "Conversion of primordial germ cells to pluripotent stem cells: methods for cell tracking and culture conditions." Methods Mol Biol **1052**: 49-56.

Primordial germ cells (PGCs) are unipotent cells committed to germ lineage: PGCs can only differentiate into gametes in vivo. However, upon fertilization, germ cells acquire the capacity to differentiate into all cell types in the body, including germ cells. Therefore, germ cells are thought to have the potential for pluripotency. PGCs can convert to pluripotent stem cells in vitro when cultured under specific conditions that include bFGF, LIF, and the membrane-bound form of SCF (mSCF). Here, the culture conditions which efficiently convert PGCs to pluripotent embryonic germ (EG) cells are described, as well as methods used for identifying pluripotent candidate cells during culture.

Nguyen, P. N., et al. (2017). "Selective activation of miRNAs of the primate-specific chromosome 19 miRNA cluster (C19MC) in cancer and stem cells and possible contribution to regulation of apoptosis." J Biomed Sci **24**(1): 20.

BACKGROUND: The human chromosome 19 miRNA cluster (C19MC) of 43 genes is a primate-specific miRNA cluster that may have biological significance in the genetic complexity of the primate. Despite previous reports on individual C19MC miRNA expression in cancer and stem cells, systematic studies on C19MC miRNA expression and biological functions are lacking. RESULTS: Cluster-wide C19MC miRNA

expression profiling by microarray analysis showed wholesome C19MC activation in embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs). However, in multipotent adipose-derived mesenchymal stem cells (MSCs) and a unipotent human white pre-adipocyte cell line, only selected C19MC miRNAs were expressed. MiRNA copy number analysis also showed selective C19MC expression in cancer cells with expression patterns highly similar to those in MSCs, suggesting similar miRNA regulatory mechanisms in these cells. Selective miRNA expression also suggests complex transcriptional mechanism(s) regulating C19MC expression under specific cellular and pathological conditions. Bioinformatics analysis showed that sixteen of the C19MC miRNAs share the same "AAGUGC" seed sequence with members of the miR-302/-372 family, which are known cellular reprogramming factors. In particular, C19MC-AAGUGC-miRNAs with the nucleotides 2-7 canonical seed position as in miR-302/-372 miRNAs, may play similar roles as miR-302/-372 in induced pluripotency. A biased 3p-arm selection of the C19MC-AAGUGC-miRNAs was observed indicating that targets of the 3p species of these miRNAs may be biologically significant in regulating stemness. Furthermore, bioinformatics analysis of the putative targets of the C19MC-AAGUGC-miRNAs predicted significant involvement of signaling pathways in reprogramming, many of which contribute to promoting apoptosis by indirect activation of the pro-apoptotic proteins BAK/BAX via suppression of genes of the cell survival pathways, or by enhancing caspase-8 activation through targeting inhibitors of TRAIL-inducing apoptosis. CONCLUSIONS: This work demonstrated selective C19MC expression in MSCs and cancer cells, and, through miRNA profiling and bioinformatics analysis, predicted C19MC modulation of apoptosis in induced pluripotency and tumorigenesis.

Nishikii, H., et al. (2015). "Unipotent Megakaryopoietic Pathway Bridging Hematopoietic Stem Cells and Mature Megakaryocytes." Stem Cells **33**(7): 2196-2207.

Recent identification of platelet/megakaryocyte-biased hematopoietic stem/repopulating cells requires revision of the intermediate pathway for megakaryopoiesis. Here, we show a unipotent megakaryopoietic pathway bypassing the bipotent megakaryocyte/erythroid progenitors (biEMPs). Cells purified from mouse bone marrow by CD42b (GPIbalpha) marking were demonstrated to be unipotent megakaryocytic progenitors (MKPs) by culture and transplantation. A subpopulation of freshly isolated CD41(+) cells in the lineage Sca1(+) cKit(+) (LSK) fraction (subCD41(+) LSK) differentiated only into MKP and mature megakaryocytes in culture. Although CD41(+) LSK cells as a whole were capable of differentiating into all myeloid and lymphoid cells in vivo, they produced unipotent MKP, mature megakaryocytes, and platelets in vitro and in vivo much more efficiently than Flt3(+) CD41(-) LSK cells, especially at the early phase after transplantation. In single cell polymerase chain reaction and thrombopoietin (TPO) signaling analyses, the MKP and a fraction of CD41(+) LSK, but not the biEMP, showed the similarities in mRNA expression profile and visible TPO-mediated phosphorylation. On increased demand of platelet production after 5-FU treatment, a part of CD41(+) LSK population expressed CD42b on the surface, and 90% of them showed unipotent megakaryopoietic capacity in single cell culture and predominantly produced platelets in vivo at the early phase after transplantation. These results suggest that the CD41(+) CD42b(+) LSK are straightforward progenies of megakaryocytes/platelet-biased stem/repopulating cells, but not progenies of biEMP. Consequently, we show a unipotent/highly biased megakaryopoietic pathway interconnecting stem/repopulating cells and mature megakaryocytes, the one that may play physiologic roles especially in emergency megakaryopoiesis.

Nishikii, H., et al. (2017). "The Road Map for Megakaryopoietic Lineage from Hematopoietic Stem/Progenitor Cells." Stem Cells Transl Med **6**(8): 1661-1665.

Megakaryocytes (Mgks) are terminally differentiated blood cells specified to produce platelets, whereas hematopoietic stem cells (HSCs) are the most undifferentiated blood cells that retain multipotency to produce all kinds of blood cells. As such, these two cell types reside at the bottom and the top of the hematopoietic hierarchy, respectively. In spite of this distance, they share several important cell surface molecules as well as transcription factors. In the conventional step-wise differentiation model, HSCs gradually lose their self-renewal capacity and differentiate into multipotent progenitors (MPPs), which is the first branch point of myeloid and lymphoid lineage. In this model, common myeloid progenitors can differentiate into bipotent Mgk/erythroid progenitors (MEPs), and MEPs eventually differentiate into unipotent mature Mgks. However, it has been recently reported that a subpopulation within the HSC and MPP compartments demonstrates an Mgk-biased differentiation potential. These reports imply that revisions to the HSC-to-Mgk differentiation pathway should be discussed. In this review, we summarize recent findings about Mgk differentiation from HSCs and discuss future directions

in this research field. Stem Cells Translational Medicine 2017;6:1661-1665.

Nowak-Imialek, M., et al. (2011). "Pluripotent stem cells and reprogrammed cells in farm animals." Microsc Microanal **17**(4): 474-497.

Pluripotent cells are unique because of their ability to differentiate into the cell lineages forming the entire organism. True pluripotent stem cells with germ line contribution have been reported for mice and rats. Human pluripotent cells share numerous features of pluripotentiality, but confirmation of their in vivo capacity for germ line contribution is impossible due to ethical and legal restrictions. Progress toward derivation of embryonic stem cells from domestic species has been made, but the derived cells were not able to produce germ line chimeras and thus are termed embryonic stem-like cells. However, domestic animals, in particular the domestic pig (Sus scrofa), are excellent large animals models, in which the clinical potential of stem cell therapies can be studied. Reprogramming technologies for somatic cells, including somatic cell nuclear transfer, cell fusion, in vitro culture in the presence of cell extracts, in vitro conversion of adult unipotent spermatogonial stem cells into germ line derived pluripotent stem cells, and transduction with reprogramming factors have been developed with the goal of obtaining pluripotent, germ line competent stem cells from domestic animals. This review summarizes the present state of the art in the derivation and maintenance of pluripotent stem cells in domestic animals.

Peng, Y. C., et al. (2013). "Sonic hedgehog signals to multiple prostate stromal stem cells that replenish distinct stromal subtypes during regeneration." Proc Natl Acad Sci U S A **110**(51): 20611-20616.

The adult mouse prostate has a seemingly endless capacity for regeneration, and sonic hedgehog (SHH) signaling has been implicated in this stem cell-driven process. However, it is not clear whether SHH acts on the epithelium or stromal cells that secrete factors required for epithelial expansion. Because little is known about stromal stem cells compared with their epithelial counterparts, we used in vivo mouse genetics tools to characterize four prostate stromal subtypes and their stem cells. Using knockin reporter alleles, we uncovered that SHH signals from prostate basal epithelial cells to adjacent stromal cells. Furthermore, the SHH target gene Gli1 is preferentially expressed in subepithelial fibroblast-like cells, one of four prostate stromal subtypes and the subtype closest to the epithelial source of SHH. Using Genetic Inducible Fate Mapping to mark adult Gli1- or Smooth muscle actin-expressing cells and follow their fate during regeneration, we uncovered that Gli1-expressing cells exhibit long-term self-renewal capacity during multiple rounds of androgen-mediated regeneration after castration-induced involution, and depleted smooth muscle cells are mainly replenished by preexisting smooth muscle cells. Based on our Genetic Inducible Fate Mapping studies, we propose a model where SHH signals to multiple stromal stem cells, which are largely unipotent in vivo.

Pojda, Z. and A. Tsuboi (1990). "In vivo effects of human recombinant interleukin 6 on hemopoietic stem and progenitor cells and circulating blood cells in normal mice." Exp Hematol **18**(9): 1034-1037.

Recombinant human interleukin 6 (rhIL-6) was administered s.c. every 12 h at a daily dose of 10 micrograms/kg body weight to normal healthy mice. After 4 days the numbers of progenitor cells (erythroid burst-forming units, BFU-E and granulocyte-macrophage colony-forming cells, GM-CFC) were significantly increased (p less than 0.01) in the bone marrows and spleens of treated animals. There was no significant change in spleen colony forming unit (CFU-S) number, whereas mixed-lineage colony-forming cell (Mix-CFC) number was elevated only in bone marrow. The number of nucleated cells in peripheral blood was increased in rhIL-6-treated mice, resulting from a significant (p less than 0.01) increase in neutrophil numbers and a decrease in lymphocyte numbers. The number of platelets in these animals was also higher than in controls (p less than 0.05). These results suggest that rhIL-6 is an effective stimulator of unipotent hemopoietic cells of myeloid, erythroid, and thrombocytic lineages when administered in vivo to mice and indicate a possible therapeutic potential of IL-6 in clinical situations.

Prpar, S., et al. (2012). "Identification of goat mammary stem/progenitor cells." Biol Reprod **86**(4): 117.

Goat mammary gland epithelial cells have been used to establish primary and permanent cell lines, but to date, no data have been available regarding mammary stem cells (MaSCs) in this species. The detection and characterization of goat MaSCs is an important task for a better understanding of the cyclic character of mammary gland development, which will also offer the potential for manipulation of lactation yield and persistency. The objective of the present study was to demonstrate that a subpopulation of goat MaSCs resides in the goat mammary gland. Mammary tissue from lactating Saanen goats (Capra hircus) was dissociated and processed to a single-cell suspension. Using an in vitro colony-forming assay, we demonstrated that distinct colony types, which expressed specific lineage markers, arose from unipotent progenitors. Using two different growth

media, we showed that the frequencies of caprine clonogenic progenitors differed according to growth conditions. Goat epithelial cells were transplanted under the kidney capsule of nonobese diabetic/severe combined immunodeficient (NOD/SCID) mice, where they formed organized, bilayered structures. Our results indicate the presence of goat MaSCs in the caprine mammary gland. To our knowledge, these data represent the first description of the tissue hierarchy of the goat mammary gland and demonstrate the regenerative potential of adult goat MaSCs.

Rios, A. C., et al. (2014). "In situ identification of bipotent stem cells in the mammary gland." Nature **506**(7488): 322-327.

The mammary epithelium undergoes profound morphogenetic changes during development. Architecturally, it comprises two primary lineages, the inner luminal and outer myoepithelial cell layers. Two opposing concepts on the nature of mammary stem cells (MaSCs) in the postnatal gland have emerged. One model, based on classical transplantation assays, postulates that bipotent MaSCs have a key role in coordinating ductal epithelial expansion and maintenance in the adult gland, whereas the second model proposes that only unipotent MaSCs identified by lineage tracing contribute to these processes. Through clonal cell-fate mapping studies using a stochastic multicolour cre reporter combined with a new three-dimensional imaging strategy, we provide evidence for the existence of bipotent MaSCs as well as distinct long-lived progenitor cells. The cellular dynamics at different developmental stages support a model in which both stem and progenitor cells drive morphogenesis during puberty, whereas bipotent MaSCs coordinate ductal homeostasis and remodelling of the mouse adult gland.

Rosenbaum, A. J., et al. (2008). "The use of mesenchymal stem cells in tissue engineering: A global assessment." Organogenesis **4**(1): 23-27.

Mesenchymal stem cells (MSCs) are of great interest to both clinicians and researchers for their great potential to enhance tissue engineering. Their ease of isolation, manipulability and potential for differentiation are specifically what have made them so attractive. These multipotent cells have been found to differentiate into cartilage, bone, fat, muscle, tendon, skin, hematopoietic-supporting stroma and neural tissue. Their diverse in vivo distribution includes bone marrow, adipose, periosteum, synovial membrane, skeletal muscle, dermis, pericytes, blood, trabecular bone, human umbilical cord, lung, dental pulp and periodontal ligament. Despite their frequent use in research, no standardized criteria exist for the identification of mesenchymal stem cells; The International Society for Cellular Therapy has sought to change this with a set of guidelines elucidating the major surface markers found on these cells. While many studies have shown MSCs to be just as effective as unipotent cells for certain types of tissue regeneration, limitations do exist due to their immunosuppressive properties. This paper serves as a review pertaining to these issues, as well as others related to the use of MSCs in tissue engineering.

Russell, K. C., et al. (2010). "In vitro high-capacity assay to quantify the clonal heterogeneity in trilineage potential of mesenchymal stem cells reveals a complex hierarchy of lineage commitment." Stem Cells **28**(4): 788-798.

In regenerative medicine, bone marrow is a promising source of mesenchymal stem cells (MSCs) for a broad range of cellular therapies. This research addresses a basic prerequisite to realize the therapeutic potential of MSCs by developing a novel high-capacity assay to quantify the clonal heterogeneity in potency that is inherent to MSC preparations. The assay utilizes a 96-well format to (1) classify MSCs according to colony-forming efficiency as a measure of proliferation capacity and trilineage potential to exhibit adipo-, chondro-, and osteogenesis as a measure of multipotency and (2) preserve a frozen template of MSC clones of known potency for future use. The heterogeneity in trilineage potential of normal bone marrow MSCs is more complex than previously reported: all eight possible categories of trilineage potential were detected. In this study, the average colony-forming efficiency of MSC preparations was 55-62%, and tripotent MSCs accounted for nearly 50% of the colony-forming cells. The multiple phenotypes detected in this study infer a more convoluted hierarchy of lineage commitment than described in the literature. Greater cell amplification, colony-forming efficiency, and colony diameter for tri- versus unipotent clones suggest that MSC proliferation may be a function of potency. CD146 may be a marker of multipotency, with approximately 2-fold difference in mean fluorescence intensity between tri- and unipotent clones. The significance of these findings is discussed in the context of the efficacy of MSC therapies. The in vitro assay described herein will likely have numerous applications given the importance of heterogeneity to the therapeutic potential of MSCs.

Sahare, M. G., et al. (2018). "Recent advances of in vitro culture systems for spermatogonial stem cells in mammals." Reprod Med Biol **17**(2): 134-142.

Background: Spermatogonial stem cells (SSCs) in the mammalian testis are unipotent stem cells for spermatozoa. They show unique cell characteristics as stem cells and germ cells after being isolated from the

testis and cultured in vitro. This review introduces recent progress in the development of culture systems for the establishment of SSC lines in mammalian species, including humans. Methods: Based on the published reports, the isolation and purification of SSCs, identification and characteristics of SSCs, and culture system for mice, humans, and domestic animals have been summarized. Results: In mice, cell lines from SSCs are established and can be reprogrammed to show pluripotent stem cell potency that is similar to embryonic stem cells. However, it is difficult to establish cell lines for animals other than mice because of the dearth of understanding about species-specific requirements for growth factors and mechanisms supporting the self-renewal of cultured SSCs. Among the factors that are associated with the development of culture systems, the enrichment of SSCs that are isolated from the testis and the combination of growth factors are essential. Conclusion: Providing an example of SSC culture in cattle, a rational consideration was made about how it can be possible to establish cell lines from neonatal and immature testes.

Sanguinetti, A., et al. (2011). "Stem cells and breast cancer, where we are? A concise review of literature." G Chir **32**(10): 438-446.

There is an analogy between embryogenesis and cancer and the attention is on increasing the rate of cell division and on a small percentage of perennial cells . The key to understanding is to be found in the properties of these cells developed in the form of perennial totipotency, multipotency and unipotent. The normal life cycle involves epigenetic mechanisms that are deregulated in cancer cells, these tumor cells appear to belong to deregulation since its progeny. Here is a review of the literature on embryogenesis of the breast, endocrine system interactions Delna the proper development and functioning of the various cell lines and to the importance of cancer stem cells.

Sawitzky, C. and R. A. Kuhn (1986). "[First results of in vitro cultivation of stem cells from bone marrow and peripheral blood in an autologous test system of patients with hematological diseases]." Folia Haematol Int Mag Klin Morphol Blutforsch **113**(3): 351-357.

In 17 patients with haematological diseases an autologous test system was elaborated for determining the percentage of unipotent myeloic stem cells in the bone-marrow and peripheral blood and implemented by experiments. In comparing the results obtained by means of the traditional heterologous culture method, differences (diminutions, increase of aggregate numbers) could be found which allow certain conclusions to be drawn on the patient's real bone marrow function. For reasons of standardization, cultivation in the heterologous system cannot be abandoned. The investigations are continued.

Sekai, M., et al. (2014). "Medullary thymic epithelial stem cells maintain a functional thymus to ensure lifelong central T cell tolerance." Immunity **41**(5): 753-761.

Medullary thymic epithelial cells (mTECs) are crucial for central T cell self-tolerance. Although progenitors of mTECs have been demonstrated in thymic organogenesis, the mechanism for postnatal mTEC maintenance remains elusive. We demonstrate that implantation of embryonic TECs expressing claudin-3 and claudin-4 (Cld3,4) in a medulla-defective thymic microenvironment restores medulla formation and suppresses multiorgan autoimmunity throughout life. A minor SSEA-1(+) fraction within the embryonic Cld3,4(hi) TECs contained self-renewable clonogenic TECs, capable of preferentially generating mature mTECs in vivo. Adult SSEA-1(+)Cld3,4(hi) TECs retained mTEC reconstitution potential, although the activity decreased. The clonogenicity of TECs also declined rapidly after birth in wild-type mice, whereas it persisted in Rag2(?/?) adult mice with defective thymopoiesis. The results suggest that unipotent mTEC-restricted stem cells that develop in the embryo have the capacity to functionally reconstitute the thymic medulla long-term, thus ensuring lifelong central T cell self-tolerance.

Sher, A., et al. (1981). "Transformation of hemopoietic stem cells by phytohemagglutinin (PHA) II. Mechanism of action." Exp Pathol **19**(4): 257-262.

It has long been known that phytohemagglutinin (PHA) stimulates transformation and growth of immune competent lymphocytes. Lymphoid cell colonies have previously been shown in the spleen with PHA treated lymph node cells from donor mice were injected into irradiated mice. This communication reports the results of in vivo effects of PHA stimulation on agar colony forming units and spleen colony forming units (CFU). C3H/Hej mice injected with 1 ml of PHA-M were found to secrete colony stimulating factors (PHA-CSF) which lead to an increase in the number of agar colony forming units (granulopoiesis). Serum obtained on day 6 after PHA injection showed enhanced granulopoiesis which was four times higher than in the controls. It was found that 1.0 ml and 0.15 ml of PHA-CSF were more effective in promoting the growth of agar colony forming units in agar plates. Intravenous injection of PHA increased the number of spleen-as well as agar colony forming units (CFU). Day 3 appeared to be optimal for in vivo effects of PHA on granulopoietic cells. An increase in the colony forming units was obtainable when previously treated bone marrow and spleen cells taken on day 3

were injected into irradiated mice. There was a fourfold increase of the colony forming units (CFUs) in the spleen and a twofold one in bone marrow cells. As compared to the controls, the increase in agar colony forming units (CFUc) of bone marrow was fourfold and that of the spleen tenfold. On day 5 some effect was still noticeable but it was lower than on day 3. On weight and cell count basis it was found that on day 6 PHA had a significant in vivo effect on the spleen. On the basis of our findings it can be concluded that PHA supports the survival of transplanted stem cells by stimulating their differentiation into unipotent erythroid progenitor cells. It may also be concluded that PHA activates the immune competent stem cells (mostly T lymphocytes) and displays a supporting function for a better stem cell survival and differentiation into the erythroid progenitor cells. The activated lymphocytes secrete a colony-stimulating like factor which stimulates granulopoiesis and also helps in the differentiation of the stem cells.

Shigematsu, A., et al. (2005). "[2-14C]Thymidine incorporation activity of stem cells in either tumor or cradle tissues in a normal or transplanted animals." Eur J Drug Metab Pharmacokinet **30**(1-2): 29-39.

A novel autoradiographic procedure was developed for such continuously cycling cells as stem cells on account of proliferating rate of which is astronomically high per min. Negative visualization is observed over any mitotic image by use of a biomarker, "[2-14C]thymidine" for a few minutes in both cases, either in vivo or in vitro systems. But, good visualization images were realized by many 14C-beta tracks over stem cells with a few minute labelling of [2-14C]thymidine in originated cradles as predicted by Burkitt, H.G(1993). It is clearly elucidated that a short and quick labelling procedure of [2-14C]thymidine is useful to evaluate toxicity and efficacy of new drug candidates and to diagnose cluster of unknown malignity or proliferation rate of respective stem cell in in vivo or Ex-vivo system. Results show that the cell proliferation rate of the stem cells in respective tissues was markedly suppressed, dependent on time after dosing and the dose of 90Y; 3.7, 37, 370, 3,700, and 37,000 kBq per mouse (25g). In addition to the above, the sensitivity of the proliferation rate was dependent on amitosis or mitosis and the AUC value of 90Y-concentration at specific locations of the cells in the mouse body. The most sensitive cells were the plasmacytoma cells, followed by the pluripotent and unipotent stem cells, the intestinal crypts, epiphysial growth plate and liver cells. Results in this presentation, also gives a clear evidence showing a revival of facultative divider line from G0 stage of epithelium and mascular meditate into the unipotent stem cell cycle. Application of [2-14C]thymidine is useful for evaluation of a grade of maturation in differentiation of malignant cells or replicable unipotent stem cells.

Shiozawa, Y., et al. (2008). "The bone marrow niche: habitat to hematopoietic and mesenchymal stem cells, and unwitting host to molecular parasites." Leukemia **22**(5): 941-950.

In post-fetal life, hematopoiesis occurs in unique microenvironments or 'niches' in the marrow. Niches facilitate the maintenance of hematopoietic stem cells (HSCs) as unipotent, while supporting lineage commitment of the expanding blood populations. As the physical locale that regulates HSC function, the niche function is vitally important to the survival of the organism. This places considerable selective pressure on HSCs, as only those that are able to engage the niche in the appropriate context are likely to be maintained as stem cells. Since niches are central regulators of stem cell function, it is not surprising that molecular parasites like neoplasms are likely to seek out opportunities to harvest resources from the niche environment. As such, the niche may unwittingly participate in tumorigenesis as a leukemic or neoplastic niche. The niche may also promote metastasis or chemo-resistance of hematogenous neoplasms or solid tumors. This review focuses on what is known about the physical structures of the niche, how the niche participates in hematopoiesis and neoplastic growth and what molecules are involved. Further understanding of the interactions between stem cells and the niche may be useful for developing therapeutic strategies.

Smith, G. H. and D. Medina (2018). "Does the Mouse Mammary Gland Arise from Unipotent or Multipotent Mammary Stem/Progenitor Cells?" J Mammary Gland Biol Neoplasia **23**(1-2): 1-3.

The presence of long-lived lineage restricted progenitor and multipotent progenitor cells in adult mouse mammary gland for cancer development is compelling. Mammary cancers are phenotypically diverse This might be explained by transformation of long-lived, lineage-limited progenitor subpopulations. Mammary multipotent epithelial stem cells and their environmental niches must be considered, since their niche(s), once empty might be occupied by lineage-limited progenitors that are proximal. The existence of premalignant mammary populationst that manifest characteristics of lineage limitation argues strongly for this proposition.

Surani, M. A., et al. (2008). "Germ line, stem cells, and epigenetic reprogramming." Cold Spring Harb Symp Quant Biol **73**: 9-15.

The germ cell lineage has the unique attribute of generating the totipotent state. Development of

blastocysts from the totipotent zygote results in the establishment of pluripotent primitive ectoderm cells in the inner cell mass of blastocysts, which subsequently develop into epiblast cells in postimplantation embryos. The germ cell lineage in mice originates from these pluripotent epiblast cells of postimplantation embryos in response to specific signals. Pluripotent stem cells and unipotent germ cells share some fundamental properties despite significant phenotypic differences between them. Additionally, early primordial germ cells can be induced to undergo dedifferentiation into pluripotent embryonic germ cells. Investigations on the relationship between germ cells and pluripotent stem cells may further elucidate the nature of the pluripotent state. Furthermore, comprehensive epigenetic reprogramming of the genome in early germ cells, including extensive erasure of epigenetic modifications, is a critical step toward establishment of totipotency. The mechanisms involved may be relevant for gaining insight into events that lead to reprogramming of somatic cells into pluripotent stem cells.

Tanaka, T., et al. (2013). "Identification of stem cells that maintain and regenerate lingual keratinized epithelial cells." Nat Cell Biol **15**(5): 511-518.

Lingual keratinized epithelial cells, which constitute the filiform papillae of the tongue, have one of the most rapid tissue turnover rates in the mammalian body and are thought to be the source of squamous cell carcinoma of the tongue. However, the mechanism of tissue maintenance and regeneration is largely unknown for these cells. Here, we show that stem cells positive for Bmi1, keratin 14 and keratin 5 are present in the base but not at the very bottom of the interpapillary pit (observed most frequently in the second or third layer (position +2 or +3) from the basal cells). Using a multicolour lineage tracing method, we demonstrated that one stem cell per interpapillary pit survives long-term. The cells were shown to be unipotent stem cells for keratinized epithelial cells but not for taste bud cells, and were found to usually be in a slow-growing or resting state; however, on irradiation-induced injury, the cells rapidly entered the cell cycle and regenerated tongue epithelium. The elimination of Bmi1-positive stem cells significantly suppressed the regeneration. Taken together, these results suggest that the stem cells identified in this study are important for tissue maintenance and regeneration of the lingual epithelium.

Tiede, S., et al. (2007). "Hair follicle stem cells: walking the maze." Eur J Cell Biol **86**(7): 355-376.

The discovery of epithelial stem cells (eSCs) in the bulge region of the outer root sheath of hair follicles in mice and man has encouraged research into utilizing the hair follicle as a therapeutic source of stem cells (SCs) for regenerative medicine, and has called attention to the hair follicle as a highly instructive model system for SC biology. Under physiological circumstances, bulge eSCs serve as cell pool for the cyclic regeneration of the anagen hair bulb, while they can also regenerate the sebaceous gland and the epidermis after injury. More recently, melanocyte SCs, nestin+, mesenchymal and additional, as yet ill-defined "stem cell" populations, have also been identified in or immediately adjacent to the hair follicle epithelium, including in the specialized hair follicle mesenchyme (connective tissue sheath), which is crucial to wound healing. Thus the hair follicle and its adjacent tissue environment contain unipotent, multipotent, and possibly even pluripotent SC populations of different developmental origin. It provides an ideal model system for the study of central issues in SC biology such as plasticity and SC niches, and for the identification of reliable, specific SC markers, which distinguish them from their immediate progeny (e.g. transient amplifying cells). The current review attempts to provide some guidance in this growing maze of hair follicle-associated SCs and their progeny, critically reviews potential or claimed hair follicle SC markers, highlights related differences between murine and human hair follicles, and defines major unanswered questions in this rapidly advancing field.

Toh, W. S., et al. (2009). "Differentiation and enrichment of expandable chondrogenic cells from human embryonic stem cells in vitro." J Cell Mol Med **13**(9B): 3570-3590.

Human embryonic stem cells (hESCs) are considered as useful tools for pre-clinical studies in regenerative medicine. Although previous reports have shown direct chondrogenic differentiation of mouse and hESCs, low yield and cellular heterogenicity of the resulting cell population impairs the generation of sufficient numbers of differentiated cells for further testing and applications. Based on our previously established high-density micromass model system to study hESC chondrogenesis, we evaluated the effects of transforming growth factor (TGF)-beta(1) and bone morphogenetic protein-2 on early stages of chondrogenic differentiation and commitment by hESCs. Significant chondrogenic induction of hESCs, as determined by quantitative measurements of cartilage-related gene expression and matrix protein synthesis, was achieved in the presence of TGF-beta(1). By means of selective growth factor combination (TGF-beta(1), FGF-2 and platelet-derived growth factor-bb) and plating on extracellular matrix substratum, we report here the reproducible isolation of a highly expandable, homogenous and unipotent chondrogenic cell population, TC1, from chondrogenically committed hESCs. Like primary

chondrocytes, TC1 rapidly dedifferentiates upon isolation and monolayer expansion but retains the chondrogenic differentiation potential and responds to TGF-beta(1) for cartilaginous tissue formation both in vitro and in vivo. In addition, TC1 displays a somatic cell cycle kinetics, a normal karyotype and does not produce teratoma in vivo. Thus, TC1 may provide a potential source of chondrogenic cells for drug testing, gene therapy and cell-based therapy.

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.

Uryvaeva, I. V. (2001). "[The replicative potential of hepatocytes and liver stem cells]." Izv Akad Nauk Ser Biol(6): 728-737.

The cellular basis of liver growth is reviewed from overall recent and previous data. According to the present-day ideas, the adult mammalian liver contains at least two cellular populations with many properties similar to the stem cells of renewing tissues that provide for the liver postnatal growth and parenchyma regeneration under various conditions. According to the present nomenclature, the differentiated parenchyma cells--hepatocytes--are a unipotent committed population of stem cells. In addition, there is a system of nonparenchymal multipotent stem cells or oval cells in the liver. Certain key models of liver growth, regeneration, and repopulation that contributed to development of these notions are considered. The recent data are discussed in the context of yet unclear cellular mechanisms providing for the tremendous replicative potential of hepatocytes, the role of polyploidy in the growth effects, and the sources of malignant transformation in the liver.

van de Kamp, J., et al. (2012). "Epithelial morphogenesis of germline-derived pluripotent stem cells on organotypic skin equivalents in vitro." Differentiation **83**(3): 138-147.

For tissue engineering, cultivation of pluripotent stem cells on three-dimensional scaffolds allows the generation of organ-like structures. Previously, we have established an organotypic culture system of skin to induce epidermal differentiation in adult stem cells. Multipotent stem cells are not able to differentiate across germinal boundaries. In contrast, pluripotent stem cells readily differentiate into tissues of all three germ layers. Germline-derived pluripotent stem cells (gPS cells) can be generated by induction of pluripotency in mouse unipotent germline stem cells without the introduction of exogenous transcription factors. In the current study, we analyzed the influence of organotypic culture conditions of skin on the epithelial differentiation of gPS cells in comparison to the well-established HM1 ES cell line. Quantitative RT-PCR data of the pluripotency gene Oct4 showed that gPS cells are characterized by an accelerated Oct4-downregulation compared to HM1 ES cells. When subjected to the organotypic culture conditions of skin, gPS cells formed tubulocystic structures lined by stratified (CK5/6(+), CK14(+), CK8/18(-)) epithelia. HM1 ES cells formed only small tubulocystic structures lined by simple, CK8/18(+) epithelia. BMP-4, an epidermal morphogen, significantly enhanced the expression of epithelial markers in HM1 ES cells, but

did not significantly affect the formation of complex (squamous) epithelia in gPS cells. In HM1 ES cells the differentiation into squamous epithelium was only inducible in the presence of mature dermal fibroblasts. Both pluripotent stem cell types spontaneously differentiated into mesodermal, endodermal and into neuroectodermal cells at low frequency, underlining their pluripotent differentiation capacity. Concluding, the organotypic culture conditions of skin induce a multilayered, stratified epithelium in gPS cells, in HM1 ES cells only in the presence of dermal fibroblasts. Thus, our data show that differentiation protocols strongly depend on the stem cell type and have to be modified for each specific stem cell type.

Van Keymeulen, A., et al. (2017). "Lineage-Restricted Mammary Stem Cells Sustain the Development, Homeostasis, and Regeneration of the Estrogen Receptor Positive Lineage." Cell Rep **20**(7): 1525-1532.

The mammary gland (MG) is composed of different cell lineages, including the basal and the luminal cells (LCs) that are maintained by distinct stem cell (SC) populations. LCs can be subdivided into estrogen receptor (ER)(+) and ER(-) cells. LCs act as the cancer cell of origin in different types of mammary tumors. It remains unclear whether the heterogeneity found in luminal-derived mammary tumors arises from a pre-existing heterogeneity within LCs. To investigate LC heterogeneity, we used lineage tracing to assess whether the ER(+) lineage is maintained by multipotent SCs or by lineage-restricted SCs. To this end, we generated doxycycline-inducible ER-rtTA mice that allowed us to perform genetic lineage tracing of ER(+) LCs and study their fate and long-term maintenance. Our results show that ER(+) cells are maintained by lineage-restricted SCs that exclusively contribute to the expansion of the ER(+) lineage during puberty and their maintenance during adult life.

Van Keymeulen, A., et al. (2011). "Distinct stem cells contribute to mammary gland development and maintenance." Nature **479**(7372): 189-193.

The mammary epithelium is composed of several cell lineages including luminal, alveolar and myoepithelial cells. Transplantation studies have suggested that the mammary epithelium is maintained by the presence of multipotent mammary stem cells. To define the cellular hierarchy of the mammary gland during physiological conditions, we performed genetic lineage-tracing experiments and clonal analysis of the mouse mammary gland during development, adulthood and pregnancy. We found that in postnatal unperturbed mammary gland, both luminal and myoepithelial lineages contain long-lived unipotent stem cells that display extensive renewing capacities, as demonstrated by their ability to clonally expand during morphogenesis and adult life as well as undergo massive expansion during several cycles of pregnancy. The demonstration that the mammary gland contains different types of long-lived stem cells has profound implications for our understanding of mammary gland physiology and will be instrumental in unravelling the cells at the origin of breast cancers.

Visvader, J. E. and J. Stingl (2014). "Mammary stem cells and the differentiation hierarchy: current status and perspectives." Genes Dev **28**(11): 1143-1158.

The mammary epithelium is highly responsive to local and systemic signals, which orchestrate morphogenesis of the ductal tree during puberty and pregnancy. Based on transplantation and lineage tracing studies, a hierarchy of stem and progenitor cells has been shown to exist among the mammary epithelium. Lineage tracing has highlighted the existence of bipotent mammary stem cells (MaSCs) in situ as well as long-lived unipotent cells that drive morphogenesis and homeostasis of the ductal tree. Moreover, there is accumulating evidence for a heterogeneous MaSC compartment comprising fetal MaSCs, slow-cycling cells, and both long-term and short-term repopulating cells. In parallel, diverse luminal progenitor subtypes have been identified in mouse and human mammary tissue. Elucidation of the normal cellular hierarchy is an important step toward understanding the "cells of origin" and molecular perturbations that drive breast cancer.

Weible, M. W., 2nd and T. Chan-Ling (2007). "Phenotypic characterization of neural stem cells from human fetal spinal cord: synergistic effect of LIF and BMP4 to generate astrocytes." Glia **55**(11): 1156-1168.

If cell based therapy for spinal cord injury is to become a reality, greater insights into the biology of human derived spinal cord stem cells are a prerequisite. Significant species differences and regional specification of stem cells necessitates determining the effects of growth factors on human spinal cord stem cells. Fetal spinal cords were dissociated and expanded as neurospheres in medium with bone morphogenetic protein 4 (BMP4), leukemia inhibitory factor (LIF) or BMP4 and LIF. First-generation neurospheres comprised a heterogeneous population of neural cell types and after plating emergent cells included neurons, oligodendrocytes and GFAP(+) cells which coexpressed stem cells markers and those of the neuronal lineage and were thus identified as GFAP(+) neural precursor cells (NPC). When plated, neurospheres maintained in BMP4 demonstrated a reduced proportion of emergent oligodendrocytes from 13 to 4%, whereas LIF had no statistically significant effect on cell type distribution. Combining BMP4 and LIF reduced the proportion of oligodendrocytes to 3%

and that of neurons from 37 to 16% while increasing the proportion of GFAP(+) NPC from 45 to 79%. After 10 passages in control media aggregates gave rise to multiple neural phenotypes and only continued passage of neurospheres in the presence of BMP4 and LIF resulted in unipotent aggregates giving rise to only astrocytes. These results provide a means of obtaining pure populations of human spinal-cord derived astrocytes, which could be utilized for further studies of cell replacement strategies or in vitro evaluation of therapeutics.

White-Cooper, H. and S. Caporilli (2013). "Transcriptional and post-transcriptional regulation of Drosophila germline stem cells and their differentiating progeny." Adv Exp Med Biol **786**: 47-61.

In this chapter we will concentrate on the transcriptional and translational regulations that govern the development and differentiation of male germline cells. Our focus will be on the processes that occur during differentiation, that distinguish the differentiating population of cells from their stem cell parents. We discuss how these defining features are established as cells transit from a stem cell character to that of a fully committed differentiating cell. The focus will be on how GSCs differentiate, via spermatogonia, to spermatocytes. We will achieve this by first describing the transcriptional activity in the differentiating spermatocytes, cataloguing the known transcriptional regulators in these cells and then investigating how the transcription programme is set up by processes in the progentior cells. This process is particularly interesting to study from a stem cell perspective as the male GSCs are unipotent, so lineage decisions in differentiating progeny of stem cells, which occurs in many other stem cell systems, do not impinge on the behaviour of these cells.

Wolf, N. S. and J. J. Trentin (1968). "Hemopoietic colony studies. V. Effect of hemopoietic organ stroma on differentiation of pluripotent stem cells." J Exp Med **127**(1): 205-214.

In heavily irradiated mice, bone marrow regeneration of either endogenous or exogenous origin was shown to occur in discrete foci comparable to the more intensively studied spleen colonies. The number of endogenous bone marrow colonies was inversely related to dose of whole body X-irradiation. Endogenous marrow colonies were found after higher doses of irradiation than were endogenous spleen colonies. Most of them were granulocytic in nature. Exogenous bone marrow colonies in lethally irradiated mice injected with bone marrow cells were proportional in number to the dose of cells injected, appeared at a time comparable to spleen colonies like which, at 7 or 8 days, they were of single differentiated cell line, either granuloid or erythroid or megakaryocytic, with a small percentage of "mixed" colonies. Whereas erythroid colonies outnumber granuloid colonies in spleen, either in situ or subcutaneously transplanted (E:G colony ratio of about 3.5), granuloid colonies outnumber erythroid in bone marrow (E:G colony ratio of about 0.7). The characteristic E:G colony ratios of spleen and marrow appear more likely to be the result of a hemopoietic organ stromal influence on pluripotent colony forming units (CFU's) than of selective lodgment of committed (unipotent) granuloid and erythroid CFU's in bone marrow and spleen, respectively, as indicated by the following. Bone marrow stem cells (CFU) which had reseeded the marrow cavity of irradiated primary recipients 18-24 hr earlier, were reharvested and retransplanted intravenously into irradiated secondary hosts. The E:G colony ratio of the colonies formed in the spleen of the secondary hosts was typical of primary spleen colonies (2.8), that of the colonies formed in the marrow cavity was typical of bone marrow colonies (0.6). Pieces of marrow stroma containing reseeded CPU's from the contralateral femur of these same primary recipients were implanted by trocar directly into the spleens of other irradiated secondary recipients. Those CPU's that developed in the intrasplenic-implanted marrow stroma yielded an. E:G colony ratio of 0.1. Those that migrated into the contiguous and remote portions of the spleen gave E:G colony ratios of 2.9 and 2.4, respectively. Irradiated marrow stroma and normal spleen CPU's (a 1 mm cube of spleen) were loaded into the same trocar and implanted directly into the spleens of irradiated mice. The spleen CFU's that migrated into the implanted marrow stroma yielded five granuloid and two mixed colonies. The larger number that developed in the host spleen yielded an E:G colony ratio of 2.9 or higher. Of those 19 mixed colonies that bridged the junction of spleen and implanted marrow stroma in each of the above two experiments, in every case, the erythroid portion of the colony was in the splenic stroma, the granuloid portion was in the marrow stroma.

Wuidart, A., et al. (2016). "Quantitative lineage tracing strategies to resolve multipotency in tissue-specific stem cells." Genes Dev **30**(11): 1261-1277.

Lineage tracing has become the method of choice to study the fate and dynamics of stem cells (SCs) during development, homeostasis, and regeneration. However, transgenic and knock-in Cre drivers used to perform lineage tracing experiments are often dynamically, temporally, and heterogeneously expressed, leading to the initial labeling of different cell types and thereby complicating their interpretation. Here, we developed two methods: the first one based on statistical analysis of multicolor lineage tracing,

allowing the definition of multipotency potential to be achieved with high confidence, and the second one based on lineage tracing at saturation to assess the fate of all SCs within a given lineage and the "flux" of cells between different lineages. Our analysis clearly shows that, whereas the prostate develops from multipotent SCs, only unipotent SCs mediate mammary gland (MG) development and adult tissue remodeling. These methods offer a rigorous framework to assess the lineage relationship and SC fate in different organs and tissues.

Young, H. E. (2004). "Existence of reserve quiescent stem cells in adults, from amphibians to humans." Curr Top Microbiol Immunol **280**: 71-109.

Several theories have been proposed to explain the phenomenon of tissue restoration in amphibians and higher order animals. These theories include dedifferentiation of damaged tissues, transdifferentiation of lineage-committed stem cells, and activation of quiescent stem cells. Young and colleagues demonstrated that connective tissues throughout the body contain multiple populations of quiescent lineage-committed progenitor stem cells and lineage-uncommitted pluripotent stem cells. Subsequent cloning and cell sorting studies identified quiescent lineage-uncommitted pluripotent mesenchymal stem cells, capable of forming any mesodermal cell type, and pluripotent epiblastic-like stem cells, capable of forming any somatic cell type. Based on their studies, they propose at least 11 categories of quiescent reserve stem cells resident within postnatal animals, including humans. These categories are pluripotent epiblastic-like stem cells, pluripotent ectodermal stem cells, pluripotent epidermal stem cells, pluripotent neuronal stem cells, pluripotent neural crest stem cells, pluripotent mesenchymal (mesodermal) stem cells, pluripotent endodermal stem cells, multipotent progenitor stem cells, tripotent progenitor stem cells, bipotent progenitor stem cells, and unipotent progenitor stem cells. Thus, activation of quiescent reserve stem cells, i.e., lineage-committed progenitor stem cells and lineage-uncommitted pluripotent stem cells, resident within the connective tissues could provide for the continual maintenance and repair of the postnatal organism after birth.

Young, H. E. and A. C. Black, Jr. (2004). "Adult stem cells." Anat Rec A Discov Mol Cell Evol Biol **276**(1): 75-102.

Development of a multicellular organism is accomplished through a series of events that are preprogrammed in the genome. These events encompass cellular proliferation, lineage commitment, lineage progression, lineage expression, cellular inhibition, and regulated apoptosis. The sequential progression of cells through these events results in the formation of the differentiated cells, tissues, and organs that constitute an individual. Although most cells progress through this sequence during development, a few cells leave the developmental continuum to become reserve precursor cells. The reserve precursor cells are involved in the continual maintenance and repair of the tissues and organs throughout the life span of the individual. Until recently it was generally assumed that the precursor cells in postnatal individuals were limited to lineage-committed progenitor cells specific for various tissues. However, studies by Young, his colleagues, and others have demonstrated the presence of two categories of precursor cells that reside within the organs and tissues of postnatal animals. These two categories of precursor cells are lineage-committed (multipotent, tripotent, bipotent, and unipotent) progenitor cells and lineage-uncommitted pluripotent (epiblastic-like, ectodermal, mesodermal, and endodermal) stem cells. These reserve precursor cells provide for the continual maintenance and repair of the organism after birth.

Yuan, H. and Y. M. Yamashita (2010). "Germline stem cells: stems of the next generation." Curr Opin Cell Biol **22**(6): 730-736.

Germline stem cells (GSCs) sustain gametogenesis during the life of organisms. Recent progress has substantially extended our understanding of GSC behavior, including the mechanisms of stem cell self-renewal, asymmetric stem cell division, stem cell niches, dedifferentiation, and tissue aging. GSCs typically are highly proliferative, owing to organismal requirement to produce large number of differentiated cells. While many somatic stem cells are multipotent, with multiple differentiation pathways, GSCs are unipotent. For these relatively simple characteristics (e.g. constant proliferation and unipotency), GSCs have served as ideal model systems for the study of adult stem cell behavior, leading to many important discoveries. Here, we summarize recent progress in GSC biology, with an emphasis on evolutionarily conserved mechanisms.

Zhang, Y., et al. (2003). "Hepatic stem cells: existence and origin." World J Gastroenterol **9**(2): 201-204.

Stem cells are not only units of biological organization, responsible for the development and the regeneration of tissue and organ systems, but also are units in evolution by natural selection. It is accepted that there is stem cell potential in the liver. Like most organs in a healthy adult, the liver maintains a perfect balance between cell gain and loss. It has three levels of cells that can respond to loss of hepatocytes: (1) Mature hepatocytes, which proliferate after normal

liver tissue renewal, less severe liver damage, etc; they are numerous, unipotent, "committed" and respond rapidly to liver injury. (2) Oval cells, which are activated to proliferate when the liver damage is extensive and chronic, or if proliferation of hepatocytes is inhibited; they lie within or immediately adjacent to the canal of Hering (CoH); they are less numerous, bipotent and respond by longer, but still limited proliferation. (3) Exogenous liver stem cells, which may derive from circulating hematopoietic stem cells (HSCs) or bone marrow stem cells; they respond to allyl alcohol injury or hepatocarcinogenesis; they are multipotent, rare, but have a very long proliferation potential. They make a more significant contribution to regeneration, and even completely restore normal function in a murine model of hereditary tyrosinaemia. How these three stem cell populations integrate to achieve a homeostatic balance remains enigmatic. This review focuses on the location, activation, markers of the three candidates of liver stem cell, and the most importantly, therapeutic potential of hepatic stem cells.

Zhao, X., et al. (2012). "Derivation of myoepithelial progenitor cells from bipotent mammary stem/progenitor cells." PLoS One **7**(4): e35338.

There is increasing evidence that breast and other cancers originate from and are maintained by a small fraction of stem/progenitor cells with self-renewal properties. Recent molecular profiling has identified six major subtypes of breast cancer: basal-like, ErbB2-overexpressing, normal breast epithelial-like, luminal A and B, and claudin-low subtypes. To help understand the relationship among mammary stem/progenitor cells and breast cancer subtypes, we have recently derived distinct hTERT-immortalized human mammary stem/progenitor cell lines: a K5(+)/K19(-) type, and a K5(+)/K19(+) type. Under specific culture conditions, bipotent K5(+)/K19(-) stem/progenitor cells differentiated into stable clonal populations that were K5(-)/K19(-) and exhibit self-renewal and unipotent myoepithelial differentiation potential in contrast to the parental K5(+)/K19(-) cells which are bipotent. These K5(-)/K19(-) cells function as myoepithelial progenitor cells and constitutively express markers of an epithelial to mesenchymal transition (EMT) and show high invasive and migratory abilities. In addition, these cells express a microarray signature of claudin-low breast cancers. The EMT characteristics of an un-transformed unipotent mammary myoepithelial progenitor cells together with claudin-low signature suggests that the claudin-low breast cancer subtype may arise from myoepithelial lineage committed progenitors. Availability of immortal MPCs should allow a more definitive analysis of their potential to give rise to claudin-low breast cancer subtype and facilitate biological and molecular/biochemical studies of this disease.

Zhdanov, V. V., et al. (2005). "Function of hemopoietic stem cells under conditions of cytostatic myelosuppression and treatment with hemostimilators." Bull Exp Biol Med **140**(5): 631-634.

We compared the function of hemopoietic stem cells under conditions of cytostatic myelosuppression (cyclophosphamide treatment) and during treatment with granulocytopoiesis stimulators. It was found that unipotent hemopoietic precursor cells are most sensitive to cyclophosphamide. Different effects of hemostimulators on stem cells are determined by different proportions between proliferation and differentiation processes.

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