Stem Cell and Transdifferentiation Literatures

Mark H Smith

Queens, New York 11418, USA
mark20082009@gmail.com

Abstract: The definition of stem cell is "an unspecialized cell that gives rise to a specific specialized cell, such as a blood cell". Stem Cell is the original of life. All cells come from stem cells. Serving as a repair system for the living body, the stem cells can divide without limit to replenish other cells as long as the living body is still alive. When a stem cell divides, each new cell has the potential to either remain a stem cell situuition or become another type of cell with a more specialized function, such as a muscle cell, a red blood cell, a bone cell, a nerve cell, or a brain cell. Stem cell research is a tipical and important topic of life science. This material collects some literatures on stem cell and transdifferentiation.
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Key words: stem cell; life; gene; DNA; protein; transdifferentiation

1. Introduction

Stem cell is the origin of an orgnism's life. Stem cells have the potential to develop into many different types of cells in life bodies, that are exciting to scientists because of their potential to develop into many different cells, tissues and organs. Stem cells can be used in the clinical medicine to treat patients with a variety of diseases (Daar, 2003). Serving as a repair system for the living body, the stem cells can divide without limit to replenish other cells as long as the living body is still alive. When a stem cell divides, each new cell has the potential to either remain a stem cell situuition or become another type of cell with a more specialized function, such as a muscle cell, a red blood cell, a bone cell, a nerve cell, or a brain cell. Stem cell research is a tipical and important topic of life science.

2. Definition of Stem Cells

The definition of stem cell is "an unspecialized cell that gives rise to a specific specialized cell, such as a blood cell" (Stedman's Medical Dictionary, 2002).

Abdouh, M., S. Facchino, et al. (2009). "BMI1 sustains human glioblastoma multiforme stem cell renewal." J Neurosci **29**(28): 8884-96.

Glioblastoma multiforme (GBM) is one of the most common and aggressive types of brain tumors. In GBM, a subpopulation of CD133-positive cancer initiating cells displays stem cell characteristics. The Polycomb group (PcG) and oncogene BMI1 is part of the Polycomb repressive complex 1 (PRC1) that regulates gene expression by modifying chromatin organization. Here we show that BMI1 is expressed in human GBM tumors and highly enriched in CD133-positive cells. Stable BMI1 knockdown using short hairpin RNA-expressing lentiviruses resulted in inhibition of clonogenic potential in vitro and of brain tumor formation in vivo. Cell biology studies support the notion that BMI1 prevents CD133-positive cell apoptosis and/or differentiation into neurons and astrocytes, depending on the cellular context. Gene expression analyses suggest that BMI1 represses alternate tumor suppressor pathways that attempt to compensate for INK4A/ARF/P53 deletion and PI(3)K/AKT hyperactivity. Inhibition of EZH2, the main component of the PRC2, also impaired GBM tumor growth. Our results reveal that PcG proteins are involved in GBM tumor growth and required to sustain cancer initiating stem cell renewal.

Aktas, B., M. Tewes, et al. (2009). "Stem cell and epithelial-mesenchymal transition markers are frequently overexpressed in circulating tumor cells of metastatic breast cancer patients." Breast Cancer Res **11**(4): R46.

INTRODUCTION: The persistence of circulating tumor cells (CTC) in breast cancer patients might be associated with stem cell like tumor cells which have been suggested to be the active source of metastatic spread in primary tumors. Furthermore, these cells also may undergo phenotypic changes, known as epithelial-mesenchymal transition (EMT), which allows them to travel to the site of metastasis formation without getting affected by conventional treatment. Here we evaluated 226 blood samples of 39 metastatic breast cancer patients during a follow-up of palliative chemo-, antibody - or hormonal therapy for the expression of the stem cell marker ALDH1 and markers for EMT and correlated these findings with the presence of CTC and response to therapy. METHODS: 2 x 5 ml blood was analyzed for CTC

with the AdnaTest BreastCancer (AdnaGen AG) for the detection of EpCAM, MUC-1 and HER2 transcripts. The recovered c-DNA was additionally multiplex tested for three EMT markers [Twist1, Akt2, PI3Kalpha] and separately for the tumor stem-cell markers ALDH1. The identification of EMT markers was considered positive if at least one marker was detected in the sample. RESULTS: 97% of 30 healthy donor samples investigated were negative for EMT and 95% for ALDH1 transcripts. CTC were detected in 69/226 (31%) cancer samples. In the CTC (+) group, 62% were positive for at least one of the EMT markers and 69% for ALDH1, respectively. In the CTC (-) group the percentages were 7% and 14%, respectively. In non-responders, EMT and ALDH1 expression was found in 62% and 44% of patients, in responders the rates were 10% and 5%, respectively. CONCLUSIONS: Our data indicate that a major proportion of CTC of metastatic breast cancer patients shows EMT and tumor stem cell characteristics. Further studies are needed to prove whether these markers might serve as an indicator for therapy resistant tumor cell populations and, therefore, an inferior prognosis.

Boucherie, C., S. Schafer, et al. (2009). "Chimerization of astroglial population in the lumbar spinal cord after mesenchymal stem cell transplantation prolongs survival in a rat model of amyotrophic lateral sclerosis." J Neurosci Res **87**(9): 2034-46.

Adult mesenchymal stem cells (MSCs) exhibit neuroprotective properties when introduced into the degenerating central nervous system through different putative mechanisms including secretion of growth factors and transdifferentiation. In the present study, we injected MSCs into the cerebrospinal fluid of symptomatic hSOD1(G93A) rats, a transgenic animal model of familial amyotrophic lateral sclerosis (ALS) expressing a mutated form of the human superoxide dismutase. MSCs were found to infiltrate the nervous parenchyma and migrate substantially into the ventral gray matter, where motor neurons degenerate. Even though overall astrogliosis was not modified, MSCs differentiated massively into astrocytes at the site of degeneration. The intrathecal delivery of MSCs and the subsequent generation of healthy astrocytes at symptomatic stage decreased motor neuron loss in the lumbar spinal cord, preserving motor functions and extending the survival of hSOD1(G93A) rats. This neuroprotection was correlated with decreased inflammation, as shown by the lower proliferation of microglial cells and the reduced expressiontion of COX-2 and NOX-2. Together, these data highlight the protective capacity of adult MSC-derived astrocytes when grafted into the central nervous system and illustrate an attractive strategy to target excessive inflammation in ALS.

Bouwens, L. (1998). "Transdifferentiation versus stem cell hypothesis for the regeneration of islet beta-cells in the pancreas." Microsc Res Tech **43**(4): 332-6.

The pancreas is composed of at least three types of differentiated tissue: the hormone-containing cells in islets (4 different cell types), the exocrine zymogen-containing acini, and the centroacinar cells, ductules and ducts (ductal tree). All of these cells appear to have a common origin during embryogenesis in the form of duct-like protodifferentiated cells. Later in life, the acinar and ductal cells retain a significant proliferative capacity that can ensure cell renewal and growth, whereas the islet cells become mitotically inactive. Interestingly, new islet cells, including the insulin-producing beta-cells, can regenerate after tissue injury by a process called neogenesis. The neogenetic process involves differentiation of duct-like (exocrine) epithelial cells to hormone-expressing cells. In this paper, we review the question whether islet beta-cell regeneration or neogenesis in the pancreas depends on "embryonic-like" stem cells or on transdifferentiation of "fully differentiated" cells. This issue is important to find the right model for in vitro research aiming at controlling the process of beta-cell neogenesis. The latter could lead to applications in the treatment of diabetes where functional beta-cells are deficient. We conclude from the available evidence that there is as yet no evidence for the existence of "dormant" stem cells in the adult pancreas. There is some evidence, however, that differentiated exocrine acinar and/or duct cells retain the capacity to transdifferentiate into insulin-expressing beta-cells.

Braun, K. M., C. Niemann, et al. (2003). "Manipulation of stem cell proliferation and lineage commitment: visualisation of label-retaining cells in wholemounts of mouse epidermis." Development **130**(21): 5241-55.

Mammalian epidermis is maintained by stem cells that have the ability to self-renew and generate daughter cells that differentiate along the lineages of the hair follicles, interfollicular epidermis and sebaceous gland. As stem cells divide infrequently in adult mouse epidermis, they can be visualised as DNA label-retaining cells (LRC). With whole-mount labelling, we can examine large areas of interfollicular epidermis and many hair follicles simultaneously, enabling us to evaluate stem cell markers and examine the effects of different stimuli on the LRC population. LRC are not confined to the hair follicle, but also lie in sebaceous glands and interfollicular epidermis. LRC reside throughout the permanent region of the

hair follicle, where they express keratin 15 and lie in a region of high alpha6beta4 integrin expression. LRC are not significantly depleted by successive hair growth cycles. They can, nevertheless, be stimulated to divide by treatment with phorbol ester, resulting in near complete loss of LRC within 12 days. Activation of Myc stimulates epidermal proliferation without depleting LRC and induces differentiation of sebocytes within the interfollicular epidermis. Expression of N-terminally truncated Lef1 to block beta-catenin signalling induces transdifferentiation of hair follicles into interfollicular epidermis and sebocytes and causes loss of LRC primarily through proliferation. We conclude that LRC are more sensitive to some proliferative stimuli than others and that changes in lineage can occur with or without recruitment of LRC into cycle.

Chien, K. R. (2006). "Lost and found: cardiac stem cell therapy revisited." J Clin Invest **116**(7): 1838-40.

Several clinical trials of bone marrow stem cell therapy for myocardial infarction are ongoing, but the mechanistic basis for any potential therapeutic effect is currently unclear. A growing body of evidence suggests that the potential improvement in cardiac function is largely independent of cardiac muscle regeneration. A study by Fazel et al. in this issue of the JCI provides evidence that bone marrow-derived c-kit+ cells can lead to an improvement in cardiac function in mutant hypomorphic c-kit mice that is independent of transdifferentiation into either cardiac muscle or endothelial cells, but rather is associated with the release of angiogenic cytokines and associated neovascularization in the infarct border zone (see the related article beginning on page 1865). These findings suggest the potential therapeutic effect of specific paracrine pathways for angiogenesis in improving cardiac function in the injured heart.

Corti, S., F. Locatelli, et al. (2005). "Nuclear reprogramming and adult stem cell potential." Histol Histopathol **20**(3): 977-86.

Cell-based therapy may represent a new strategy to treat a vast array of clinical disorders including neurodegenerative diseases. Recent observations indicate that adult somatic stem cells have the capacity to contribute to the regeneration of different tissues, suggesting that differentiative restrictions are not completely irreversible and can be reprogrammed. Cell fusion might account for some changed phenotype of adult cells but it seems to be biologically irrelevant for its extreme rarity. Other experimental evidences are compatible with the hypothesis of wide multipotency of well-defined stem cell populations, but also with transdifferentiation and/or dedifferentiation. Further studies on nuclear reprogramming mechanisms are necessary to fulfil the promise for developing autologous cellular therapies.

Corti, S., F. Locatelli, et al. (2004). "Somatic stem cell research for neural repair: current evidence and emerging perspectives." J Cell Mol Med **8**(3): 329-37.

Recent evidence supports the existence of adult mammalian stem cell subpopulations, particularly within the bone marrow, that may be able to "transdifferentiate" across tissue lineage boundaries, thus offering an accessible source for therapeutic applications even for neural tissue repair. However, the difficulties in reproducing some experimental data, the rarity of the transdifferentiation events and observations that cell fusion may be an alternative explanation argue against the idea of stem cell plasticity. Investigations going beyond descriptive experiments and more mechanicistic approaches may provide a more solid foundation to adult stem cell therapeutic potential.

Cova, L., A. Ratti, et al. (2004). "Stem cell therapy for neurodegenerative diseases: the issue of transdifferentiation." Stem Cells Dev **13**(1): 121-31.

In the past few years research on stem cells has exploded as a tool to develop potential therapies to treat incurable neurodegenerative diseases. Stem cell transplantation has been effective in several animal models, but the underlying restorative mechanisms are still unknown. Several events such as cell fusion, neurotrophic factor release, endogenous stem cell proliferation, and transdifferentiation (adult cell acquisition of new unexpected identities) may explain therapeutic success, in addition to replacement of lost cells. This issue needs to be clarified further to maximize the potential for effective therapies. Preliminary stem transplantation trials have already been performed for some neurodegenerative diseases. There is no effective pharmacological treatment for amyotrophic lateral sclerosis, but recent preliminary data both in experimental and clinical settings have targeted it as an ideal candidate disease for the development of stem cell therapy in humans. This review summarizes recent advances gained in stem cell research applied to neurodegenerative diseases with a special emphasis to the criticisms put forward.

Currle, D. S., J. S. Hu, et al. (2007). "Culture of mouse neural stem cell precursors." J Vis Exp(2): 152.

Primary neural stem cell cultures are useful for studying the mechanisms underlying central nervous system development. Stem cell research will increase our understanding of the nervous system and may allow us to develop treatments for currently incurable brain diseases and injuries. In addition, stem cells should be used for stem cell research aimed at

the detailed study of mechanisms of neural differentiation and transdifferentiation and the genetic and environmental signals that direct the specialization of the cells into particular cell types. This video demonstrates a technique used to disaggregate cells from the embryonic day 12.5 mouse dorsal forebrain. The dissection procedure includes harvesting E12.5 mouse embryos from the uterus, removing the "skin" with fine dissecting forceps and finally isolating pieces of cerebral cortex. Following the dissection, the tissue is digested and mechanically dissociated. The resuspended dissociated cells are then cultured in "stem cell" media that favors growth of neural stem cells.

Dahlke, M. H., F. C. Popp, et al. (2004). "Stem cell therapy of the liver--fusion or fiction?" Liver Transpl **10**(4): 471-9.

Various stem cell populations have been described in distinct models of liver regeneration. This review provides an overview of these different stem cell populations aimed at unifying diverse views of liver stem cell biology. Embryonic stem cells, hemopoietic stem cells, mesenchymal stem cells, liver-derived hepatic stem cells, bone marrow-derived hepatic stem cells, and mature hepatocytes (as cells with stemlike properties) are considered separately. In so doing, we seek to clarify the nomenclature of putative liver stem cell types. Experiments that address the question of cellular fusion versus transdifferentiation as explanations for observed liver regeneration are highlighted. This review concludes with a series of open questions that should be addressed in the context of clinical liver disease before attempts at human therapeutic interventions.

Dalakas, E., P. N. Newsome, et al. (2005). "Hematopoietic stem cell trafficking in liver injury." Faseb J **19**(10): 1225-31.

Bone marrow (BM) hematopoietic stem cells (HSCs) have been shown to facilitate regeneration in multiple nonhematopoietic tissues by either generating epithelial cells or altering the inflammatory response. Depending on injury type, the predominant mechanism of epithelial lineage regeneration occurs by spontaneous cell fusion or transdifferentiation. Irrespective of the mechanism, mobilization from the BM is a prerequisite. Mechanisms by which HSCs mobilize into damaged organs are currently under scrutiny. Murine and human studies have shown that the chemokine SDF-1 and its receptor CXCR4 participate in the mobilization of HSCs from BM and in the migration of HSCs to injured liver. SDF-1 is a potent HSC chemoattractant and is produced by the liver. Production is increased during liver injury leading to increased HSC migration to the liver, a finding diminished by neutralizing anti-CXCR4 antibodies. Additional factors have been implicated in the control of hepatic migration of HSCs such as IL-8, hepatocyte growth factor, and MMP-9. Matriceal remodeling is an essential component in HSC engraftment, and MMP-9 expression is increased in liver injury. This review focuses on the complex interaction of chemokines, adhesion molecules, and extracellular matrix factors required for successful migration and engraftment of HSCs into the liver.

Davidoff, M. S., R. Middendorff, et al. (2009). "The neuroendocrine Leydig cells and their stem cell progenitors, the pericytes." Adv Anat Embryol Cell Biol **205**: 1-107.

The Leydig cells of the testis represent the main source of androgens. The idea of Leydig cells as endocrine cells has been the leading characteristic of this interesting cell population till now. Our studies of the last 2 decades allowed us to reveal a new important feature of Leydig cells that is their obvious similarity with structures of the central and peripheral nervous system. This includes the expression of neurohormones, neurotransmitters, neuropeptides and glial cell antigens. In this way, it became evident that in addition to the well established control by steroids and systemic hormones, important local auto- and paracrine control me chanisms of testicular functions exist. Thus, the Leydig cells represent a specialized cell population with both endocrine and neuroendocrine properties. The discovery of the neuroendocrine features of Leydig cells gave rise to the hypothesis of a potential neuroectodermal and/or neural crest origin of testicular Leydig cells. In an experimental animal model we revealed that adult Leydig cells originate by transdifferentiation from stem/progenitor cells (pericytes and smooth muscle cells), underlying the close relationship of Leydig cells with testis microvasculature. This and the supporting data from the literature provided the basis for revealing the pericytes as a common adult stem cell type of mammalian species. Distributed by the microvasculature through the entire body, the pericyte, acting as a resting early pluripotent adult stem cell, provides an ingenious system to assure the maintenance, physiological repair and regeneration of organs, each under the influence of specific local environmental factors.

Di Campli, C., A. C. Piscaglia, et al. (2004). "A human umbilical cord stem cell rescue therapy in a murine model of toxic liver injury." Dig Liver Dis **36**(9): 603-13.

BACKGROUND: Several studies have demonstrated that bone marrow contains a subpopulation of stem cells capable of participating in

the hepatic regenerative process, even if some reports indicate quite a low level of liver repopulation by human stem cells in the normal and transiently injured liver. AIMS: In order to overcome the low engraftment levels seen in previous models, we tried the direct intraperitoneal administration of human cord blood stem cells, using a model of hepatic damage induced by allyl alcohol in NOD/SCID mice. METHODS: We designed a protocol based on stem cell infusion following liver damage in the absence of irradiation. Flow cytometry, histology, immunohistochemistry and RT-PCR for human hepatic markers were performed to monitor human cell engraftment. RESULTS: Human stem cells were able to transdifferentiate into hepatocytes, to improve liver regeneration after damage and to reduce the mortality rate both in both protocols, even if with qualitative and quantitative differences in the transdifferentiation process. CONCLUSIONS: We demonstrated for the first time that the intraperitoneal administration of stem cells can guarantee a rapid liver engraftment. Moreover, the new protocol based on stem cell infusion following liver damage in the absence of irradiation may represent a step forward for the clinical application of stem cell transplantation.

Di Campli, C., A. C. Piscaglia, et al. (2005). "Improvement of mortality rate and decrease in histologic hepatic injury after human cord blood stem cell infusion in a murine model of hepatotoxicity." Transplant Proc **37**(6): 2707-10.

BACKGROUND AND AIMS: Because of their plasticity potential local and systemic application of cord blood stem cells may represent excellent candidates for cell-based therapeutic strategies in toxic liver injuries. It is already known that intraperitoneal administration of hematopoietic stem cells provides rapid liver homing in animal models of hepatic injury. We sought to assess the efficacy of a hematopoietic stem cell infusion to decrease the histologic damage and the mortality rate of animals previously damaged by allyl alcohol. MATERIAL AND METHODS: NOD/SCID mice were divided into two groups. (1) animals treated by intraperitoneal administration of allyl alcohol and (2) animals treated with allyl alcohol and 24 hours later with an intraperitoneal infusion of human cord blood cells. Flow cytometry, histology, immunohistochemistry, and RT-PCR were performed to monitor human cell engraftment by evidences of human hepatic markers. RESULTS: Human stem cells were able to transdifferentiate into hepatocytes, improve liver regeneration after damage, and reduce the mortality rate even when requiring qualitative and quantitative differences in the transdifferentiation processes. The mortality rate decreased from 70% to 20%, with a significant improvement in the histologic findings. CONCLUSION: We demonstrated that the infusion of hematopoietic stem cells into the liver in the early stage of damage might initiate endogenous hepatic tissue regeneration that oppose the injury inflicted by toxicants.

Diaz-Flores, L., Jr., J. F. Madrid, et al. (2006). "Adult stem and transit-amplifying cell location." Histol Histopathol **21**(9): 995-1027.

Adult stem cells (ASC)--able to self renew and to intervene in maintaining the structural and functional integrity of their original tissue--can express greater plasticity than traditionally attributed to them, adopting functional phenotypes and expression profiles of cells from other tissues. Therefore, they could be useful to regenerative medicine and tissue engineering. Transit-amplifying cells (TAC) are committed progenitors among the ASC and their terminally differentiated daughter cells. The ASC reside in a specialized physical location named niche, which constitutes a three-dimensional microenviroment where ASC and TAC are protected and controlled in their self-renewing capacity and differentiation. The niche can be located near or far from the recruitment point, requiring a short or long-distance cellular migration, respectively. This paper briefly reviews the current status of research about ASC plasticity, transdifferentiation, fusion and functional adaptation mechanisms. Subsequently, ASC and TAC occurrence, characteristics and location have been considered in the skin, cornea, respiratory tract, teeth, gastrointestinal tract, liver, pancreas, salivary glands, kidney, breast, prostate, endometrium, mesenchyma, bone marrow, skeletal and cardiac muscle, nervous system and pituitary gland. Moreover, the role of cancer ASC has also been revised.

Eisenberg, L. M. and C. A. Eisenberg (2003). "Stem cell plasticity, cell fusion, and transdifferentiation." Birth Defects Res C Embryo Today **69**(3): 209-18.

One of the most contentious issues in biology today concerns the existence of stem cell plasticity. The term "plasticity" refers to the capacity of tissue-derived stem cells to exhibit a phenotypic potential that extends beyond the differentiated cell phenotypes of their resident tissue. Although evidence of stem cell plasticity has been reported by multiple laboratories, other scientists have not found the data persuasive and have remained skeptical about these new findings. This review will provide an overview of the stem cell plasticity controversy. We will examine many of the major objections that have been made to challenge the stem cell plasticity data. This controversy will be placed in the context of the traditional view of stem cell potential and cell phenotypic diversification.

What the implications of cell plasticity are, and how its existence may modulate our present understanding of stem cell biology, will be explored. In addition, we will examine a topic that is usually not included within a discussion of stem cell biology--the direct conversion of one differentiated cell type into another. We believe that these observations on the transdifferentiation of differentiated cells have direct bearing on the issue of stem cell plasticity, and may provide insights into how cell phenotypic diversification is realized in the adult and into the origin of cell phenotypes during evolution.

Enzmann, G. U., R. L. Benton, et al. (2006). "Functional considerations of stem cell transplantation therapy for spinal cord repair." J Neurotrauma **23**(3-4): 479-95.

Stem cells hold great promise for therapeutic repair after spinal cord injury (SCI). This review compares the current experimental approaches taken towards a stem cell-based therapy for SCI. It critically evaluates stem cell sources, injury paradigms, and functional measurements applied to detect behavioral changes after transplantation into the spinal cord. Many of the documented improvements do not exclusively depend on lineage-specific cellular differentiation. In most of the studies, the functional tests used cannot unequivocally demonstrate how differentiation of the transplanted cells contributes to the observed effects. Standardized cell isolation and transplantation protocols could facilitate the assessment of the true contribution of various experimental parameters on recovery. We conclude that at present embryonic stem (ES)-derived cells hold the most promise for therapeutic utility, but that non-neural cells may ultimately be optimal if the mechanism of possible transdifferentiation can be elucidated.

Fang, T. C. and R. Poulsom (2003). "Cell-based therapies for birth defects: a role for adult stem cell plasticity?" Birth Defects Res C Embryo Today **69**(3): 238-49.

Cell therapy can offer a reasonable approach to the treatment of specific birth defects, particularly those for which hematopoietic stem cells (HSCs) can be used to restore (even partially) the number of cells, protein levels, or enzyme activity. Relatively few clinical experiences have been published on this subject, but when a natural selective advantage exists for the cell graft, a degree of "rescue" is possible. Strategies have been developed to confer a selective advantage through genetic engineering of donor cells, and this approach may prove valuable in the treatment of birth defects, as it is in hematological malignancy. Stem cell (SC) plasticity, or transdifferentiation, may offer another route for delivery of cells to established or developing organs. A wide variety of studies support the concept that adult tissue-specific SCs can, if displaced from their normal niche to another, be reprogrammed to produce cell types appropriate to their new environment. Clinical observations reveal that persistent tissue microchimerism develops not only in blood lineages after transfusion, but also in thyroid follicular epithelium via transplacental exchange. In addition, hepatic and renal parenchyma also become chimeric following allografts or bone marrow transplantation (BMT). Experimental models indicate that a renal glomerulosclerosis phenotype can be transferred by grafting whole BM, and that a severe liver disorder in fah-/- mice can be overcome by grafting HSCs and then exerting a selection pressure. It may be possible in the future to exploit the ability of adult SCs to contribute to diverse tissues; however, our understanding of the processes involved is at a very early stage.

Ferretti, P. (2004). "Neural stem cell plasticity: recruitment of endogenous populations for regeneration." Curr Neurovasc Res **1**(3): 215-29.

Lower vertebrates, such as fish and urodele amphibians can regenerate complex body structures including significant portions of their central nervous system by recruiting progenitor cells to repair the damage. Significant ability to regenerate the nervous system is observed also during development in higher vertebrates, for example in the chick spinal cord, though it is not yet clear whether this involves de novo neurogenesis, in addition to axonal re-growth, also at the latest stages of development permissive for regeneration. The mechanisms underlying recruitment of progenitor cells in response to injury, particularly within the nervous system, are still poorly understood. Although it has been suggested that some neurogenesis can be induced even in regions of the adult mammalian brain, this potential is largely lost with evolution and development. Following tail amputation in urodeles, an ependymal tube, resembling a developing neural tube, forms from ependymal cells that migrate from the cord stump towards the terminal vesicle, and elongates by cell proliferation. The new cord might originate from stem cells, with possibly only a subset of ependymal cells displaying such properties, or via a process of dedifferentiation / transdifferentiation of these cells. Data currently available are more supportive of the latter hypothesis. Whereas dedifferentiation is a well demonstrated phenomenon in a broad range of urodele tissues, transdifferentiation seems to occur less widely and in extreme circumstances, and may contribute significantly to regeneration only in a few cases. In higher vertebrates it is even less clear how common

and relevant to repair transdifferentiation is, as much work both in favour and against it has recently been published. However, the existence of multipotent neural progenitors in adult mammalian CNS and of a much higher neural cell plasticity, at least in vitro, than previously believed, encourages the view that if we were to better understand progenitor cell recruitment and plasticity in species where it does occur spontaneously, we might then find the way to make it happen effectively in mammals.

Filip, S., D. English, et al. (2004). "Issues in stem cell plasticity." J Cell Mol Med **8**(4): 572-7.

Experimental biology and medicine work with stem cells more than twenty years. The method discovered for in vitro culture of human embryonal stem cells acquired at abortions or from "surplus" embryos left from in vitro fertilization, evoked immediately ideas on the possibility to aim development and differentiation of these cells at regeneration of damaged tissues. Recently, several surprising observations proved that even tissue-specific (multipotent) stem cells are capable, under suitable conditions, of producing a whole spectrum of cell types, regardless, whether these tissues are derived from the same germ layer or not. This ability is frequently called stem cell plasticity but other authors also use different names - "non-orthodox differentiation" or "transdifferentiation". In this paper we wish to raise several important questions and problems related to this theme. Let us remind some of them: Is it possible to force cells of one-type tissue to look and act as cells of another tissue? Are these changes natural? Could these transformations be used to treat diseases? What about the bioethic issue? However, the most serious task "still remains to be solved - how to detect, harvest and culture stem cells for therapy of certain diseases".

Filip, S., J. Mokry, et al. (2005). "Stem cell plasticity and issues of stem cell therapy." Folia Biol (Praha) **51**(6): 180-7.

Today, there is much evidence suggesting that organ-specific stem cells need not rely completely on their own sources for maintenance and regeneration of an organism. In certain circumstances, mostly related to tissue damage, stem cell populations residing past the affected organ can contribute to its recovery--that means from different cell lines and also in tissues from another germ layer. The key factor in formation of self-renewing cellular clones is the presence of stem cells either from the tissue of origin or stem cells migrating from other areas and their successful settlement in an empty niche of the damaged tissue. Stem cell plasticity is the ability of adult tissue-specific stem cells to switch to new identities. The term plasticity also means stem cell phenotypic potential, which is broader than phenotypes of differentiated cells in their original tissues. Many laboratories have given evidence on stem cell plasticity; however, the presented results met with many objections from others. In the first part of our report we wish to refer to several issues associated with stem cell plasticity, transdifferentiation and fusion. Recent experimental results show that stem cells will play a key role in cell therapy. But there are still many questions to answer for scientists engaged in stem cell research. Is it possible to induce cells from one type of tissue to look and act as cells of another tissue? Do these changes occur naturally? Could plasticity be used in the treatment of fatal diseases? Cell therapy is one of the methods to treat damaged myocardial tissue. However, recent results with autologous bone marrow cells in the treatment of damaged myocardium show that this method has still many unanswered questions concerning cells, cytokines, microenvironment and other factors responsible for reparation. To date, there are many opinions either recommending or denying this method in different modifications. One question has not yet been definitely solved: What are the conditions for us to accept this method--its safety and efficacy? The future will show whether these our hopes and expectations will be fulfiled. Many experiments are needed before at least some of these questions may be answered and cell therapy become an important method for the benefit of our patients.

Fu, R. H., S. P. Liu, et al. (2009). "Alternative splicing modulates stem cell differentiation." Cell Transplant **18**(9): 1029-38.

Stem cells have the surprising potential to develop into many different cell types. Therefore, major research efforts have focused on transplantation of stem cells and/or derived progenitors for restoring depleted diseased cells in degenerative disorders. Understanding the molecular controls, including alternative splicing, that arise during lineage differentiation of stem cells is crucial for developing stem cell therapeutic approaches in regeneration medicine. Alternative splicing to allow a single gene to encode multiple transcripts with different protein coding sequences and RNA regulatory elements increases genomic complexities. Utilizing differences in alternative splicing as a molecular marker may be more sensitive than simply gene expression in various degrees of stem cell differentiation. Moreover, alternative splicing maybe provide a new concept to acquire induced pluripotent stem cells or promote cell-cell transdifferentiation for restorative therapies and basic medicine researches. In this review, we highlight the recent advances of alternative splicing regulation

in stem cells and their progenitors. It will hopefully provide much needed knowledge into realizing stem cell biology and related applications.

Gao, F., D. Q. Wu, et al. (2008). "In vitro cultivation of islet-like cell clusters from human umbilical cord blood-derived mesenchymal stem cells." Transl Res **151**(6): 293-302.

A major obstacle to successful islet transplantation for both type 1 and 2 diabetes is an inadequate supply of insulin-producing tissue. In vitro transdifferentiation of human umbilical cord blood-derived mesenchymal stem cells (UCB-MSCs) into insulin-producing cells could provide an abundant source of cells for this procedure. For this study, we isolated and characterized human UCB-MSCs and induced them in vitro to differentiate into islet-like cell clusters using a 15-day protocol based on a combination of high-glucose, retinoic acid, nicotinamide, epidermal growth factor, and exendin-4. These clusters appeared about 9 days after pancreatic differentiation; expressed pancreatic beta-cell markers, including insulin, glucagon, Glut-2, PDX1, Pax4, and Ngn3; and could synthesize and secrete functional islet proteins at the end of the inducing protocol. The insulin-positive cells accounted for (25.2-3.36)% of whole induced cells. Although insulin secretion of those insulin-producing cells did not respond to glucose challenge very well, human UCB-MSCs have the ability to differentiate into islet-like cells in vitro and may be a potential new source for islet transplantation.

Gnecchi, M., Z. Zhang, et al. (2008). "Paracrine mechanisms in adult stem cell signaling and therapy." Circ Res **103**(11): 1204-19.

Animal and preliminary human studies of adult cell therapy following acute myocardial infarction have shown an overall improvement of cardiac function. Myocardial and vascular regeneration have been initially proposed as mechanisms of stem cell action. However, in many cases, the frequency of stem cell engraftment and the number of newly generated cardiomyocytes and vascular cells, either by transdifferentiation or cell fusion, appear too low to explain the significant cardiac improvement described. Accordingly, we and others have advanced an alternative hypothesis: the transplanted stem cells release soluble factors that, acting in a paracrine fashion, contribute to cardiac repair and regeneration. Indeed, cytokines and growth factors can induce cytoprotection and neovascularization. It has also been postulated that paracrine factors may mediate endogenous regeneration via activation of resident cardiac stem cells. Furthermore, cardiac remodeling, contractility, and metabolism may also be influenced in a paracrine fashion. This article reviews the potential paracrine mechanisms involved in adult stem cell signaling and therapy.

Goodell, M. A. (2003). "Stem-cell "plasticity": befuddled by the muddle." Curr Opin Hematol **10**(3): 208-13.

In the past 4 years, multiple reports have suggested that stem cells derived from adult tissues can differentiate outside their tissue of origin, challenging long-accepted tenets of developmental biology. This concept of stem-cell "plasticity" has helped to galvanize research on stem cells due to the myriad therapeutic possibilities. However, there are wide discrepancies in the reported frequencies of so-called transdifferentiation events, from recent reports of negative data to reports of the contribution in some tissues and systems reaching as much as 20%. The evidence for and against stem-cell plasticity is reviewed here as well as some of the possible sources of the experimental variation.

Graziano, A., R. d'Aquino, et al. (2008). "The stem cell hypothesis in head and neck cancer." J Cell Biochem **103**(2): 408-12.

Cancer stem cells (CSCs) are tumoral cells which have stem features such as self-renewal, high migration capacity, drug resistance, high proliferation abilities. In the last 10 years the pathological meaning and the existence of CSCs have been matter of discussion and a large number of articles have been published about the role that these cells play in the development and maintenance of the tumors. Head and neck squamous-cell carcinoma (HNSCC) is the sixth most common cancer worldwide: early diagnosis of high-risk premalignant lesions are high priorities for reducing deaths due to head and neck cancer. In the last years the CSCs hypothesis has been faced also for head and neck cancer, with the aim of a better comprehension of the tumor biology and an early diagnosis. The evidence that the development of a tumor comes from a small number of cells with stem-like characteristic, could bring too to the identification of therapies against these cellular target, fundamental for maintenance and progression of the lesion. Here, a literature review has been reported about the detection of supposed CSCs in head and neck cancer.

Guhathakurta, S., U. R. Subramanyan, et al. (2009). "Stem cell experiments and initial clinical trial of cellular cardiomyoplasty." Asian Cardiovasc Thorac Ann **17**(6): 581-6.

Growing myocardial cells from human stem cells and stem cell transplantation to repair injured myocardium are new frontiers in cardiovascular

research. The 1st stage of this study was conducted to determine whether transplantation of autologous bone marrow stem cells into infarcted myocardium of sheep could differentiate into beating cardiomyocytes. The 2nd stage was to demonstrate transdifferentiation of human bone marrow mesenchymal stem cells to precursor cardiomyocytes in vitro, using a novel conditioning medium. In the 3rd stage, a clinical trial of stem cell implantation in patients with severe myocardial dysfunction involved injection of peripheral blood-derived endothelial precursor cells in 11 patients and autologous bone marrow mononuclear cells in 29. A marginal improvement in myocardial function was noted at 3 months (mean increase in ejection fraction, 6% +/- 1%), although it plateaued at 6 months. The trial proved to be safe because there was no procedure-related mortality. There is growing optimism that stem cell therapy may delay heart transplantation.

Haas, S., N. Weidner, et al. (2005). "Adult stem cell therapy in stroke." Curr Opin Neurol **18**(1): 59-64.

PURPOSE OF REVIEW: Acute cerebral infarction causes irreversible locally restricted loss of the neuronal circuitry and supporting glial cells with consecutive functional deficits and disabilities. The currently available and effective therapy targets fast vessel recanalization accompanied by symptomatic measures. Research activities focusing on stem cells, which represent a promising source for organotypic cell replacement and functional recovery after stroke, have gained momentum in recent years, making regenerative cell-based therapies a much more feasible realistic approach. This review provides an update about preclinical and clinical cell-based studies in stroke focusing on stem cells derived from the adult central nervous and hematopoetic systems. RECENT FINDINGS: Endogenous neural stem cells, which have been shown to reside throughout life in the central nervous system, have the capacity to replace lost neurons in models for numerous disorders, including cerebral ischemia. Considering adult neural stem cell transplantation as a regenerative strategy after stroke, progress has been made in isolating human adult neural stem cells and demonstrating the feasibility of autologous neural stem cell transplantation. An increasing number of studies provide evidence that hematopoietic stem cells, either after stimulation of endogenous stem cell pools or after exogenous hematopoietic stem cell application (transplantation), improve functional outcome after ischemic brain lesions. Various underlying mechanisms such as transdifferentiation into neural lineages, neuroprotection through trophic support, and cell fusion have been deciphered. SUMMARY: Many preclinical studies employing adult stem cell-based strategies hold great promise. For endogenous approaches the correlate of cell replacement underlying functional improvement needs to be demonstrated. Transplantation approaches on the experimental level need further development before clinical application can be considered.

Hussain, M. A. and N. D. Theise (2004). "Stem-cell therapy for diabetes mellitus." Lancet **364**(9429): 203-5.

CONTEXT: Curative therapy for diabetes mellitus mainly implies replacement of functional insulin-producing pancreatic beta cells, with pancreas or islet-cell transplants. However, shortage of donor organs spurs research into alternative means of generating beta cells from islet expansion, encapsulated islet xenografts, human islet cell-lines, and stem cells. Stem-cell therapy here implies the replacement of diseased or lost cells from progeny of pluripotent or multipotent cells. Both embryonic stem cells (derived from the inner cell mass of a blastocyst) and adult stem cells (found in the postnatal organism) have been used to generate surrogate beta cells or otherwise restore beta-cell functioning. STARTING POINT: Recently, Andreas Lechner and colleagues failed to see transdifferentiation into pancreatic beta cells after transplantation of bone-marrow cells into mice (Diabetes 2004; 53: 616-23). Last year, Jayaraj Rajagopal and colleagues failed to derive beta cells from embryonic stem cells (Science 2003; 299: 363). However, others have seen such effects. WHERE NEXT? As in every emerging field in biology, early reports seem confusing and conflicting. Embryonic and adult stem cells are potential sources for beta-cell replacement and merit further scientific investigation. Discrepancies between different results need to be reconciled. Fundamental processes in determining the differentiation pathways of stem cells remain to be elucidated, so that rigorous and reliable differentiation protocols can be established. Encouraging studies in rodent models may ultimately set the stage for large-animal studies and translational investigation.

Imanishi, Y., S. Miyagawa, et al. (2009). "Impact of synovial membrane-derived stem cell transplantation in a rat model of myocardial infarction." J Artif Organs **12**(3): 187-93.

To explore a new source of cell therapy for myocardial infarction (MI), we assessed the usefulness of mesenchymal stem cells derived from synovial membrane samples (SM MSCs). We developed a model of MI by ligation of the proximal left anterior descending coronary artery (LAD) in Lewis rats. Two weeks after ligation, 5 x 10(6) SM MSCs were injected into the MI scar area (T group, n = 9), while buffer was injected into the control group

(C group, n = 9). Cardiac performances measured by echocardiography at 4 weeks after transplantation were significantly increased in the T group as compared with the C group. Masson's trichrome staining showed that SM MSC transplantation decreased collagen volume in the myocardium. Engrafted SM MSCs were found in the border zone of the infarct area. Immunohistological analysis showed that these cells were positive for the sarcomeric markers alpha-actinin and titin, and negative for desmin, troponin T, and connexin 43. SM MSC transplantation improved cardiac performance in a rat model of MI in the subacute phase, possibly through transdifferentiation of the engrafted cells into a myogenic lineage, which led to inhibition of myocardial fibrosis. Our results suggest that SM MSCs are a potential new regeneration therapy candidate for heart failure.

Ishikawa, F., H. Shimazu, et al. (2006). "Purified human hematopoietic stem cells contribute to the generation of cardiomyocytes through cell fusion." Faseb J **20**(7): 950-2.

To obtain insights into the cardiomyogenic potential of hematopoietic tissue, we intravenously (i.v.) injected purified hematopoietic stem/progenitor cells into newborn recipients that may fully potentiate the developmental plasticity of stem cells. Transplantation of mouse bone marrow (BM) lineage antigen-negative (Lin-) cells resulted in the generation of the cells that displayed cardiomyocyte-specific antigenic profiles and contractile function when transplanted into syngeneic newborn recipients. To clarify the mechanism underlying the cardiomyogenic potential, green fluorescent protein (GFP)-labeled BM Lin-ScaI+ hematopoietic progenitors were transplanted into neonatal mice constitutively expressing cyan fluorescence protein (CFP). Lambda image acquisition and linear unmixing analysis using confocal microscopy successfully separated GFP and CFP, and revealed that donor GFP+ cardiomyocytes coexpressed host-derived CFP. We further reconstituted human hemopoietic- and immune systems in mice by injecting human cord blood (CB)-derived Lin-CD34+CD38- hematopoietic stem cells (HSCs) into neonatal T cell(-)B cell(-)NK cell-immune-deficient NOD/SCID/IL2rgamma(null) mice. Fluoroescence in situ hybridization analysis of recipient cardiac tissues demonstrated that human and murine chromosomes were colocalized in the same cardiomyocytes, indicating that cell fusion occurred between human hematopoietic progeny and mouse cardiomyocytes. These syngeneic- and xenogeneic neonatal transplantations provide compelling evidence that hematopoietic stem/progenitor cells contribute to the postnatal generation of cardiomyocytes through cell fusion, not through transdifferentiation.

Kashofer, K. and D. Bonnet (2005). "Gene therapy progress and prospects: stem cell plasticity." Gene Ther **12**(16): 1229-34.

With the identification of stem cell plasticity several years ago, multiple reports raised hopes that tissue repair by stem cell transplantation could be within reach in the near future. Krause et al reported that a single purified hematopoietic stem cell not only repopulated the bone marrow of a host animal, but also integrated into unrelated tissues. Lagasse et al demonstrated that in a genetic model of liver disease, purified hematopoietic stem cells can give rise to hepatocytes and rescue fatal liver damage. More recent work by Jiang et al demonstrated that cultured cells can retain their stem cell potential. There are a number of possible mechanisms that could explain these phenomena, and recent experiments have raised controversy about which mechanism is prevalent. One possibility is transdifferentiation of a committed cell directly into another cell type as a response to environmental cues. Transdifferentiation has been shown mainly in vitro, but some in vivo data also support this mechanism. Direct transdifferentiation would clinically be limited by the number of cells that can be introduced into an organ without removal of resident cells. If bone marrow cells could on the other hand give rise to stem cells of another tissue, then they could in theory repopulate whole organs from a few starting cells. This model of dedifferentiation is consistent with recent data from animal models. Genetic analysis of cells of donor origin in vivo and in vitro has brought to light another possible mechanism. The fusion of host and donor cells can give rise to mature tissue cells without trans- or dedifferentiation. The resulting heterokaryons are able to cure a lethal genetic defect and do not seem to be prone to give rise to cancer. All these models will clinically face the problem of accessibility of healthy primary cells for transplantation. This underlines the importance of the recent identification of a population of mesenchymal stem cells (MSCs) with stem cell properties similar to embryonic stem (ES) cells. These cells can be cultured and expanded in vitro without losing their stem cell potential making them an attractive target for cell therapy. Finally, it is still not clear if stem cells for various tissues are present in peripheral blood, or bone marrow and thus can be directly purified from these sources. Identification of putative tissue stem cells would be necessary before purification strategies can be devised. In this review, we discuss the evidence for these models, and the conflicting results obtained to date.

Keilhoff, G., A. Goihl, et al. (2006). "Transdifferentiation of mesenchymal stem cells into Schwann cell-like myelinating cells." Eur J Cell Biol **85**(1): 11-24.

Bone marrow stromal cells (MSC) are multipotent stem cells that differentiate into cells of the mesodermal lineage. Although adult, their differentiation potential is remarkable, and they are able to transdifferentiate. Transdifferentiated cultivated rat MSC (tMSC) changed morphologically into cells resembling typical spindle-shaped Schwann cells (SC) with enhanced expression of LNGF receptor, Krox-20, CD104 and S100beta protein and decreased expression of bone morphogenetic protein receptor-1A compared to untreated rat MSC (rMSC). Transdifferentiation was reversible and repeatable. To evaluate the myelinating capacity, rMSC, tMSC, or SC cultured from male rats were grafted into an autologous muscle conduit bridging a 2-cm gap in the female rat sciatic nerve. The presence of the male-specific SRY gene (as revealed by PCR analysis) and S100 immunoreactivity of pre-labeled tMSC confirmed the presence of the implanted cells in the grafts. Three weeks after grafting, an appropriate regeneration was noted in the SC and in the tMSC groups, while regeneration in the rMSC group and in the control group without any cells was impaired. In contrast to SC, in some cases, single tMSC were able to myelinate more than one axon. Our findings demonstrate that it may be possible to differentiate MSC into therapeutically useful cells for clinical applications.

Kindler, V. (2005). "Postnatal stem cell survival: does the niche, a rare harbor where to resist the ebb tide of differentiation, also provide lineage-specific instructions?" J Leukoc Biol **78**(4): 836-44.

Postnatal stem cells regulate the homeostasis of the majority of our tissues. They continuously generate new progenitors and mature, functional cells to replace old cells, which cannot assume the tissue function anymore and are eliminated. Blood, skin, gut mucosa, muscle, cartilage, nerves, cornea, retina, liver, and many other structures are regulated by stem cells. As a result of their ability to produce large numbers of functionally mature cells, postnatal stem cells represent a promising tool for regenerative therapy. Indeed, unmanipulated stem cells or their progeny amplified in vitro are already used in some clinical applications to restore the function of injured or genetically deficient tissues. However, despite our cumulating understanding concerning postnatal stem cells, many aspects of their functionality remain unclear. For instance, in most tissues, we cannot reliably define the phenotype of the postnatal stem cells sustaining its survival. We do not know to which extent the environment surrounding the stem cell-the niche-which is a key actor insuring stem cell self-maintenance, is also implicated in the maintenance of stem cell lineage specificity. Moreover, we have to clarify whether postnatal stem cells are capable of undertaking "transdifferentiation", that is, the conversion of one cell type into another under physiological conditions. Answering these questions should help us to draw a more accurate picture of postnatal stem cell biology and should lead to the design of safe, effective therapies.

Kume, S. (2005). "Stem-cell-based approaches for regenerative medicine." Dev Growth Differ **47**(6): 393-402.

Recent success in transplantation of islets raises the hopes of diabetic patients that replacement therapies may be a feasible treatment of their disease. Although several lines of evidence suggest that stem cells exist in the pancreas, it is still technically hard for us to isolate or maintain the stem cells in vitro. The establishment of human embryonic stem (ES) cells has excited scientists regarding their potential medical use in tissue replacement therapy. When applied with appropriate signals, ES cells can be directed to differentiate into a specific cell lineage. Therefore, ES cells are no doubt an excellent source not only for regenerative medicine but also for studies of early events of pancreatic development, and to portray the pancreatic progenitor cells. Despite many attempts that have been tried, the efficiency of differentiation of ES cells into islets is still very low. This low efficiency reflects our lack of understanding of the intrinsic and extrinsic signals which regulate the developmental processes of the pancreas. In this review, I present a summary of recent works on ES cells, the identification of pancreatic progenitor cells from the adult pancreas, and refer to the possibilities of transdifferentiation from adult stem cells derived from other tissues.

Kurdi, M. and G. W. Booz (2007). "G-CSF-based stem cell therapy for the heart--unresolved issues part B: Stem cells, engraftment, transdifferentiation, and bioengineering." Congest Heart Fail **13**(6): 347-51.

The authors extend their coverage of recent developments in stem cell-based therapy for repairing the heart to cover the basic questions of what stem cells should be used and how best to favor their survivability within the injured heart. The authors focus their attention on those adult stem/progenitor cells that have been best investigated in animal studies for repairing the infarcted heart and are the focus of completed or ongoing clinical trials. In addition, they discuss the promise that resident cardiac stem cells offer and the recent identification of specialized

architecturally defined niches within the heart to nurse their development. Bioengineering approaches employing off-the-shelf mesenchymal stem cell patches may soon provide a way to recreate these niches in the scarred heart. Conceivably, these patches might also be seeded with prescribed mixtures of culturally expanded autologous stem/progenitor cells that would lead to new blood vessel and cardiac myocyte formation. The convergence of bioengineering and molecular biology on stem cell therapy would seem to make what was once unimaginable, cardiac regeneration, a clinical reality in less than one generation.

Labat, M. L., G. Milhaud, et al. (2000). "On the track of a human circulating mesenchymal stem cell of neural crest origin." Biomed Pharmacother **54**(3): 146-62.

The neural markers present in the normal circulating monocytoid cells able, in pathological situations, to trans-differentiate into different mesenchymal-type cells, confirm the hypothesis previously raised that these cells derive from the neural crest. In culture, the normal cells display a great plasticity very reminiscent of microglial cells in culture. Almost a quiescent cell in normal individuals, this monocytoid cell shows its division potentialities in pathological situations of fibrosis and cancer (chondrosarcoma) where it is found to spontaneously proliferate. While the normal neofibroblasts are rapidly recognized and destroyed by fibrophagic T-lymphocytes, the pathological cells escape this control and, as a result, they accumulate in vitro giving rise to a tissue sometimes organized as nodules. Although basically the transdifferentiation process is similar in all the pathological situations of fibrosis and cancer studied so far, the end-result phenotype evokes the pathology the patient is suffering from. It evokes osteoblasts in a case of osteomyelosclerosis, chondroidocytes in a case of chondrosarcoma, myelofibroblasts in a case of fibrosis of lung and kidney in a patient under ciclosporine treatment. Hence, this circulating monocytoid cell is a multipotent cell with great division potentiality. These are characteristics of stem/preprogenitor cells. Since this circulating monocytoid cell also bears the neural markers we called it a monocytoid ectomesenchymal stem/preprogenitor cell. Therefore, the existence of an ectomesenchymal system is discussed here. The circulating monocytoid ectomesenchymal stem/preprogenitor cell might be involved in the normal cicatrisation process while the fibrophagic T lymphocytes might be involved in its termination. Impairment of this controlled mechanism might result in the development of fibrosis and/or cancer such as chondrosarcoma in vivo. Interestingly, at least in vitro, proliferation is restricted to the monocytoid cell before transdifferentiation takes place. In this model, fibrosis and cancer might share some common steps going from the proliferation of the monocytoid cells to their transdifferentiation into mesenchymal-type cells and the accumulation of these transdifferentiated cells in the tissues. Then, cancer might be distinguished from fibrosis by the additional acquisition of the ability to proliferate by the transdifferentiated cells. The monocytoid ectomesenchymal stem/preprogenitor cell might also be involved in brain neurodegenerative diseases characterized by an accumulation of microglia. The circulating monocytoid ectomesenchymal stem/preprogenitor cell appears as a target for gene therapy in pathological situations of fibrosis and/or cancer where it proliferates out of control. If the normal cell can be expanded and if its transdifferentiation can be directed, the circulating monocytoid ectomesenchymal stem/preprogenitor cell may become a useful tool for cellular therapy, in case of failure in wound healing and tissue regeneration.

LaPar, D. J., I. L. Kron, et al. (2009). "Stem cell therapy for ischemic heart disease: where are we?" Curr Opin Organ Transplant **14**(1): 79-84.

PURPOSE OF REVIEW: Stem cell transplantation is currently generating a great deal of interest in the treatment of ischemic heart disease (IHD) as the replacement of akinetic scar tissue by viable myocardium should improve cardiac function, impede progressive left ventricular remodeling, and revascularize ischemic areas. Substantial work in stem cell therapy for ischemic heart disease has recently been reported. RECENT FINDINGS: Stem cell populations have been expanding. Most recently, induced pluripotent stem (iPS) cells have been discovered that have the potential to revolutionize stem cell therapy. Many of the efforts in stem cell therapy for ischemic heart disease have been inconclusive and often contradicting. Transdifferentiation of stem cells into cardiomyocytes remains controversial. The therapeutic effect of the stem cell seems consistent with paracrine function rather than transdifferentiation. Systemic and micromilieu factors appear to dictate the fate of implanted stem cells. SUMMARY: Although animal studies produce controversial results, and many basic questions remain unanswered, more and more clinical trials are underway. Consequently, researchers must begin to focus upon a few basic critical issues: the modulation of the systemic and microenvironment for stem cells in order to augment stem cell survival and transdifferentiation; the underlying mechanisms of stem cell therapy and the fate of stem cells; differentiation into myocytes or other terminal cell populations with favorable paracrine functions.

Majka, M., M. Kucia, et al. (2005). "Stem cell biology: a never ending quest for understanding." Acta Biochim Pol **52**(2): 353-8.

Stem cells (SC) research is an important part of biotechnology that could lead to the development of new therapeutic strategies. A lot of effort has been put to understand biology of the stem cells and to find genes and subsequently proteins that are responsible for their proliferation, self-renewal and differentiation. Different cytokines and growth factors has been used to expand stem cells, but no combination of these factors was identified that could effectively expand the most primitive stem cells. Recently, however, genes and receptors responsible for SC proliferation and differentiation have been described. Ligands for these receptors or these genes themselves are being already used for ex vivo expansion of stem cells and the first data are very promising. New markers, such as CXCR4 and CD133, have been discovered and shown to be present on surface of hematopoietic stem cells. The same markers were recently also found to be expressed on neuronal-, hepatic- or skeletal muscle-stem cells. By employing these markers several laboratories are trying to isolate stem cells for potential clinical use. New characteristics of stem cells such as transdifferentiation and cell fusion have been described. Our team has identified a population of tissue committed stem cells (TCSC). These cells are present in a bone marrow and in other tissues and they can differentiate into several cell types including cardiac, neural and liver cells.

Mancuso, S. (2003). "Stem cell research need not be carried out utilizing human embryos." Reprod Biomed Online **6**(2): 168-9.

Stem cells still lack integral and exhaustive legislation in Italy and in the European Union. The use of pluripotent embryonic stem cells (ESC) for cell therapy seems to be encumbered with several disadvantages, such as the frequency of aneuploidy and the risk of tumour development (i.e. formation of teratomes). In addition, the capacity for indefinite growth of ESC, which first seems to confer them an advantage, may become potentially harmful if some ESC contaminate the transplantation of their derived differentiated cells. This is, in part, contrasted by the ease of obtaining and expanding adult or cord blood-derived stem cells in vitro, and by their transdifferentiation capacity (the so-called somatic stem cell 'plasticity'). Moreover, ethical considerations make us plead against the use of human embryos for stem cell research. First and foremost, there is the ethical position that it is never permissible to stop human life in order to prolong human life, except in self-defence. We must maintain that a human embryo certainly constitutes a new human life with the direct potential of one day becoming a human infant. Therefore, human embryo should not be considered just a 'cluster of cells' but a 'person'. Humanity is at a philosophical crossroads and we need to speak up in favour of the dignity of human life from its very inception.

Masson, S., D. J. Harrison, et al. (2004). "Potential of hematopoietic stem cell therapy in hepatology: a critical review." Stem Cells **22**(6): 897-907.

Adult stem cell plasticity raised expectations regarding novel cellular therapies of regenerative medicine after findings of unexpected plasticity were reported. In this review, reports of hematopoietic stem cells (HSCs) contributing to hepatocytic lineages are critically discussed with reference to rodent and human models. In particular, the role of liver injury and the potential contribution HSCs make to hepatic regeneration in both injury and physiological maintenance is reviewed. The relative contributions of genomic plasticity and cell fusion are studied across different model systems, highlighting possible factors that may explain differences between often conflicting reports. Insights from experimental studies will be described that shed light on the mechanisms underlying the migration, engraftment, and transdifferentiation of HSCs in liver injury. Although it appears that under differing circumstances, macrophage fusion, HSC fusion, and HSC transdifferentiation can all contribute to hepatic epithelial lineages, a much greater understanding of the factors that regulate the long-term efficacy of such cells is needed before this phenomenon can be used clinically.

Moviglia, G. A., G. Varela, et al. (2006). "Autoreactive T cells induce in vitro BM mesenchymal stem cell transdifferentiation to neural stem cells." Cytotherapy **8**(3): 196-201.

BACKGROUND: The degree of post-injury inflammation of the damaged area of a spinal cord is the main difference between the natural successful repair in inferior vertebrates and failure in superior vertebrates. The treatment of rats with anti-myelin lymphocytes after experimental spinal cord injury induces their functional recovery. On the other hand, mesenchymal stem cells (MSC) from adult BM implanted in injured areas recover the morphology and function of spinal cord in mammals. The purpose of this study was to determine whether there is a direct relationship between anti-nervous tissue T cells and MSC reparatory properties. METHODS: Circulating autoreactive lymphocytes of patients with spinal cord injuries and amyotrophic lateral sclerosis were isolated and activated in vitro. These cells were

cocultured with autologous MSC for 2-15 days. Cocultures of non-selected lymphocytes were used as controls. RESULTS: After 48 h of coculture, MSC adopted a spindle shape with polarization of the cytoplasm that resembled bipolar neurons. Their nuclei diminished the nucleolus number and the chromatin lost its granular appearance. After 15 days of culture the cells developed the typical structure of a neural network. No morphologic changes were observed in control cultures. The differentiated cells reacted positively to tubuline III, GFAP and nestin. No differences were observed between the different patient cell sources. DISCUSSION: We observed that autoreactive cells may induce the transdifferentiation of MSC to neural stem cells. This T-cell-MSC interaction may be a common phenomenon during physiologic nerve tissue repair.

Nagy, R. D., B. M. Tsai, et al. (2005). "Stem cell transplantation as a therapeutic approach to organ failure." J Surg Res **129**(1): 152-60.

BACKGROUND: Stem cell transplantation is one of the next great frontiers for surgery. Stem cells, which are undifferentiated and self-renewing, have shown the ability to differentiate into cardiomyocytes, as well as many other cell types for potential therapeutic use by surgeons. MATERIALS AND METHODS: As a result, stem cells have the potential to undo irreversible cellular damage, something traditional therapies could not cure. However, numerous issues must be resolved to permit safe and effective clinical application of stem cell therapy. These include the interpretation of cellular labeling, the origin of replicating myocytes, the homing mechanism of stem cells, and the differentiation process. RESULTS: Successful translational research will depend on precise delivery of these cells in real time to the area of interest, e.g., the spinal cord, liver, or heart. Surgeons will be better able to excise and replace/regrow, rather than excise alone. As such, a basic understanding of stem cell biology will benefit the surgeon scientist and clinical surgeon. CONCLUSIONS: The review: 1) discusses myocardial regeneration; 2) defines and categorizes stem cells; 3) presents evidence of stem cell transdifferentiation into cardiomyocytes; and, 4) delineates the therapeutic potential of stem cells in the treatment of ischemic heart disease.

Neri, T., M. Monti, et al. (2007). "Mouse fibroblasts are reprogrammed to Oct-4 and Rex-1 gene expression and alkaline phosphatase activity by embryonic stem cell extracts." Cloning Stem Cells **9**(3): 394-406.

A recent remarkable study has shown that when mouse NIH-3T3 fibroblasts are exposed to an embryonic stem cell (ESC) extract, the majority of them expresses the Oct-4 gene, form ESC-like colonies, and embryoid-like bodies that differentiate into cells of the three germ layers. The use of cell extracts for inducing cell dedifferentiation could be a powerful system to obtain large quantities of pluripotent cells. It is thus of crucial importance that the robustness of this method of cell transdifferentiation is tested by other laboratories before it is advanced to a more ambitious use in cell therapy programs. We report here our experimental observations using the same reprogramming protocol on STO and NIH-3T3 mouse fibroblasts. Three are the main results: first, we confirmed an enduring reprogramming activity of the ESC extract, although on a much smaller number of cells that varies from approximately 0.003 to 0.04% of the total population of fibroblasts and with an effect limited to the induction of Oct-4 and Rex-1 gene expression and alkaline phosphatase activity. Second, the expression of OCT-4, SSEA-1, and Forssman antigen proteins was never detected. Third, our work has clearly demonstrated that ESCs may survive the procedure of extract preparation, may be source of contamination that is expanded in culture and give false positive results.

Paul, D., S. M. Samuel, et al. (2009). "Mesenchymal stem cell: present challenges and prospective cellular cardiomyoplasty approaches for myocardial regeneration." Antioxid Redox Signal **11**(8): 1841-55.

Myocardial ischemia and cardiac dysfunction have been known to follow ischemic heart diseases (IHDs). Despite a plethora of conventional treatment options, their efficacies are associated with skepticism. Cell therapies harbor a promising potential for vascular and cardiac repair, which is corroborated by adequate preclinical evidence. The underlying objectives behind cardiac regenerative therapies subsume enhancing angiomyogenesis in the ischemic myocardium, ameliorating cellular apoptosis, regenerating the damaged myocardium, repopulating the lost resident myocardial cells (smooth muscle, cardiomyocyte, and endothelial cells), and finally, decreasing fibrosis with a consequent reduction in ventricular remodeling. Although-cell based cardiomyoplasty approaches have an immense potential, their clinical utilization is limited owing to the increased need for better candidates for cellular cardiomyoplasty, better routes of delivery, appropriate dose for efficient engraftment, and better preconditioning or genetic-modification strategies for the progenitor and stem cells. Mesenchymal stem cells (MSCs) have emerged as powerful candidates in mediating myocardial repair owing to their unique properties of multipotency, transdifferentiation,

intercellular connection with the resident cardiomyocytes via connexin 43 (Cx43)-positive gap junctions in the myocardium, and most important, immunomodulation. In this review, we present an in-depth discussion on the complexities associated with stem and progenitor cell therapies, the potential of preclinical approaches involving MSCs for myocardial repair, and an account of the past milestones and ongoing MSC-based trials in humans.

Pisati, F., P. Bossolasco, et al. (2007). "Induction of neurotrophin expression via human adult mesenchymal stem cells: implication for cell therapy in neurodegenerative diseases." Cell Transplant **16**(1): 41-55.

In animal models of neurological disorders for cerebral ischemia, Parkinson's disease, and spinal cord lesions, transplantation of mesenchymal stem cells (MSCs) has been reported to improve functional outcome. Three mechanisms have been suggested for the effects of the MSCs: transdifferentiation of the grafted cells with replacement of degenerating neural cells, cell fusion, and neuroprotection of the dying cells. Here we demonstrate that a restricted number of cells with differentiated astroglial features can be obtained from human adult MSCs (hMSCs) both in vitro using different induction protocols and in vivo after transplantation into the developing mouse brain. We then examined the in vitro differentiation capacity of the hMSCs in coculture with slices of neonatal brain cortex. In this condition the hMSCs did not show any neuronal transdifferentiation but expressed neurotrophin low-affinity (NGFR(p75)) and high-affinity (trkC) receptors and released nerve growth factor (NGF) and neurotrophin-3 (NT-3). The same neurotrophin's expression was demonstrated 45 days after the intracerebral transplantation of hMSCs into nude mice with surviving astroglial cells. These data further confirm the limited capability of adult hMSC to differentiate into neurons whereas they differentiated in astroglial cells. Moreover, the secretion of neurotrophic factors combined with activation of the specific receptors of transplanted hMSCs demonstrated an alternative mechanism for neuroprotection of degenerating neurons. hMSCs are further defined in their transplantation potential for treating neurological disorders.

Prockop, D. J., C. A. Gregory, et al. (2003). "One strategy for cell and gene therapy: harnessing the power of adult stem cells to repair tissues." Proc Natl Acad Sci U S A **100 Suppl 1**: 11917-23.

Most recent evidence suggests that the process of tissue repair is driven by stem-like cells that reside in multiple tissues but are replenished by precursor cells from bone marrow. Among the candidates for the reparative cells are the adult stem cells from bone marrow referred to as either mesenchymal stem cells or marrow stromal cells (MSCs). We recently found that after MSCs were replated at very low densities to generate single-cell-derived colonies, they did not exit a prolonged lag period until they synthesized and secreted considerable quantities of Dickkopf-1, an inhibitor of the canonical Wnt signaling pathway. We also found that when the cells were cocultured with heat-shocked pulmonary epithelial cells, they differentiated into epithelial cells. Most of the MSCs differentiated without evidence of cell fusion but up to one-quarter underwent cell fusion with the epithelial cells. A few also underwent nuclear fusion. The results are consistent with the interesting possibility that MSCs and similar cells repair tissue injury by three different mechanisms: creation of a milieu that enhances regeneration of endogenous cells, transdifferentiation, and perhaps cell fusion.

Quesenberry, P. J., M. Abedi, et al. (2004). "Stem cell plasticity: an overview." Blood Cells Mol Dis **32**(1): 1-4.

The capacity of adult bone marrow cells to convert to cells of other tissues, referred to by many as stem cell plasticity, was the focus of the meeting in Providence entitled "Challenges in the Era of Stem Cell Plasticity". The meeting provided a showcase for the many impressive positive results on tissue restoration including the capacity of purified marrow stem cells to restore heart, skin, and liver function in impaired mice or humans. This area of research has become a center of controversy, although it is not clear why. Calls for clonality, robustness, and function have been shown to be erroneous or premature. A call for clonality (which has been shown nicely in one study) is meaningless on a predefined stem cell population which is intrinsically heterogeneous, as they all are. Robustness means nothing; it all depends on the details of the situation. Function on an organ level is, of course, the goal of many investigators and should not be raised as a limiting consideration. Lastly, fusion has been highlighted as undermining studies with adult stem cells. It, of course, does not. Fusion is simply a means to a final goal, which occurs in certain settings of marrow conversions (transdifferentiation) and not in others. We hypothesize that the conversion phenomena may, in fact, be due to one or several marrow stem cells with broad differentiation potential which can be expressed when the cell is placed in an environment with the appropriate inductive signals. Furthermore, initial events may be relatively rare and significant conversion numbers may be obtained with massive or ongoing selection. Fusion appears in an initial

mechanism in some cases and not in others. Overall, the therapeutic potential of adult marrow stem cells is very intriguing, and successful use therapeutically will probably depend on definition of the most appropriate transplant model and tissue injury.

Rajasingh, J., E. Lambers, et al. (2008). "Cell-free embryonic stem cell extract-mediated derivation of multipotent stem cells from NIH3T3 fibroblasts for functional and anatomical ischemic tissue repair." Circ Res **102**(11): e107-17.

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

Ratajczak, M. Z., M. Kucia, et al. (2004). "Stem cell plasticity revisited: CXCR4-positive cells expressing mRNA for early muscle, liver and neural cells 'hide out' in the bone marrow." Leukemia **18**(1): 29-40.

It has been suggested that bone marrow (BM)-derived hematopoietic stem cells transdifferentiate into tissue-specific stem cells (the so-called phenomenon of stem cell plasticity), but the possibility of committed tissue-specific stem cells pre-existing in BM has not been given sufficient consideration. We hypothesized that (i) tissue-committed stem cells circulate at a low level in the peripheral blood (PB) under normal steady-state conditions, maintaining a pool of stem cells in peripheral tissues, and their levels increase in PB during stress/tissue injury, and (ii) they could be chemoattracted to the BM where they find a supportive environment and that the SDF-1-CXCR4 axis plays a prominent role in the homing/retention of these cells to BM niches. We performed all experiments using freshly isolated cells to exclude the potential for 'transdifferentiation' of hematopoietic stem or mesenchymal cells associated with in vitro culture systems. We detected mRNA for various early markers for muscle (Myf-5, Myo-D), neural (GFAP, nestin) and liver (CK19, fetoprotein) cells in circulating (adherent cell-depleted) PB mononuclear cells (MNC) and increased levels of expression of these markers in PB after mobilization by G-CSF (as measured using real-time RT-PCR). Furthermore, SDF-1 chemotaxis combined with real-time RT-PCR analysis revealed that (i) these early tissue-specific cells reside in normal murine BM, (ii) express CXCR4 on their surface and (iii) can be enriched (up to 60 x) after chemotaxis to an SDF-1 gradient. These cells were also highly enriched within purified populations of murine Sca-1(+) BM MNC as well as of human CD34(+)-, AC133(+)- and CXCR4-positive cells. We also found that the expression of mRNA for SDF-1 is upregulated in damaged heart, kidney and liver. Hence our data provide a new perspective on BM not only as a home for hematopoietic stem cells but also a 'hideout' for already differentiated CXCR4-positive tissue-committed stem/progenitor cells that follow an SDF-1 gradient, could be mobilized into PB, and subsequently take part in organ/tissue regeneration.

Regitnig, P., E. Spuller, et al. (2001). "Insulinoma of the pancreas with insular-ductular differentiation in its liver metastasis--indication of a common stem-cell origin of the exocrine and endocrine components." Virchows Arch **438**(6): 624-8.

We describe an insulinoma of the pancreas in a 56-year-old patient, which showed insular-ductular differentiation in its liver metastasis. Although the primary tumor was uniformly endocrine in nature with insulin production, the metastasis contained two distinct cell types in organoid arrangement. One cell type was insulin-positive and was arranged in islet-like structures; the other was insulin-negative but distinctly pan-cytokeratin and cytokeratin 7 positive and arranged in ducts. In the primary tumor and the metastasis, the tumor cells were surrounded by a desmoplastic stroma. As to the histogenesis of the tumor and its metastasis, we discuss the following possibilities: (1) the tumor cells might derive from a common stem cell that matures into two phenotypically different cell lines, resembling the situation in embryogenesis and (2) one tumor cell type originates from the other by transdifferentiation (metaplasia). We conclude that the parallel occurrence of endocrine and ductal differentiation supports the concept that, under certain conditions, islet cells and ductular cells may also originate from islets and that

mixed endocrine/exocrine pancreatic tumors do not necessarily arise from totipotent duct cells but might also have a primary endocrine cell origin.

Roper, S. and M. Hemberger (2009). "Defining pathways that enforce cell lineage specification in early development and stem cells." Cell Cycle **8**(10): 1515-25.

The molecular processes that govern the first cell lineage decisions after fertilization also dictate the developmental potency of stem cells derived from the early mouse embryo. Our understanding of these mechanisms is therefore instrumental for stem cell biology and regenerative medicine. A number of transcription factors are known that determine a cell's fate towards either the embryonic or extraembryonic trophoblast lineages. Recent insights have shown that the definitive fixation of cell lineage fate is achieved by an epigenetic restriction through DNA methylation of the transcription factor Elf5. Lineage crossover can be induced, however, by manipulation of lineage determinants and gatekeepers, or their epigenetic regulation. Here we summarize the accumulating number of experimental conditions where such 'transdifferentiation' is observed that shed light onto the genetic and epigenetic pathways involved in lineage separation and the developmental potential of stem cells.

Rovo, A. and A. Gratwohl (2008). "Plasticity after allogeneic hematopoietic stem cell transplantation." Biol Chem **389**(7): 825-36.

The postulated almost unlimited potential of transplanted hematopoietic stem cells (HSCs) to transdifferentiate into cell types that do not belong to the hematopoietic system denotes a complete paradigm shift of the hierarchical hemopoietic tree. In several studies during the last few years, donor cells have been identified in almost all recipient tissues after allogeneic HSC transplantation (HSCT), supporting the theory that any failing organ could be accessible to regenerative cell therapy. However, the putative potential ability of the stem cells to cross beyond lineage barriers has been questioned by other studies which suggest that hematopoietic cells might fuse with non-hematopoietic cells and mimic the appearance of transdifferentiation. Proof that HSCs have preserved the capacity to transdifferentiate into other cell types remains to be demonstrated. In this review, we focus mainly on clinical studies addressing plasticity in humans who underwent allogeneic HSCT. We summarize the published data on non-hematopoietic chimerism, donor cell contribution to tissue repair, the controversies related to the methods used to detect donor-derived non-hematopoietic cells and the functional impact of this phenomenon in diverse specific target tissues and organs.

Rutenberg, M. S., T. Hamazaki, et al. (2004). "Stem cell plasticity, beyond alchemy." Int J Hematol **79**(1): 15-21.

Cell plasticity is a central issue in stem cell biology. Differentiated somatic nuclei have the flexibility to dedifferentiate when transferred into oocytes or when fused to pluripotent embryonic stem cells. Recent publications also claim that somatic stem cells can convert into developmentally unrelated cell types both in vivo and ex vivo without such drastic cell manipulations. Some of these claims are still controversial, making it difficult for us to determine the reality of somatic stem cell plasticity. Indeed, we have heard enough about the "potentials" of cell plasticity; how much do we know about mechanisms? A fundamental issue in current stem cell biology is to understand the mechanisms underlying cell plasticity. In this short review, we overview three research fields related to cell plasticity: nuclear transfer, transdifferentiation, and cell fusion, with an emphasis on studies of molecular mechanisms underlying cell plasticity.

Safford, K. M. and H. E. Rice (2005). "Stem cell therapy for neurologic disorders: therapeutic potential of adipose-derived stem cells." Curr Drug Targets **6**(1): 57-62.

There is growing evidence to suggest that reservoirs of stem cells may reside in several types of adult tissue. These cells may retain the potential to transdifferentiate from one phenotype to another, presenting exciting possibilities for cellular therapies. Recent discoveries in the area of neural differentiation are particularly exciting given the limited capacity of neural tissue for intrinsic repair and regeneration. Adult adipose tissue is a rich source of mesenchymal stem cells, providing an abundant and accessible source of adult stem cells. These cells have been termed adipose derived stem cells (ASC). The characterization of these ASCs has defined a population similar to marrow-derived and skeletal muscle-derived stem cells. The success seen in differentiating ASC into various mesenchymal lineages has generated interest in using ASC for neuronal differentiation. Initial in vitro studies characterized the morphology and protein expression of ASC after exposure to neural induction agents. Additional in vitro data suggests the possibility that ASCs are capable of neuronal activity. Progress in the in vitro characterization of ASCs has led to in vivo modeling to determine the survival, migration, and engraftment of transplanted ASCs. While work to define the mechanisms behind the transdifferentiation

of ASCs continues, their application to neurological diseases and injuries should also progress. The subject of this review is the capacity of adipose derived stem cells (ASC) for neural transdifferentiation and their application to the treatment of various neurologic disorders.

Sasaki, M., R. Abe, et al. (2008). "Mesenchymal stem cells are recruited into wounded skin and contribute to wound repair by transdifferentiation into multiple skin cell type." J Immunol **180**(4): 2581-7.

Mesenchymal stem cells (MSCs) can differentiate not only into mesenchymal lineage cells but also into various other cell lineages. As MSCs can easily be isolated from bone marrow, they can be used in various tissue engineering strategies. In this study, we assessed whether MSCs can differentiate into multiple skin cell types including keratinocytes and contribute to wound repair. First, we found keratin 14-positive cells, presumed to be keratinocytes that transdifferentiated from MSCs in vitro. Next, we assessed whether MSCs can transdifferentiate into multiple skin cell types in vivo. At sites of mouse wounds that had been i.v. injected with MSCs derived from GFP transgenic mice, we detected GFP-positive cells associated with specific markers for keratinocytes, endothelial cells, and pericytes. Because MSCs are predominantly located in bone marrow, we investigated the main MSC recruitment mechanism. MSCs expressed several chemokine receptors; especially CCR7, which is a receptor of SLC/CCL21, that enhanced MSC migration. Finally, MSC-injected mice underwent rapid wound repaired. Furthermore, intradermal injection of SLC/CCL21 increased the migration of MSCs, which resulted in an even greater acceleration of wound repair. Taken together, we have demonstrated that MSCs contribute to wound repair via processes involving MSCs differentiation various cell components of the skin.

Seipel, K., N. Yanze, et al. (2004). "The germ line and somatic stem cell gene Cniwi in the jellyfish Podocoryne carnea." Int J Dev Biol **48**(1): 1-7.

In most animal phyla from insects to mammals, there is a clear division of somatic and germ line cells. This is however not the case in plants and some animal phyla including tunicates, flatworms and the basal phylum Cnidaria, where germ stem cells arise de novo from somatic cells. Piwi-like genes represent essential stem cell genes in diverse multicellular organisms. The cnidarian Piwihomolog Cniwiwas cloned from Podocoryne carnea, a hydrozoan with a full life cycle. CniwiRNA is present in all developmental stages with highest levels in the egg and the medusa. In the adult medusa, Cniwi expression is prominent in the gonads where it likely functions as a germ stem cell gene. The gene is also expressed, albeit at low levels, in differentiated somatic cells like the striated muscle of the medusa. Isolated striated muscle cells can be induced to transdifferentiate into smooth muscle cells which proliferate and differentiate into nerve cells. Cniwi expression is upregulated transiently after induction of transdifferentiation and again when the emerging smooth muscle cells proliferate and differentiate. The continuous low-level expression of an inducible stem cell gene in differentiated somatic cells may underlie the ability to form medusa buds from polyp cells and explain the extraordinary transdifferentation and regeneration potential of Podocoryne carnea.

Sena, G., X. Wang, et al. (2009). "Organ regeneration does not require a functional stem cell niche in plants." Nature **457**(7233): 1150-3.

Plants rely on the maintenance of stem cell niches at their apices for the continuous growth of roots and shoots. However, although the developmental plasticity of plant cells has been demonstrated, it is not known whether the stem cell niche is required for organogenesis. Here we explore the capacity of a broad range of differentiating cells to regenerate an organ without the activity of a stem cell niche. Using a root-tip regeneration system in Arabidopsis thaliana to track the molecular and functional recovery of cell fates, we show that re-specification of lost cell identities begins within hours of excision and that the function of specialized cells is restored within one day. Critically, regeneration proceeds in plants with mutations that fail to maintain the stem cell niche. These results show that stem-cell-like properties that mediate complete organ regeneration are dispersed in plant meristems and are not restricted to niches, which nonetheless seem to be necessary for indeterminate growth. This regenerative reprogramming of an entire organ without transition to a stereotypical stem cell environment has intriguing parallels to recent reports of induced transdifferentiation of specific cell types in the adult organs of animals.

Siebert, S., F. Anton-Erxleben, et al. (2008). "Cell type complexity in the basal metazoan Hydra is maintained by both stem cell based mechanisms and transdifferentiation." Dev Biol **313**(1): 13-24.

Understanding the mechanisms controlling the stability of the differentiated cell state is a fundamental problem in biology. To characterize the critical regulatory events that control stem cell behavior and cell plasticity in vivo in an organism at the base of animal evolution, we have generated transgenic Hydra lines [Wittlieb, J., Khalturin, K., Lohmann, J., Anton-Erxleben, F., Bosch, T.C.G.,

2006. Transgenic Hydra allow in vivo tracking of individual stem cells during morphogenesis. Proc. Natl. Acad. Sci. U. S. A. 103, 6208-6211] which express eGFP in one of the differentiated cell types. Here we present a novel line which expresses eGFP specifically in zymogen gland cells. These cells are derivatives of the interstitial stem cell lineage and have previously been found to express two Dickkopf related genes [Augustin, R., Franke, A., Khalturin, K., Kiko, R., Siebert, S. Hemmrich, G., Bosch, T.C.G., 2006. Dickkopf related genes are components of the positional value gradient in Hydra. Dev. Biol. 296 (1), 62-70]. In the present study we have generated transgenic Hydra in which eGFP expression is under control of the promoter of one of them, HyDkk1/2/4 C. Transgenic Hydra recapitulate faithfully the previously described graded activation of HyDkk1/2/4 C expression along the body column, indicating that the promoter contains all elements essential for spatial and temporal control mechanisms. By in vivo monitoring of eGFP+ gland cells, we provide direct evidence for continuous transdifferentiation of zymogen cells into granular mucous cells in the head region. We also show that in this tissue a subpopulation of mucous gland cells directly derives from interstitial stem cells. These findings indicate that both stem cell-based mechanisms and transdifferentiation are involved in normal development and maintenance of cell type complexity in Hydra. The results demonstrate a remarkable plasticity in the differentiation capacity of cells in an organism which diverged before the origin of bilaterian animals.

Silani, V. and M. Corbo (2004). "Cell-replacement therapy with stem cells in neurodegenerative diseases." Curr Neurovasc Res **1**(3): 283-9.

In the past few years, research on stem cells has expanded greatly as a tool to develop potential therapies to treat incurable neurodegenerative diseases. Stem cell transplantation has been effective in several animal models, but the underlying restorative mechanisms are still unknown. Several mechanisms such as cell fusion, neurotrophic factor release, endogenous stem cell proliferation, and transdifferentiation may explain positive therapeutic results, in addition to replacement of lost cells. The biological issue needs to be clarified in order to maximize the potential for effective therapies. The absence of any effective pharmacological treatment and preliminary data both in experimental and clinical settings has recently identified Amyotrophic Lateral Sclerosis (ALS) as an ideal candidate disease for the development of stem cell therapy in humans. Preliminary stem transplantation trials have already been performed in patients. The review discusses relevant topics regarding the application of stem cell research to ALS but in general to other neurodegenerative diseases debating in particular the issue of transdifferentiation, endogenous neural stem cell, and factors influencing the stem cell fate.

Silani, V., L. Cova, et al. (2004). "Stem-cell therapy for amyotrophic lateral sclerosis." Lancet **364**(9429): 200-2.

CONTEXT: With the lack of effective drug treatments for amyotrophic lateral sclerosis (ALS), and compelling preclinical data, stem-cell research has highlighted this disease as a candidate for stem-cell treatment. Stem-cell transplantation is an attractive strategy for neurological diseases and early successes in animal models of neurodegnerative disease generated optimism about restoring function or delaying degeneration in human beings. The restricted potential of adult stem cells has been challenged over the past 5 years by reports on their ability to acquire new unexpected fates beyond their embryonic lineage (transdifferentiation). Therefore, autologous or allogeneic stem cells, undifferentiated or transdifferentiated and manipulated epigenetically or genetically, could be a candidate source for local or systemic cell-therapies in ALS. STARTING POINT: Albert Clement and colleagues (Science 2003; 302: 113-17) showed that in SOD1G93A chimeric mice, motorneuron degeneration requires damage from mutant SOD1 acting in non-neuronal cells. Wild-type non-neuronal (glial) cells could delay degeneration and extend survival of mutant-expressing motorneurons. Letizia Mazzini and colleagues (Amyotroph Lateral Scler Other Motor Neuron Disord 2003; 4: 158-61) injected autologous bone-marrow-derived stem cells into the spinal cord of seven ALS patients. These investigators reported that the procedure had a reasonable margin of clinical safety. WHERE NEXT? The success of cell-replacement therapy in ALS will depend a lot on preclinical evidence, because of the complexity and precision of the pattern of connectivity that needs to be restored in degenerating motoneurons. Stem-cell therapy will need to be used with other drugs or treatments, such as antioxidants and/or infusion of trophic molecules.

Smart, N. and P. R. Riley (2008). "The stem cell movement." Circ Res **102**(10): 1155-68.

Stem or progenitor cell-based strategies to combat ischemic heart disease and myocardial infarction, whether autologous transplantation or stimulation of resident populations, not only require detailed insight into transdifferentiation potential and functional coupling, but the efficacy of this approach is underpinned by the need to induce appropriate migration and homing to the site of injury. This

review focuses on existing insights into the trafficking of stem cells in the context of cardiac regenerative therapy, with particular focus on the wide variety of potential sources of cells, critical factors that may regulate their migration, and how extrapolating from embryonic stem/progenitor cell behavior during cardiogenesis may reveal pathways implicit in the adult heart postinjury.

Somoza, R., P. Conget, et al. (2008). "Neuropotency of human mesenchymal stem cell cultures: clonal studies reveal the contribution of cell plasticity and cell contamination." Biol Blood Marrow Transplant **14**(5): 546-55.

Various studies have shown neuropotency of bone marrow-derived human mesenchymal stem cells (hMSC) based on the appearance of cells with neural phenotype before or after neural induction protocols. However, to date, it is unclear which mechanisms account for this observation. We hypothesized that neural phenotypes observed in hMSC cultures can be because of both intrinsic cell plasticity and contamination by cells of neural origin. Therefore, we characterized 38 clones from hMSC cultures by assessing their adipogenic/osteogenic potential with specific mesenchymal differentiation protocols, and their molecular neural phenotype by RT-PCR analysis before and after exposure to a defined neural stem cell (NSC) medium for 8 days (neural protocol). We found 33 clones with mesenchymal potential and 15 of them also showed a neural phenotype. As neural phenotypes were maintained during the neural protocol, this suggested neural cell plasticity in 39% of all clones through pluripotency. Importantly, we were able to induce neural phenotypes in 11 of mesenchymal clones applying the neural protocol, demonstrating neural cell plasticity in 29% of all clones through the mechanism of transdifferentiation. Finally, 2 of 5 nonmesenchymal clones (5% of all clones) displayed a neural phenotype indicating neural cell contamination of hMSC cultures. In conclusion, we found 2 different ways of neuropotency of hMSC cultures: cell plasticity and cell contamination.

Song, L., N. E. Webb, et al. (2006). "Identification and functional analysis of candidate genes regulating mesenchymal stem cell self-renewal and multipotency." Stem Cells **24**(7): 1707-18.

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

Song, W. J., R. Shah, et al. (2009). "The use of animal models to study stem cell therapies for diabetes mellitus." Ilar J **51**(1): 74-81.

The two main forms of human diabetes mellitus (DM) are characterized by an absolute (type 1) and a relative (type 2) reduction in functional insulin-producing beta cell mass in the pancreas. Type 1 DM results from autoimmune assault of beta cells, and type 2 from the failure of pancreatic beta cells to sufficiently compensate for insulin resistance. Studies indicate that the incidence of both types is increasing rapidly to levels that constitute a global epidemic. Researchers are experimentally developing several conceptual approaches for increasing pancreatic beta cell mass and testing them for feasibility in treating the disease. The main sources for derivation of insulin-producing cells are embryonic and induced pluripotent stem cells, endogenous progenitor cells (both within and outside the pancreas), stimulation of beta cell proliferation, and genetic "reprogramming" of cells. Strategies to effectively address immune- and inflammation-mediated assault on existing and newly formed beta cells need to be refined. This review provides a description of beta cell ablation methods and a discussion of various types of studies of regenerative approaches-beta cell proliferation, islet cell transplantation, transdifferentiation, and the use of embryonic and induced pluripotent stem cells-to the treatment of diabetes mellitus. Although there has been much progress in this area, further research is

needed to enhance understanding and improve therapeutic strategies for this widespread disease.

Steindler, D. A. (2006). "Redefining cellular phenotypy based on embryonic, adult, and cancer stem cell biology." Brain Pathol **16**(2): 169-80.

Stem cell biology has provided constant alteration if not reversal of dogma related to the understanding of the behaviors of primitive and dynamic cells. This review summarizes recent findings on dynamic changes of phenotype that accompany the in vitro growth and differentiation of not only stem and progenitor cells, but also differentiated cells derived from a variety of normal and pathological tissues. As there are examples of apparent dedifferentiation and transdifferentiation of neural cells that appear to be terminally differentiated, there is a need to reconsider elements of cellular fate choice that have relevance to neurooncology and neural repair. Recent findings of dynamic behaviors and mixed phenotype of both normal and cancer stem cells suggest that some of the diverse lineage attributes of different solid tumors may owe their existence to dynamic cellular phenotypy gone awry.

Stojanoski, Z., B. Georgievski, et al. (2008). "Stem cell transplantation - new treatment approaches." Prilozi **29**(2): 71-84.

Stem cell research still remains one of the most controversial fields of science today on account cell plasticity and its capability of transdifferentiation or de-differentiations to certain tissue types, as well as the clinical application of this scientific concept. Stem cells derived from bone marrow, peripheral blood or the umbilical cords are a common therapeutic approach for treatment of haematological malignancies as part of established transplant procedures (allogeneic, autologous, syngeneic stem cell transplantation). But recent clinical data have revealed the potential role of stem cells in the treatment of other nonhaematological diseases, degenerative disorders, cardiovascular diseases and autoimmune diseases. The experience with stem cell transplantation in haematological malignancies at the Hematology Department, Skopje, has been established since it was set up 7 years ago, with more than 130 patients undergoing transplant procedures (87 autologous and 43 allogeneic recipients). Encouraging results were also reported from the Skopje Cardiology Clinic in the field of intracoronary application of bone marrow derived stem cells for the treatment of patients with acute myocardial infarction. But this new rout in tissue regeneration should still be further extended and evaluated in clinically randomized studies that will confirm the therapeutic potential of stem cells.

Stokman, G., J. C. Leemans, et al. (2005). "Hematopoietic stem cell mobilization therapy accelerates recovery of renal function independent of stem cell contribution." J Am Soc Nephrol **16**(6): 1684-92.

Acute renal failure and tubular cell loss as a result of ischemia constitute major challenges in renal pathophysiology. Increasing evidence suggests important roles for bone marrow stem cells in the regeneration of renal tissue after injury. This study investigated whether the enhanced availability of hematopoietic stem cells, induced by stem cell factor and granulocyte colony-stimulating factor, to the injured kidney provides an adequate strategy for stem cell-based therapy to counteract renal ischemia/reperfusion injury. It is interesting that cytokine treatment before injury resulted in significant enhancement of function recovery of the kidney. This, however, was not due to increased incorporation of tubular epithelial cells from bone marrow origin. Importantly, cytokine treatment resulted in impaired influx of granulocytes into the injured kidney. Although cytokine treatment improved renal function rapidly after ischemic injury, the results show that the underlying mechanism likely is not based on stem cell transdifferentiation but rather on altered inflammatory kinetics.

Tang, P. H. (2003). "Current basic research of hematopoietic stem cells in China and comments on stem cell plasticity." Zhongguo Shi Yan Xue Ye Xue Za Zhi **11**(1): 1-6.

The basic studies selected were mainly published since 1998 and related to stem cell biology and engineering and particularly the efforts for developing new sources of hematopoietic stem/progenitor cells ex vivo. Hematopoietic cells and lymphocytes can be developed by induced differentiation in a appropriate way of culture, originating in the embryo- or adult-derived stem cells or tissue-committed stem cells which still exist in the tissue of adults. The most primitive multipotential embryonic stem cell from embryo or adult tissue has the plasticity to differentiate into every kind of progenies, the committed tissue-specific stem cell, by different proper ways of induction in vitro. The committed tissue-specific stem cell, however, can only be induced to differentiate along the line of its committed origin of tissue. No studies in China strongly confirmed yet the existence of "transdifferentiation" among the tissue- or organ-specific stem cells.

Torrente, Y. and E. Polli (2008). "Mesenchymal stem cell transplantation for neurodegenerative diseases." Cell Transplant **17**(10-11): 1103-13.

Neurodegenerative diseases are characterized by a progressive degeneration of selective neural populations. The lack of effective treatment and the characteristic of their pathology make these diseases appropriate candidates for cell therapy. Mesenchymal stem cells (MSCs) are multipotent stem-like cells that are capable of differentiating into mesenchymal and nonmesenchymal lineages. Their regenerative capacity after in vivo transplantation into animal models of neurodegenerative diseases has suggested that they could be useful against human diseases. Human bone marrow-derived MSCs (hMSCs) can be easily amplified in vitro and their transdifferentiation has been claimed in vitro and in vivo in neural cells. There are some doubts concerning the exact mechanisms responsible for the beneficial outcome observed after MSC transplantation into neurodegenerating tissues. Possible interpretations include cell replacement, trophic factor delivery, and immunomodulation. This review mainly concerns hMSCs transplantation in neurodegenerative diseases, because it has proven to be feasible, safe, and potentially effective. Although they have been used in hundreds of clinical trials, mixed results and no functional and long-lasting integration have so far been observed. hMSCs transplantations therefore still have their "dark side." However, the challenge in well-planned clinical trials merits discussion.

Udani, V. M. (2006). "The continuum of stem cell transdifferentiation: possibility of hematopoietic stem cell plasticity with concurrent CD45 expression." Stem Cells Dev **15**(1): 1-3.

Recent years have seen a surge of scientific research examining adult stem cell plasticity. For example, the hematopoietic stem cell has been shown to give rise to skin, respiratory epithelium, intestinal epithelium, renal epithelium, liver parenchyma, pancreas, skeletal muscle, vascular endothelium, myocardium, and central nervous system (CNS) neurons. The potential for such stem cell plasticity seems to be enhanced by stressors such as injury and neoplasia. Interestingly, recent studies have demonstrated that hematopoietic stem cells may be able to adopt certain nonhematopoietic phenotypes, such as endothelial, neural, or skeletal muscle phenotypes, without entirely losing their initial hematopoietic identity. We propose that transdifferentiation can, in certain conditions, be a partial rather than a complete event, and we encourage further investigation into the phenomenon of a stem cell simultaneously expressing phenotypic features of two distinct cell fates.

van der Bogt, K. E., A. Y. Sheikh, et al. (2008). "Comparison of different adult stem cell types for treatment of myocardial ischemia." Circulation **118**(14 Suppl): S121-9.

BACKGROUND: A comparative analysis of the efficacy of different cell candidates for the treatment of heart disease remains to be described. This study is designed to evaluate the therapeutic efficacy of 4 cell types in a murine model of myocardial infarction. METHODS AND RESULTS: Bone marrow mononuclear cells (MN), mesenchymal stem cells (MSC), skeletal myoblasts (SkMb), and fibroblasts (Fibro) expressing firefly luciferase (Fluc) and green fluorescence protein (GFP) were characterized by flow cytometry, bioluminescence imaging (BLI), and luminometry. Female FVB mice (n=70) underwent LAD ligation and intramyocardially received one cell type (5x10(5)) or PBS. Cell survival was measured by BLI and by TaqMan PCR. Cardiac function was assessed by echocardiography and invasive hemodynamic measurements. Fluc expression correlated with cell number in all groups ($r(2)>0.93$). In vivo BLI revealed acute donor cell death of MSC, SkMb, and Fibro within 3 weeks after transplantation. By contrast, cardiac signals were still present after 6 weeks in the MN group, as confirmed by TaqMan PCR ($P<0.01$). Echocardiography showed significant preservation of fractional shortening in the MN group compared to controls ($P<0.05$). Measurements of left ventricular end-systolic/diastolic volumes revealed that the least amount of ventricular dilatation occurred in the MN group ($P<0.05$). Histology confirmed the presence of MN, although there was no evidence of transdifferentiation by donor MN into cardiomyocytes. CONCLUSIONS: This is the first study to show that compared to MSC, SkMB, and Fibro, MN exhibit a more favorable survival pattern, which translates into a more robust preservation of cardiac function.

Yang, J., Q. Lou, et al. (2008). "Dorsal root ganglion neurons induce transdifferentiation of mesenchymal stem cells along a Schwann cell lineage." Neurosci Lett **445**(3): 246-51.

It has been reported that mesenchymal stem cells (MSCs) can transdifferentiate into Schwann cell-like cells by a series of treatments with a reducing agent, retinoic acid and a combination of trophic factors in vitro, and can transdifferentiate into myelin-forming cells to repair the demyelinated rat spinal cord in vivo. We now report that when co-cultured with dorsal root ganglion (DRG) neurons, MSCs were induced to transdifferentiate into Schwann cell-like cells that had ensheathed DRG axons. Following differentiation, MSCs underwent morphological changes similar to those of cultured Schwann cells and express GFAP and S100, the marker of Schwann cells. Moreover, 6 weeks later, MSCs wrapped their

membrane around DRG axons. Further, initiation of myelination was observed in the co-cultured DRG neurons, which was determined by signals to MBP and this initiation of axon myelination by MSCs is similar to that of Schwann cells. However, electron micrographs show that no compact myelin was present in the MSCs co-cultures, whereas the Schwann cells co-cultures had formed a multilammelar myelin sheath around the axon. These indicate that the release of cytokine by DRG neurons may promote the transdifferentiation of MSCs, but is not sufficient to elicit compact myelination by transdifferentiated MSCs. These results improve our understanding in the mechanism of MSC transdifferentiation, and the mechanism underlying ensheathment and myelination by transdifferentiated MSCs.

Yener, B., E. Acar, et al. (2008). "Multiway modeling and analysis in stem cell systems biology." BMC Syst Biol **2**: 63.

BACKGROUND: Systems biology refers to multidisciplinary approaches designed to uncover emergent properties of biological systems. Stem cells are an attractive target for this analysis, due to their broad therapeutic potential. A central theme of systems biology is the use of computational modeling to reconstruct complex systems from a wealth of reductionist, molecular data (e.g., gene/protein expression, signal transduction activity, metabolic activity, etc.). A number of deterministic, probabilistic, and statistical learning models are used to understand sophisticated cellular behaviors such as protein expression during cellular differentiation and the activity of signaling networks. However, many of these models are bimodal i.e., they only consider row-column relationships. In contrast, multiway modeling techniques (also known as tensor models) can analyze multimodal data, which capture much more information about complex behaviors such as cell differentiation. In particular, tensors can be very powerful tools for modeling the dynamic activity of biological networks over time. Here, we review the application of systems biology to stem cells and illustrate application of tensor analysis to model collagen-induced osteogenic differentiation of human mesenchymal stem cells. RESULTS: We applied Tucker1, Tucker3, and Parallel Factor Analysis (PARAFAC) models to identify protein/gene expression patterns during extracellular matrix-induced osteogenic differentiation of human mesenchymal stem cells. In one case, we organized our data into a tensor of type protein/gene locus link x gene ontology category x osteogenic stimulant, and found that our cells expressed two distinct, stimulus-dependent sets of functionally related genes as they underwent osteogenic differentiation. In a second case, we organized DNA microarray data in a three-way tensor of gene IDs x osteogenic stimulus x replicates, and found that application of tensile strain to a collagen I substrate accelerated the osteogenic differentiation induced by a static collagen I substrate. CONCLUSION: Our results suggest gene- and protein-level models whereby stem cells undergo transdifferentiation to osteoblasts, and lay the foundation for mechanistic, hypothesis-driven studies. Our analysis methods are applicable to a wide range of stem cell differentiation models.

Yoon, J., W. J. Shim, et al. (2005). "Transdifferentiation of mesenchymal stem cells into cardiomyocytes by direct cell-to-cell contact with neonatal cardiomyocyte but not adult cardiomyocytes." Ann Hematol **84**(11): 715-21.

Recent studies have demonstrated that direct cell-to-cell interaction is one of the microenvironment factors for transdifferentiation of adult stem cells into cardiomyocytes. We investigated whether transdifferentiation of mesenchymal stem cells (MSCs) into cardiomyocytes was dependent on developmental stages of cocultured cardiomyocytes, and direct cell-to-cell interaction was essential for transdifferentiation. MSCs were isolated from adult rat and cocultured in four different ways: (1) with neonatal cardiomyocytes, (2) with adult cardiomyocytes, (3) with neonatal cardiomyocytes on the cell culture inserts, and (4) with the conditioned medium from neonatal cardiomyocytes. After 5 days of coculture with neonatal cardiomyocytes, 9.40+/-1.15% of 1,1'-dioctadecyl-1-3,3,3',3'-tetramethylindocarbocyanine perchlorate labeled MSCs expressed sarcomeric-alpha-actinin. Immunocytochemistry showed that only these MSCs expressed the cardiac markers and were not observed with other coculture condition as well as conditioned medium. Calcein-AM labeling of cardiomyocytes showed gap junctional communication between 56.1+/-2.0% of MSCs (24 h after labeling, n=5) and neonatal cardiomyocytes. These findings suggest that MSCs are capable of differentiating into cardiomyocytes when directly cocultured with neonatal cardiomyocytes by cell-to-cell interaction, but not with adult cardiomyocytes or conditioned medium.

Zubko, R. and W. Frishman (2009). "Stem cell therapy for the kidney?" Am J Ther **16**(3): 247-56.

The kidney has a remarkable capacity to regenerate after injury, as it is not a terminally differentiated organ. This regenerative potential is somehow incomplete, however, and as the insult continues, progressive and irreversible scarring results

in chronic renal disease. Dialysis and organ transplantation are nonspecific and incomplete methods of renal replacement therapy. Stem cells may provide a more efficacious method for both prevention and amelioration of renal disease of many etiologies. Although many reports have claimed the existence of renal-specific stem or progenitor cells isolated and characterized by various methods, the results have been diverse and debatable. The bone marrow stem cells seem to play a minor role in renal regeneration after acute ischemia in mice through transdifferentiation and cell fusion, but their immediate paracrine effects result in considerable improvements in renal function. Therefore, as in stem cell therapy for the heart, bone marrow-derived stem cells show promise in regeneration of the kidney. Although more research is needed in the basic science of renal regeneration, clinical research in animals has demonstrated the versatility of stem cell therapy. The first phase of clinical trials of bone marrow mesenchymal cells in protection against acute kidney injury may begin shortly. This will enable further exploration of stem cell therapy in renal patients with multiple comorbidities.

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