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Adult stem cells and their ability to differentiate

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Summary

This is a review of the current status of knowledge on adult stem cells as well as the criteria and evidence for their potential to transform into different cell types and cell lineages. Reports on stem cell sources, focusing on tissues from adult subjects, were also investigated. Numerous reports have been published on the search for early markers of both stem cells and the precursors of various cell lineages. The question is still open about the characteristics of the primary stem cell. The existing proofs and hypotheses have not yielded final solutions to this problem. From a practical point of view it is also crucial to find a minimal set of markers determining the phenotypes of the precursor cells of a particular cell lineage. Several lines of evidence seem to bring closer the day when we will be able to detect the right stem cell niche and successfully isolate precursor cells that are needed for the treatment of a particular disorder. Recent reports on cases of cancer in patients subjected to stem cell therapy are yet another controversial issue looked into in this review, although the pros and cons emerging from the results of published studies still do not provide satisfying evidence to fully understand this issue.

key words: **adult stem cells • cell differentiation • progenitor cells • self-renewal • stem cells • stem cell niche**

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BACKGROUND

Stem cells are classified according to their differentiation potential as totipotent, pluripotent, or multipotent. Totipotent stem cells are capable of forming any tissue in the body, similarly to a fertilized egg which, following cleavage, produces cells which differentiate into all types of tissues. Pluripotency is the capability of the cell to create almost any type of cells in the organism, but not the entirety. Multipotent stem cells, finally, are those that can only give rise to cells of the tissue that they were isolated from. Cells in a developing embryo, totipotent at the beginning, lose this feature after several cell cycles as a completely developed organism and become pluripotent. Therefore, based on the criteria of differentiation potential, embryonic stem cells are the least differentiated when compared with bone marrow stem cells (BMSCs), tissue-specific stem cells, lineage-specific precursors, and terminally differentiated cells. Besides embryonic stem cells, bone marrow has been predominately considered the only significant source of stem cells. However, recent findings have revealed that adult stem cells can reside in most if not every tissue (*vide* [1]). The marrow and non-marrow stem cells display different characteristics and properties that will be discussed in this review.

There are some common features of adult stem cells that enable them to produce identical daughter cells during a relatively large number of cell divisions. This feature is often referred to as self-renewal or clonogenicity [2]. Another property of adult stem cells is their ability to give rise to precursors of mature, and then terminally differentiated, cells with specified morphological characteristics and functions [3]. In mature tissues, adult stem cells play a crucial role in maintaining local homeostasis by replacing dead or damaged cells as well as in the process of tissue remodeling. More recent developments have proved that adult stem cells reside in nearly every tissue, including the brain, bone marrow, peripheral blood, kidney, epithelia of the digestive system, and also the skin, retina, muscles, pancreas, and liver [3]. However, the origin of stem cells in adults, as well as whether they are distinct populations of cells or remnants of their embryonic counterparts, is still not clear. Another controversy is whether cells isolated from a particular tissue originated in this tissue or if they have been temporarily trapped in a pool of stem cells circulating in the blood, having thus been subjected to a process called homing [4,5].

Another "hot spot" in stem cell science is discussions on their plasticity. The ability to change phenotypic characteristics is still very controversial. The first "theory" that tried to explain this phenomenon was "transdifferentiation", i.e. cell reprogramming in response to external factors and successful settlement in an empty niche of damaged tissue [6]. Many studies on stem cell transdifferentiation provoked skepticism and led to another "way out", i.e. cell fusion. In this review we will try to present different views on stem cell plasticity and the results that support them in the context of different cell types. The enormous possibilities linked to the harvesting and culturing of adult stem cells are related to their multipotential and transdifferential capabilities, which could be utilized in treating a number of disorders including stroke, burns of skin and other tissues, spinal cord injuries, and degenerative disorders, as well as those related to the nervous system, such as Parkinson's and Alzheimer's disease [7,8].

HEMATOPOIETIC AND NON-HEMATOPOIETIC STEM CELLS IN BONE MARROW AND PERIPHERAL BLOOD

Maintenance of the inner environment and immunity depends mainly on blood. Such functions demand enormous power from cells for self-renewal and proliferation, especially significant after massive bleeding or following infection. Research on hematopoietic stem cells has been conducted for more than 50 years. The first discoveries where made in late 1940s. Subsequently, in 1961, Till and McCulloch [9] defined the basic features of hematopoietic stem cells (HSCs), including their capability for self-renewal and differentiation into all types of blood cell lineages.

On the basis of data collected from numerous studies performed mostly in mice, it has been well established that HSCs derived from bone marrow can reconstitute the entire hemopoietic system in a lethally irradiated individual. This was one of the definite proofs that stem cells reside in bone marrow. However, despite many years of intense research, the exact marker(s) of hematopoietic stem cells still cannot be defined. There are set of markers, such as CD34, CD59, and Thy1, that stem-like cells express (Figure 1). In the search for stem cells, investigators tried to eliminate cells that express characteristic features of certain cell lineages [10]. Among them is CD71, a marker for the erythroid lineage, and CD33, an antigen for the myeloid lineage. For B-lymphoid lineages, CD10 expression is common. Moreover, it was found that the ability to form primitive colonies decreases with the increase in expression levels of CD38. That is why the most primitive hematopoietic stem cells are found only in a small subset (about 1%) of CD34+ cells that do not co-express the CD38 antigen (Figure 1) [11]. The tagged population of cells can be sorted out using the method of fluorescence-activated cell sorting (FACS), by which recovery of a heterogeneous population, including cells with stem cell potential, can be achieved. HSCs are morphologically very difficult to distinguish, and the only verifying test for the presence of HSCs is the detection of surface markers and the ability of sorted cells to reconstitute the hematopoietic system in a myeloablated recipient.

Since the first studies on HSCs, bone marrow was the first source from which HSCs were isolated. Because of the discomfort encountered during bone marrow collection and procedural complications, other sources of HSC were also explored. Currently, rapid progress is being made in the preparation of peripheral blood-derived stem cells (PBSCs). This procedure is preferred because PBSCs can be obtained in a harmless way. Moreover, PBSCs have higher survival rates and engraft faster than bone marrow-derived stem cells [12]. However, prior to harvesting the PBSCs, the donor needs to undergo a mobilization procedure through the administration of a human recombinant granulocyte colony-stimulating factor (hr-GCSF), which increases the efficacy of harvested cells. Utilization of a cytokine cocktail (GCSF, IL-3, IL-6, Epo) shows significance in retaining hematopoietic reconstitution and expansion potentials [13]. Without the mobilization procedure it was difficult to maintain PBSCs in cultures because shortly after harvest the cells initiated proliferation with differentiation, leading to a lack of self-renewal capacities. Ema and colleagues [14] reported that in the presence of Stem Cell Factor (SCF) and following thrombopoietin induction, cell division and stem cell renew-

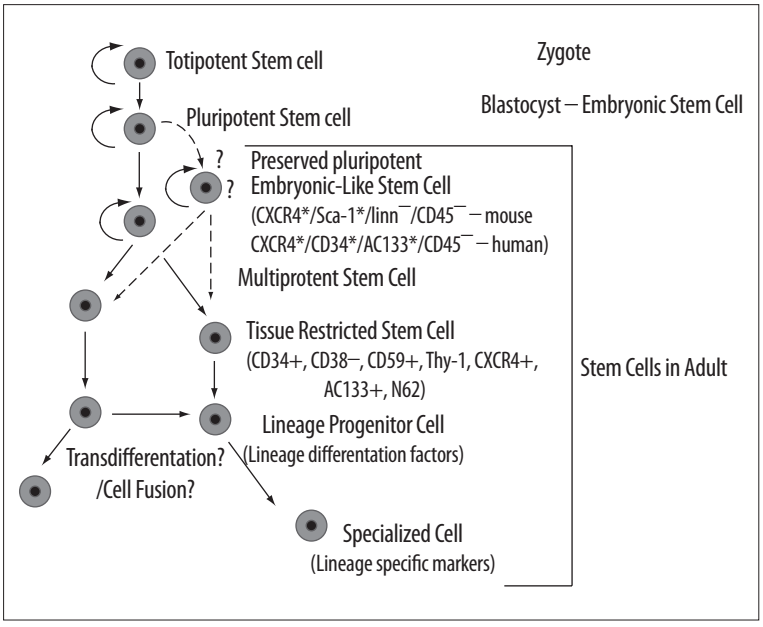

Figure 1. Ways of stem cell speciation and differentiation. Solid arrows indicate experimentally proven and dashed arrows hypothesized ways of cell speciation and/or differentiation.

al capabilities could be re-established. More recent reports have revealed that the key players in the culture are stromal cells that, through the secretion of specific signaling factors, keep stem cells in their immature state and allow their self-renewal (*vide* [15]). GCSF also plays a crucial role in mobilizing circulating tissue-committed stem cells (TCSC) that express the chemokine receptor CXCR4 [16]. Sdf-1 is very often expressed in damaged tissues and attracts circulating TCSCs, thus promoting tissue regeneration [17]. The circulating TCSCs also shed new light on the transdifferentiation/plasticity of adult stem cells (*vide* [18]).

In the population of hematopoietic cells, similarly to other types of tissues, are cells that manifest a specific flow profile with the use of Heochst 33342 dye. These cells have been named side population cells (SP cells) and, when isolated from bone marrow, they can differentiate into various types of cells different from hematopoietic lineages. Jackson et al. [19] showed that SP cells which are CD34-/low, c-Kit+, and Sca-1+ maintain capabilities for differentiation into cardiomyocytes and endothelial cells in the infracted myocardia of lethally irradiated mice. In SP cells, a transporter molecule, BCRP1/ABCG2, seems to be involved in a specific efflux of Heochst 33342 dye, with a phenotypic trait of primitive SP cells [20].

Beyond the ability to differentiate into lineages of blood cells, HSCs have sufficient plasticity to give rise to other non-hematopoietic cells, such as muscle cells, neurons, hepatocytes, adipocytes, osteoblasts, and others. In numerous experiments with rats and mice as well as studies in humans, it has been well documented that in individuals with livers injured by hepatic toxins or enzyme malfunctions, bone marrow-derived stem cells were found to have differentiated to hepatocytes after transplantation, helping in the regeneration of the organ [21,22]. In humans, sex-mismatched bone marrow transplants also helped to establish blood-to-liver differentiation that gave rise to fully functional hepatocytes [5]. However, others suggested that this result should be considered with caution, especially the application of the sex-mismatch method as well as possible stem cell fusion ([23] and reviewed by [24]). Another example of stem cell capabilities is their differentiation following bone marrow transplantation to cells of the nervous system. Braselton [25] and Mezey [26] reported that after BM transplantation, donor cells expressed neuronal antigens NeuN and class 3 β-tubulin. The results revealed that BMSCs (bone marrow stromal cells) migrated into the brain and differentiated to cells expressing neuronal antigens. Thus BMSCs acted as an alternative source of stem cells in tissue repair. Others also reported that stromal cells from bone marrow possess the capability of differentiation into cells that express the neuronal-specific markers NSE (neural-specific enolase) and NeuN [27,28]. There are also fascinating examples of BMSC plasticity, including differentiation to cell lines such as those in the kidney, lungs, and skin (*vide* review by [29]).

More examples of the plasticity of BMSCs include blood-to-muscle differentiation. An elegant study conducted by Orlic et al. [30] showed that bone marrow-derived stem cells are capable of repairing infracted myocardium and give rise to new myocytes, endothelial cells, and smooth muscle cells that generated the myocardium *de novo*. There are several studies revealing the potential of bone marrow stem cell differentiation into cardiomyocytes [31,32]. It is speculated that the cell migration, proliferation, and differentiation of transplanted cells are induced by signals released from the injured myocardium. Deb et al. [33] presented an experimental model of gender-mismatched human bone marrow-derived SCs transdifferentiated into cardiomyocytes. Following a series of studies done by Wagers et al. [34] which diminished the role and the possibility of transdifferentiation, the concept of cell fusion emerged as an alternative (Figure 1). Terada et al. and Ying et al. [35,36] observed the formation of aneuploid cells in co-cultures of bone marrow or neural stem cells with embryonic stem cells that displayed stem cell features. When bone marrow-derived stem cells were implanted into an infarcted myocardium, histological analysis revealed that the number of cells was much lower

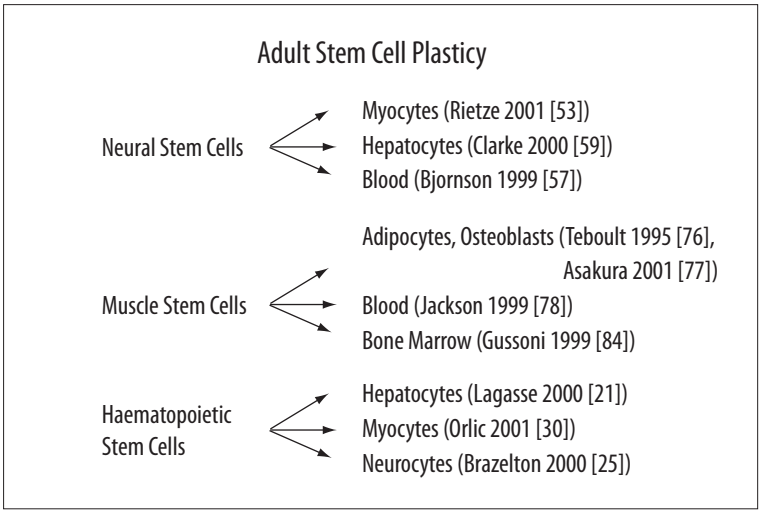

Figure 2. Adult stem cell potential and plasticity.

30 days after injection than after 2 days [37]. It appeared that the engraftment was not stable, but rather transient, and thus cells with hematopoietic characteristics were low in number. Studies by Nygren et al. [38] using the transgenic LacZ mice model confirmed that bone marrow-derived cardiomyocytes were in fact results of cell fusion rather than transdifferentiation. These studies put into question the work of Orlic and colleagues and has provoked an ongoing discussion in myocardial regeneration on the possibility of SCs to transdifferentiate [39].

Stem Cells in Neural Tissues of Adults: Yet Another Dogma of Biology Has Fallen

The long-standing and unquestioned dogma was that the brain cannot renew on its own and that the number of neurons is constant throughout an individual's entire adult life. The concept of neurogenesis did not gain wider understanding until recently, although previous studies on cell proliferation with the use of ^{3}H-tymidine or BrdU had confirmed neurogenesis throughout adulthood and the continuous generation of new neurons [40–42].

Neurogenesis in the adult brain takes place in its two major regions: the subventricular zone (SVZ) and the hippocampal dental gyrus (DG). The SVZ is the region of the highest neurogenetic activity and the place from which the first neural stem cells (NSCs) have been isolated [43]. The zone is the remnant of the embryonic germinal neuroepithelium, comprising a thin layer of mitotically active cells in the walls of the telencephalic lateral ventricles. Mature neurons are formed, for example, in the olfactory bulb (OB), the region to which NSCs migrate from the SVZ along a discrete pathway called the rostral migratory stream [40]. The SVZ contains a marrow-like structure harboring ependymal cells and astrocytes that play a role very similar to stromal cells in bone marrow (BM). The ependymal cells and astrocytes form specific channels called glial tubes [44,45] that are used by migrating neuroblasts. Neuroblasts form tight chains and migrate towards the OB, where they differentiate to periglomerular or granule neurons, changing their migration pattern from tangential to radial. Astrocytes in glial tubes provide trophic support to the migrating cells and insulation from electrical and chemical signals released from the surrounding parenchyma (*vide* [46]). In addition to astrocytes, ependymal cells, and neuroblasts, transitory amplifying progenitor (TAP) cells called type C cells are present in the SVZ. The type C cells are immature, fast-proliferating cells that do not express any features characteristic of neuroblasts or glia. Doetch and collaborators [47] reported that TAP cells are not only progenitor cells derived from stem cells, but that they also retain stem cell competence when exposed to growth factors. Moreover, depletion of mitotically active cells in the SVZ following injection with the antimitotic substance Ara-C revealed that GFAP-positive cells repopulated the zone [48]. GFAP is a member of a family of intermediate filament proteins and is involved in maintaining the shape and function of astrocytes. Therefore, GFAP is considered a specific marker of astrocytes. Astrocytes from the SVZ function as the primary precursors of rapidly dividing transit amplifying cells, and GFAP^{+} astrocytes in the SVZ give rise to olfactory-bulb inter-neurons.

In a very similar manner, the sub-granular layer of astrocytes in the hippocampus generates neurons in the dentate gyrus [49]. The main criterion distinguishing neuronal stem cells from other neural cells present in the brain is the *in vitro* formation of neurospheres by the former. Cells in neurospheres proliferate and differentiate into clusters of cells with phenotypes of neurons, glia, and oligodendrocytes (Figure 2) [43]. The most unique feature of cells in neurospheres is their ability to generate secondary spheres following dispersion and their renewing abilities even after several passages. All the observations suggest that the cells arise from pluripotent precursors and may reflect properties of *in vivo* progenitors. The formation of neurospheres could also be induced by the presence of growth factors, such as the epidermal growth factor (EGF) [50] and the basic fibroblast growth factor (bFGF) [51]. Stem cells forming neurospheres express numerous markers, including LEX/SSEA-1 [52], nestin [53], AC133 [54], and NG2 [55].

When it became apparent that NSCs really exist, that they have capabilities for self-renewal, and that it is possible to maintain them as stable cell lines, the next step was to check their plasticity. The results were very surprising and also very promising. Neural stem cells out-stretched brain (epidermal) boundaries in that they appeared to be able to transdiffer-

entiate. Transdifferentiation is a feature unique to the stem cells and their progeny, which are the only cells able to differentiate to cells of developmentally unrelated germ layers (Figure 2) [26]. The first to evaluate this statement was an elegant work published by Bjornsen and collaborators [56], who reported that clonally derived neuronal stem cells could give rise to hematopoietic cells *in vivo*. In their studies with sub-lethally irradiated mice, tagged neuronal stem cells and their progeny colonized different hematopoietic tissues in these animals, including the spleen and thymus. Moreover, the cells had the potential to differentiate into a variety of blood cell lines. Granulocytes, garnulo-macrophages, macrophages, and mixed cell colonies have been founded from a single neural stem cell precursor. However, no erythrocytes have been detected. Recently, similar data have been reported from a study conducted with neuronal stem cells in humans [57]. Galli et al. [58] also explained that neuromesodermal differentiation is possible only when SVZ-derived stem cell colonies consist of a majority of immature cells. Otherwise, differentiation of NSCs showed a negligible tendency to transdifferentiate. NSCs from adults also revealed enormous myogenic potential [53].

Broad developmental capacity has been demonstrated in two separate experiments [59]. NSCs were injected into either chick or mouse embryos. Surprisingly, in both cases NSCs gave rise to three major cell lineages and colonized many different tissues (Figure 2). The neural stem cells immunologically became hepatocytes, myocytes, etc, finally proving their ability to create progeny of all major cell lineages. An additional conclusion from these studies is that NSCs and their progeny, upon differentiation, expressed all specific markers only under particular environmental conditions and only in close contact with other cells. NSCs expressed muscle specific markers, such as MyoD and myosin heavy chain, only in situations in which neurons were co-cultured with muscle cells and cell contact between neurons and myoblasts was maintained (*vide* [46]).

Stem Cells in Skeletal Muscle: The Tissues That Seem Terminally Differentiated and Specialized

Skeletal muscle stem cells seem to possess enormous potential to respond to physiological stimuli such as growth and training, but also to injury. Muscles are under continuous stress from variable physical forces and endurance conditions. Thus the ability of renewal is one of the most important features of muscles. Since the discovery of satellite cells [60], they have been candidate stem cells for skeletal muscles. At the moment of birth, 32% of subliminal nuclei are represented by satellite cells. Their number decreases with age, and in adulthood it is maintained at a level of 1 to 5% [61]. The distribution of satellite cells is not the same in different types of muscle fibers. The presence of satellite cells is much higher in the proximity of myonuclei, motoneurons, and capillaries. Moreover, oxidative muscle fibers seem to be colonized by a higher number of satellite cells than glycolytic muscles are [62,63].

Lying dormant on the periphery of the mature, multinucleated myotubes, beneath the basal lamina of skeletal muscle fibers, satellite cells are ideally positioned to respond to injuries of muscle fiber. For most of the time the cells are quiescent; however, following muscle damage they are activated and their morphological characteristics changed by means of heterochromatin reduction, an increase in the ratio of cytoplasm to nuclear mass, as well as an increase in the number of intracellular organelles [64]. The progeny of activated satellite cells fuse to form new multinucleated fibers [65]. During the quiescent state the satellite cells do not express myogenic regulatory factors such as MyoD and MEF2 [66,67]. Due to parallelism between myogenesis in the embryo and muscle regeneration in adults, Pax 7 and Pax 3, the transcriptional factors that keep satellite cells in their quiescent state, are responsible for the satellite cells' formation and consequently for sufficient myogenesis [68,69].

Myf5 and MyoD are the myogenic regulatory factors up-regulated following injury, whereas Pax7 is at the same time down-regulated [66,70]. MyoD and Myf5 are also essential for myotube formation. In mice devoid of MyoD, the myogenic cells fail to progress through the differentiation process. Instead, there is an accumulation of mononuclear cells [67,71]. Down-regulation of Pax7 and up-regulation of MyoD are closely connected with the process of differentiation [72], but at the same time some cells maintain high levels of Pax7 and low levels of MyoD. Following aggregation in clusters, the cells become a satellite cell pool [73]. Work by Oustanina and coworkers [74] raised doubts that Pax7 is the only factor that is responsible for satellite cell specification, but emphasized its critical role in muscle renewal and homeostasis. New experiments on establishing new markers for satellite cells are still going on. Nagata and colleagues [75] discovered that levels of sphingomyelin closely correlate with the activation of quiescent muscle stem cells. Quiescent stem cells also bind lysenin, which is a sphingomyelin-specific protein and provides a new marker of myogenic pool for non-cycling stem cells.

In response to trauma, injury, training and various growth factors such as HGF, FGF, and IGF, satellite cells express a tremendous proliferation capacity. This feature fulfils the major requirement for stem-like cells, which is the ability to self-renew. Moreover, in the presence of thiazolinediones and BMPs (bone morphogenetic proteins) these cells are capable of differentiating into various types of cells, e.g. adipocytes and osteoblasts [76,77], and even to hematopoietic lineages [78] (Figure 2). What is also important, muscle stem cells are negatively regulated and their growth is mediated by myostatin and GDF-8 (growth and differentiation factor 8) [79,80]. Mutation in the myostatin gene results in increased musculature in pigs and cattle, and similar data were also reported for humans [81].

Other cells have been discovered in muscles named side population (SP) cells. Such cells can be isolated using the Hoechst 33342 dye efflux method. Cells with similar properties can also be found in other tissues [82]. SP cells possess great potency for *in vitro* differentiation into hematopoietic precursors [18] and cells of neural phenotype [83] and for the *in vivo* reconstitution of bone marrow [84]. These results ensure that muscles contain stem-like cells capable of self-renewal and transdiffrentiation to different types of tissues. The question still unanswered is whether SP cells are satellite cell progenitors or are a totally independent population of cells. The latter seems to have been recently proved by results from a study by Seale and collabora-

tors in which they discovered an absence of satellite cells in Pax7-null mice, whereas the overall number of SP cells was unaffected [68].

Results from research on muscle stem cell therapy indicate that the most important target diseases seem to be the various muscular dystrophies, among them Duchenne muscular dystrophy. Dystrophin is the protein lacking in these diseases. The role of this protein is to connect the cytoskeleton of muscle fibers with extracellular matrix. The first therapeutic attempt to use stem cell therapy was conducted in 1989 by Partridge and colleagues, who showed that the C2C12 myogenic cell line derived from adult satellite cells efficiently reconstituted fibers in dystrophic *mdx* mice [85]. Subsequently, several clinical attempts were made, but unfortunately all of them failed due to the lack of a sufficient cell delivery method (reviewed in [65]). The failure also resulted from immune responses and from a slow rate or total lack of cell migration. Currently, several *in vitro* trials are being conducted aiming to overcome these obstacles by optimizing delivery and introducing new immune suppression technologies. Additional prospects that arise in muscular stem cell therapy are linked with regenerative therapy of liver malfunctions. Previously used bone marrow-derived stem cells contributed to the repair and regeneration of renal tubules after an episode of ischemia [86]. In an experiment by Arriero and collaborators [87], mice were subjected to renal ischemia transplants of muscle-derived stem cells. The reason for utilizing such cells was a hypothesized higher affinity for homing within vasculature. Differentiation into an endothelial lineage was monitored by the appearance of a Tie-2 promoter-driven GFP. An *in vitro* experiment showed that 90% of MSCs grown on Endothelial Basal Medium expressed several endothelial-specific markers (CD31, Flk-1, and MECA). Transplantation of undifferentiated stem cells had no effect on renal dysfunction 24 h after injury, supposedly due to the lack of enough time for full differentiation to endothelial lineage. Previously differentiated SCs were found in renal microvasculature and preserved renal function.

Stem Cells in the Liver are Involved in its Regeneration

Under normal physiological conditions, the liver is proliferatively quiescent. Upon injury or following infection it rapidly responds by initiating regeneration. There are three populations of cells that contribute to restoration of liver mass. The system of the first-line response to injury consists of hepatocytes and cholangiocytes, which contribute to normal liver turnover. The intrahepatic biliary tree in the canals of Hering is the region where cells are transitional between the periportal hepatocytes and the biliary cells lining the smallest terminal bile ducts [88]. This is the potential stem cell compartment. Cells bud from the canals and differentiate into hepatocytes. Another location of what is considered to be a stem cell compartment is the periductular region [89]. Cells called "oval cells" have features similar to those of hepatoblasts in the early stages of embryonic liver development. They may also have characteristics of bile duct cells and hepatocytes. Oval cells are activated to proliferate after hepatocyte loss in the mature liver when liver damage is extensive and chronic or when the proliferation of hepatocytes is inhibited, for example by viral infection. Then their progeny expand across the liver lobule and differentiate into either hepatocytes or bile duct cells and ultimately rebuild the liver. Among the markers defining liver stem cells is the oval cell-specific marker OV-6. Different markers of hematopoietic lineage that could be expressed in oval cells are c-kit [90] and Thy-1 (CD90), also present on the surface of many early hematopoietic progenitor cells and immature B and T cells [91]. Oval cells also express CD34, a marker of early hematopoietic progenitor cells [92]. What is also important is that the ATP-binding cassette ABCG2 transporter, closely related to the SP phenotype, is upregulated in human hepatic oval cells [93]. These characteristics give support to the concept that some of the oval cells derive from a precursor of bone marrow origin [94].

In a cross-sex experiment, after suppression of hepatocyte proliferation in lethally irradiated recipients [95] or in the absence of any intentional liver injury [96], bone marrow-derived hepatocytes were found. However, reports by different groups did not confirm these findings [35]. Only a small subset of hematopoietic stem cells produced hepatocytes and there were no successful non-hematopoietic engraftments [97]. Hematopoietic stem cells contribute to hepatic regeneration, but the mechanism is not fully understood and is supposed to be connected to the presence and severity of liver injury. In 2003, Kollet and associates [98] revealed that following liver injury, chemokine Sdf-1 and its receptor CXCR4 participated in the mobilization of hematopoietic stem cells and the directional migration towards the injured liver. There are additional factors playing crucial roles in hepatic migration of HSCs, such as HGF, FGF-4, IL-8, and MMP-9 [99,100]. A crucial question worth asking is whether hematopoietic stem cells undergo transdifferentation to hepatocytes or are hepatocyte-like cells generated by cell fusion. Cell fusion between HSCs and hepatocytes was demonstrated in Fah−/− mice and heterokaryotic hybrids were detected [101,102]. It appears that the major fusion partners are cells of monocyte-macrophage lineage [103,104]. Generation of hepatocytes derived from HSCs is of a very low frequency [105], thus the contribution of HSCs to liver replacement following injury or disease is low [88]. Up to now there has been no direct evidence for transdifferentation of HSCs to hepatocytes (for a critical review, see [106]).

In the Quest for a Universal Stem Cell

The cells of great potential and plasticity are embryonic cells (Figure 1). It is, however, unlikely that embryonic stem cell (ES)-derived treatments will soon be available for clinical use. The prospect of stem cell therapy has heralded much hype and controversy, particularly as a result of the development of embryonic stem cell lines. The development of advanced treatments with ES cells has been slow because of the scientific reality that it is difficult to produce large quantities of homogeneous cells for transplantation, particularly bearing in mind that animal feeder layers, on which adult human ES cells tend to rely, might be a contaminant [107,108]. In addition, control of the immunological development of ES cells is also a significant problem that will take time to overcome [109,110]. Adult stem (ADS) cells, however, provide an alternative cell source which is more ethically acceptable and could supply cells for current transplantation. ADS therapies have had successes using bone

marrow (BM) stem cells and those derived from umbilical cord blood (UCB). One example is the treatment of myocardial infarcts with BM-derived stem cells and in hematotherapy using UCB [111–113].

Recent reports on cells with great plasticity found in mice claim that the cells residing in the nonadherent, nonhematopoietic $CXCR4^+/Sca\text{-}1^+/lin^-/CD45^-$ mononuclear cell (MNC) fraction in mice and in the $CXCR4^+/CD34^+/AC133^+/CD45^-$ BMMNC fraction in humans (Figure 1) are populations of cells that could be used for clinical applications such as repair of cardiac muscle [16]. Cells of similar phenotype were also identified in human umbilical cord blood. The cells were positive for TRA-1-60, TRA-1-81, SSEA-4, SSEA-3, and Oct-4, but not for SSEA-1. They were cultured for several weeks and expanded in large numbers [114].

Stem Cell Therapy and its Limitations Due to Cancer Risk

Stem cells have acquired a golden glow in the past few years as a possible tool for reversing the damage of various organs. The prediction was that stem cell transplants, whether derived from embryonic tissue or from adult cells that retain the flexibility to develop into various tissues, will someday repair hearts crippled by heart attacks or brains under attack by Alzheimer's or Parkinson's disease. But the very qualities that make these cells so attractive to medicine, especially their capacity to replicate ad infinitum, also hint at a dark side. Evidence suggests that they may be the source of the mutant cells that give rise to cancerous tumors (also reviewed in [115]. In studies of cells in blood cancers such as leukemia and in breast and brain cancers, cells called "cancer stem cells" have been identified. The findings have raised the possibility that the mutations that drive cancer development may have originated in the body's small supply of naturally occurring stem cells. Cancer stem cells resemble these normal cells in several ways. In particular, both types are self-renewing. Thus, when they divide, one of the daughter cells differentiates into a particular cell type that eventually stops dividing, but the other retains its stem cell properties, including the ability to divide in the same way again. Therefore, it is possible that cancer stem cells, which form only a small proportion of the total tumor cell population, are the only tumor cells with the capacity to keep tumors growing.

In the early 1990s, Dick and colleagues [116,117] used a model to study the development of human hematopoietic stem cells which give rise to various types of blood cells. The model is based on an extremely immunodeficient mouse strain, the NOD/SCID mouse. The animals were irradiated to destroy their bone marrow and then human stem cells were introduced to see if they would produce a new complement of blood cells. After showing that normal human hematopoietic stem cells could do this, Dick and his team used the approach to study the cancer-causing power of acute myeloid leukemia (AML) cells freshly harvested from human patients [118]. By a progressive dilution of a known number of leukemia cells, it was possible to establish that only a very rare AML cell, about one in a million, had the ability to reproduce the disease in the animals. Because this was a much smaller fraction of cells than that necessary to form colonies in culture, the result indicated that the simple ability to grow did not equate with the ability to develop into leukemia in living animals. Thus one could speculate that the leukemia-initiating cells had a greater developmental potential than the vast majority of clone-forming cells and might even be stem-like cells. Subsequently, the leukemia-initiating cells were characterized according to surface protein markers that distinguish the various cell types of the hematopoietic system. The leukemia-initiating cells turned out to belong to an exclusive group. They were positive for the CD34 marker and negative for CD38, the same as human hematopoietic stem cells, and did not carry the markers of more mature cells. The cancer cells' resemblance to normal stem cells holds up even though AML is a heterogeneous disease, with several different subtypes depending on which genetic abnormalities the patients' cells carry. Dick and his colleagues characterized the leukemia-initiating cells from the various AML subtypes and found that all belonged to that same $CD34^+/CD38^-$ class. When put into NOD/SCID mice, however, each cell type produced a leukemia identical to that in the patient from which it had originally been isolated. A plausible conclusion from this study is that the initial mutations that gave rise to the leukemias arose in normal stem cells, causing them to take the wrong developmental pathway.

Another line of evidence suggesting that cancers originate from stem cells comes from studies of the biological machinery underlying self-renewal. Normal and cancer stem cells show some striking similarities. Recently, for example, researchers have shown that the genes *Bmi-1* and *Wnt*, both of which can cause cancer when mutated, are needed for self-renew in normal and cancer stem cells (also reviewed in [119]. The *Bmi-1* gene participates in normal hematopoietic development, and its malfunction has been linked to AML. A study reported by Park and collaborators [120] and another by Lessard and Sauvageau [121] link the gene to self-renewal. To test whether cells missing *Bmi-1* can self-renew, the researchers transplanted stem cells from *Bmi-1* knockout mice into normal mice that had been irradiated to destroy their bone marrow. The stem cells produced a normal complement of blood cells, but only for very short period of time. After eight weeks, blood cells derived from the transplanted cells had almost disappeared, and when bone marrow taken from the animals was put into a second series of mice, no *Bmi-1*-deficient blood cells could be detected. *Bmi-1* is also needed for the self-renewal of leukemia cells [121]. In previous reports, Sauvageau and collaborators revealed that they could cause an AML-like disease in mice by introducing two oncogenes, *Meis1a* and *Hoxa9*, into the bone marrow cells of the animals [122]. This result shows that without *Bmi-1*, leukemia stem cells die out, just as normal stem cells do. The *Wnt* gene is likewise the focus of a great deal of research by both cancer researchers and developmental biologists. The protein encoded by the gene normally controls cell fate decisions during the development of many of the body's tissues. It exerts its effects by binding to, and thus activating, a receptor on the cell surface membrane. This in turn sets off a series of changes inside the cell, culminating in the activation of genes governing cell division and differentiation. Details of these processes however, are still poorly understood and require further intensive research both in the area of stem cells, including lessons learned from the biology of embryonic stem cells, as well as from the biology of various cancer cell lines and various types of cancer.

REFERENCES:

1. Preston SL, Alison MR, Forbes SJ et al: The new stem cell biology: something for everyone. Mol Pathol, 2003;56: 86–96
2. Weissman IL: Stem cells: units of development, units of regeneration, and units in evolution. Cell, 2000; 100: 157–68
3. Slack JM: Stem Cells in Epithelial Tissues. Science, 2000; 287: 1431–33
4. Hennessy B, Korbling M, Estrov Z: Circulating stem cells and tissue repair. Panminerva Med, 2004; 46: 1–11
5. Korbling M, Katz RL, Khanna A et al: Hepatocytes and epithelial cells of donor origin in recipients of peripheral-blood stem cells. N Engl J Med, 2002; 346: 738–46
6. Verfaillie CM, Pera MF, Lansdorp PM: Stem cells: hype and reality. Hematology, 2002; 369–91
7. Azizi SA, Stokes D, Augelli BJ et al: Engraftment and migration of human bone marrow stromal cells implanted in the brains of albino rats – similarities to astrocyte grafts Proc Natl Acad Sci USA, 1998; 95: 3908–13
8. Blesch A, Tuszynski MH: Gene therapy and cell transplantation for Alzheimer's disease and spinal cord injury. Yonsei Med J, 2004; 45(Suppl.): 28–31
9. Till JE, McCullough EA: A direct measurement of the radiation sensitivity of normal mouse bone marrow cells. Radiat Res, 1961; 14: 213–22
10. Spangrude GJ, Heimfeld S, Weissman IL: Purification and characterization of mouse hematopoietic stem cells. Science, 1988; 241: 58–62
11. Terstappen LW, Huang S, Safford M et al: Sequential generations of hematopoietic colonies derived from single nonlineage-committed CD34+CD38– progenitor cells. Blood, 1991; 77: 1218–27
12. Negrin RS, Atkinson K, Leemhuis T et al: Transplantation of highly purified CD34+Thy-1+ hematopoietic stem cells in patients with metastatic breast cancer. Biol. Blood Marrow Transplant, 2000; 6: 262–71
13. Yang QE, Fong SE, Li K et al: *Ex vivo* expanded murine bone marrow cells with a multiple cytokine cocktail retain long-term hematopoietic reconstitution potentials. Med Sci Monit, 2005; 11(6): BR154–61
14. Ema H, Takano H, Sudo K, Nakauchi H: *In Vitro* Self-Renewal Division of Hematopoietic Stem Cells. J Exp Med, 2000; 192: 1281–88
15. Sauvageau G, Iscove NN, Humphries RK: *In vitro* and *in vivo* expansion of hematopoietic stem cells. Oncogene, 2004; 23: 7223–32
16. Ratajczak MZ, Kucia M, Reca R et al: Stem cell plasticity revisited: CXCR4-positive cells expressing mRNA for early muscle, liver and neural cells 'hide out' in the bone marrow. Leukemia, 2004; 18: 29–40
17. Kucia M, Dawn B, Hunt G et al: Cells expressing early cardiac markers reside in the bone marrow and are mobilized into the peripheral blood after myocardial infarction. Circ Res, 2004; 95: 1191–99
18. Kucia M, Ratajczak J, Ratajczak MZ: Bone marrow as a source of circulating $CXCR4^+$ tissue-committed stem cells. Biol Cell, 2005; 97: 133–46
19. Jackson KA, Majka SM, Wang H et al: Regeneration of ischemic cardiac muscle and vascular endothelium by adult stem cells. J Clin Invest, 2001; 107: 1395–402
20. Zhou S, Morris JJ, Barnes Y et al: Bcrp1 gene expression is required for normal numbers of side population stem cells in mice, and confers relative protection to mitoxantrone in hematopoietic cells *in vivo*. Proc Natl Acad Sci USA, 2002; 99: 12339–44
21. Lagasse E, Connors H, Al-Dhalimy et al: Purified hematopoietic stem cells can differentiate into hepatocytes *in vivo*. Nat Med,k 2000; 6: 1229–34
22. Austin TW, Lagasse E: Hepatic regeneration from hematopoietic stem cells. Mech Dev, 2003; 120: 131–35
23. Brouard M, Barrandon Y, Stevens et al: Male Cells in Female Recipients of Hematopoietic-Cell Transplants. N Engl J Med, 2002; 347: 218–20
24. Masson S, Harrison DJ, Plevris JN, Newsome PN: Potential of hematopoietic stem cell therapy in hepatology: a critical review. Stem Cells, 2004; 22: 897–907
25. Brazelton TR, Rossi FM, Keshet GI, Blau HM: From marrow to brain: expression of neuronal phenotypes in adult mice. Science, 2000; 290: 1775–79
26. Mezey E, Chandross KJ, Harta G et al: Turning blood into brain: cells bearing neuronal antigens generated *in vivo* from bone marrow. Science, 2000; 290: 1779–82
27. Woodbury D, Schwarz EJ, Prockop DJ, Black IB: Adult rat and human bone marrow stromal cells differentiate into neurons. J Neurosci Res, 2000; 61: 364–70
28. Kopen GC, Prockop DJ, Phinney DG: Marrow stromal cells migrate throughout forebrain and cerebellum, and they differentiate into astrocytes after injection into neonatal mouse brains. Proc Natl Acad Sci USA, 1999; 96: 10711–16
29. Herzog EL, Chai L, Krause DS: Plasticity of marrow-derived stem cells. Blood, 2003; 102: 3483–93
30. Orlic D, Kajstura J, Chimenti S et al: Mobilized bone marrow cells repair the infarcted heart, improving function and survival. Proc Natl Acad Sci USA, 2001; 98: 10344–49
31. Toma C, Pittenger MF, Cahill KS et al: Human mesenchymal stem cells differentiate to a cardiomyocyte phenotype in the adult murine heart. Circulation, 2002; 105: 93–98
32. Xu W, Zhang X, Qian H et al: Mesenchymal stem cells from adult human bone marrow differentiate into a cardiomyocyte phenotype *in vitro*. Exp Biol Med, 2004; 229: 623–31
33. Deb A, Wang S, Skelding KA et al: Bone marrow-derived cardiomyocytes are present in adult human heart: A study of gender-mismatched bone marrow transplantation patients. Circulation, 2003; 107: 1247–49
34. Wagers AJ, Sherwood RI, Christensen JL, Weissman IL: Little evidence for developmental plasticity of adult hematopoietic stem cells. Science, 2002; 297: 2256–59
35. Terada N, Hamazaki T, Oka M et al: Bone marrow cells adopt the phenotype of other cells by spontaneous cell fusion. Nature, 2002; 416: 542–45
36. Ying QL, Nichols J, Evans EP, Smith AG: Changing potency by spontaneous fusion. Nature, 2002; 416: 545–48
37. Balsam LB, Wagers AJ, Christensen JL et al: Haematopoietic stem cells adopt mature haematopoietic fates in ischaemic myocardium. Nature, 2004; 428: 668–73
38. Nygren JM, Jovinge S, Breitbach M et al: Bone marrow-derived hematopoietic cells generate cardiomyocytes at a low frequency through cell fusion, but not transdifferentiation. Nat Med, 2004; 10: 494–501
39. Balsam LB, Robbins RC: Haematopoietic stem cells and repair of the ischaemic heart. Clinical Science, 2005; 109: 483–92
40. Altman J: Autoradiographic and histological studies of postnatal neurogenesis. IV. Cell proliferation and migration in the anterior forebrain, with special reference to persisting neurogenesis in the olfactory bulb. J Comp Neurol, 1969; 137: 433–57
41. Corotto FS, Henegar JA, Maruniak JA: Neurogenesis persists in the subependymal layer of the adult mouse brain. Neurosci Lett, 1993; 149: 111–14
42. Luskin MB: Restricted proliferation and migration of postnatally generated neurons derived from the forebrain subventricular zone. Neuron, 1993; 11: 173–89
43. Reynolds BA, Weiss S: Generation of neurons and astrocytes from isolated cells of the adult mammalian central nervous system. Science, 1992; 255: 1707–10
44. Lois C, Garcia-Verdugo J, Alvarez-Buylla A: Chain migration of neuronal precursors. Science, 1996; 271: 978–81
45. Peretto P, Merighi A, Fasolo A, Bonfanti L: Glial tubes in the rostral migratory stream of the adult rat. Brain Res Bull, 1997; 42: 9–21
46. Galli R, Gritti A, Bonfanti L, Vescovi AL: Neural stem cells: an overview. Circ Res, 2003; 92: 598–608
47. Doetsch F, Garcia-Verdugo JM, Alvarez-Buylla A: Cellular composition and three-dimensional organization of the subventricular germinal zone in the adult mammalian brain. J Neurosci, 1997; 17: 5046–61
48. Doetsch R, Caille I, Lim DA et al: Subventricular zone astrocytes are neural stem cells in the adult mammalian brain. Cell, 1999; 97: 703–16
49. Seri B, Garcia-Verdugo JM, McEwen BS, Alvarez-Buylla A: Astrocytes give rise to new neurons in the adult mammalian hippocampus. J Neurosci, 2001; 21: 7153–60
50. Morshead CM, Reynolds BA, Craig CG et al: Neural stem cells in the adult mammalian forebrain: a relatively quiescent subpopulation of subependymal cells. Neuron, 1994; 13: 1071–82
51. Gritti A, Parati EA, Cova L et al: Multipotential stem cells from the adult mouse brain proliferate and self renew in response to basic fibroblast growth factor. J Neurosci, 1996; 16: 1091–100
52. Capela A, Temple S: LeX/ssea-1 is expressed by adult mouse CNS stem cells, identifying them as nonependymal. Neuron, 2002; 35: 865–75
53. Rietze RL, Valcanis H, Brooker GF et al: Purification of a pluripotent neural stem cell from the adult mouse brain. Nature, 2001; 412: 736–39
54. Uchida N, Buck DW, He D et al: Direct isolation of human central nervous system stem cells. Proc Natl Acad Sci USA, 2000; 97: 14720–25
55. Belachew S, Chittajallu R, Aguirre AA et al: Postnatal NG2 proteoglycan-expressing progenitor cells are intrinsically multipotent and generate functional neurons. Cell Biol, 2003; 161: 169–86
56. Bjornson CR, Rietze RL, Reynolds BA et al: Turning brain into blood: a hematopoietic fate adopted by adult neural stem cells *in vivo*. Science, 1999; 283: 534–37

57. Shih C-C, Weng Y, Mamelak A et al: Identification of a candidate human neurohematopoietic stem-cell population. Blood, 2001; 98: 2412–22
58. Galli R, Borello A, Gritti A et al: Skeletal myogenic potential of human and mouse neural stem cells. Nat Neurosci, 2000; 3: 986–91
59. Clarke DL, Johansson CB, Wilbertz J et al: Generalized potential of adult neural stem cells. Science, 2000; 288: 1660–63
60. Mauro A: Satellite cell of skeletal muscle fibers. J Biophys Biochem Cytol, 1961; 9: 493–95
61. Gibson MC, Schultz E: The distribution of satellite cells and their relationship to specific fiber types in soleus and extensor digitorum longus muscles. Anat Rec, 1982; 202: 329–37
62. Gibson MC, Schultz E: Age-related differences in absolute numbers of skeletal muscle satellite cells. Muscle Nerve, 1983; 6: 574–80
63. Schmalbruch H. Hellhammer U: The number of nuclei in adult rat muscles with special reference to satellite cells. Anat Rec, 1977; 189: 169–75
64. Schultz E. McCormick KM: Skeletal muscle satellite cells. Rev Physiol Biochem Pharmacol, 1994; 123: 213–57
65. Cossu G, Mavilio F: Myogenic stem cells for the therapy of primary myopathies: wishful thinking or therapeutic perspective? J Clin Invest, 2000; 105: 1669–74
66. Cornelison DD, Wold BJ: Single-cell analysis of regulatory gene expression in quiescent and activated mouse skeletal muscle satellite cells. Dev Biol, 1997; 191: 270–83
67. Megeney LA, Kablar B, Garrett K et al: MyoD is required for myogenic stem cell function in adult skeletal muscle. Genes Dev, 1996; 10: 1173–83
68. Seale P, Sabourin L, Girgis-Gabardo A et al: Pax7 is required for the specification of myogenic satellite cells. Cell, 2000; 102: 777–86
69. Ridgeway AG, Skerjanc IS: Pax3 is essential for skeletal myogenesis and the expression of Six1 and Eya2. J Biol Chem, 2001; 276: 19033–39
70. Yablonka-Reuveni Z, Rivera AJ: Temporal expression of regulatory and structural muscle proteins during myogenesis of satellite cells on isolated adult rat fibers. Dev Biol, 1994; 164: 588–603
71. Yablonka-Reuveni Z, Rudnicki MA, Rivera AJ et al: The transition from proliferation to differentiation is delayed in satellite cells from mice lacking MyoD. DevBiol, 1999; 210: 440–55
72. Cooper RN, Tajbakhsh S, Mouly V et al: *In vivo* satellite cell activation via Myf5 and MyoD in regenerating mouse skeletal muscle. J Cell Sci, 1999; 112: 2895–901
73. Zammit PS, Golding JP, Nagata Y et al: Muscle satellite cells adopt divergent fates: a mechanism for self-renewal? J Cell Biol, 2004; 166: 347–57
74. Oustanina S, Hause G, Braun T: Pax7 directs postnatal renewal and propagation of myogenic satellite cells but not their specification. EMBO J, 2004; 23: 3430–39
75. Nagata Y, Kobayashi H, Umeda M et al: Sphingomyelin Levels in the Plasma Membrane Correlate with the Activation State of Muscle Satellite Cells. J Histochem Cytochem, 2006; 54: 375–84
76. Teboul L, Gaillard D, Staccini L et al: Thiazolidinediones and fatty acids convert myogenic cells into adipose-like cells. J Biol Chem, 1995; 270: 28183–87
77. Asakura A, Komaki M, Rudnicki M: Muscle satellite cells are multipotential stem cells that exhibit myogenic, osteogenic, and adipogenic differentiation. Differentiation, 2001; 68: 245–53
78. Jackson KA, Mi T, Goodell MA: Hematopoietic potential of stem cells isolated from murine skeletal muscle. Proc Natl Acad Sci USA, 1999; 96: 14482–86
79. Cao Y, Zhao Z, Gruszczynska-Biegala J, Zolkiewska A: Role of metalloprotease disintegrin ADAM12 in determination of quiescent reserve cells during myogenic differentiation *in vitro*. Mol Cell Biol, 2003; 23: 6725–38
80. Wagner KR: Muscle regeneration through myostatin inhibition. Curr Opin Rheumatol, 2005; 17: 720–24
81. Schuelke M, Wagner KR, Stolz LE et al: Myostatin mutation associated with gross muscle hypertrophy in a child. N Engl J Med, 2004; 350: 2682–88
82. Asakura A, Rudnicki MA: Side population cells from diverse adult tissues are capable of *in vitro* hematopoietic differentiation. Exp Hematol, 2002; 30: 1339–45
83. Schultz SS, Lucas PA: Human stem cells isolated from adult skeletal muscle differentiate into neural phenotypes J Neurosci Methods, 2006; 152: 144–55
84. Gussoni E, Soneoka Y, Strickland CD et al: Dystrophin expression in the mdx mouse restored by stem cell transplantation. Nature, 1999; 401: 390–94
85. Partridge TA, Beauchamp JR, Morgan JE: Conversion of mdx myofibers from dystrophin-negative to -positive by injection of normal myoblasts. Nature, 1989; 337: 176–79
86. Lin F, Cordes K, Li L et al: Hematopoietic stem cells contribute to the regeneration of renal tubules after renal ischemia-reperfusion injury in mice. J Am Soc Nephrol, 2003; 14: 1188–99
87. Arriero M, Brodsky SV, Gealekman O et al: Adult skeletal muscle stem cells differentiate into endothelial lineage and ameliorate renal dysfunction after acute ischemia. Am J Physiol Renal Physiol, 2004: 287: 621–27
88. Fausto N, Lemire JM, Shojiri N: Cell lineages in hepatic development and the identification of progenitor cells in normal and injured liver. Proc Soc Exp Biol Med, 1993; 204: 237–41
89. Thorgeirsson SS: Hepatic stem cells in liver regeneration. FASEB J, 1996; 10; 1249–56
90. Fujio K, Evarts RP, Hu Z et al: Expression of stem cell factor its receptor c-kit, during regeneration from putative stem cells in adult rat. Lab Invest, 1994; 70: 511–16
91. Petersen BE, Goff JP, Greenberger JS, Michalopoulos GK: Hepatic oval cells express the hematopoietic stem cell marker Thy-1 in the rat. Hepatology, 1998; 27: 433–45
92. Omori N, Omori M, Evarts et al: Partial cloning of rat CD34 cDNA expression during stem cell-dependent liver regeneration in adult rat. Hepatology, 1997; 26: 720–27
93. Ros JE, Roskams TA, Geuken M et al.: ATP binding cassette transporter gene expression in rat liver progenitor cells. Gut, 2003; 52: 1060–67
94. Petersen BE: Hepatic stem cells: coming full circle. Blood Cells, Mol Diss, 2001; 27: 590
95. Petersen BE, Bowen WC, Patrene KD et al: Bone marrow as a potential source of hepatic oval cells. Science, 1999; 284: 1168–70
96. Wang X, Montini E, Al-Dhalimy M et al: Kinetics of liver repopulation after bone marrow transplantation. Am J Pathol, 2002; 161: 565–74
97. Kanazawa Y, Verma IM: Little evidence of bone marrow derived hepatocytes in the replacement of injured liver. Proc Natl Acad Sci USA, 2003; 100: 11850–53
98. Kollet O, Shivtiel S, Chen YQ et al: HGF, SDF-1, and MMP-9 are involved in stress-induced human CD34+ stem cell recruitment to the liver. J Clin Invest, 2003; 112: 160–69
99. Kang XQ, Zang WJ, Bao LJ et al: Fibroblast growth factor-4 and hepatocyte growth factor induce differentiation of human umbilical cord blood-derived mesenchymal stem cells into hepatocytes. World J Gastroenterol, 2005; 11: 7461–65
100. Dalakas E, Newsome PN, Harrison DJ, Plevris JN: Hematopoietic stem cell trafficking in liver injury. FASEB J, 2005; 19: 1225–31
101. Wang X, Willenbring H, Akkari Y et al: Cell fusion is the principal source of bone-marrow-derived hepatocytes. Nature, 2003; 422: 897–901
102. Camargo FD, Finegold M, Goodell MA: Hematopoietic myelomonocytic cells are the major source of hepatocyte fusion partners. J Clin Invest, 2004; 113: 1266–71
103. Stadtfeld M, Graf T: Assessing the role of hematopoietic plasticity for endothelial and hepatocyte development by non-invasive lineage tracing. Development, 2004; 132: 203–12
104. Willenbring H, Bailey AS, Foster M et al: Myelomonocytic cells are sufficient for therapeutic cell fusion in liver. Nature Med, 2004; 10: 744–48
105. Sharma AD, Cantz T, Richter et al: Human cord blood stem cells generate human cytokeratin 18-negative hepatocyte-like cells in injured mouse liver. Am J Pathol, 2005; 167: 555–64
106. Thorgeirsson SS, Grisham JW: Hematopoietic cells as hepatocyte stem cells: a critical review of the evidence. Hepatology, 2006; 43: 2–8
107. Klimanskaya I, Chung Y, Meisner L et al: Human embryonic stem cells derived without feeder cells. Lancet, 2005; 365: 1636
108. Martin MJ, Muotri A, Gage F, Varki A: Human embryonic stem cells express an immunogenic non-human sialic acid. Nat Med, 2005; 11: 228
109. Tajima A, Tanaka T, Ebata T et al: Blastocyst MHC, a putative murine homologue of HLA-G, protects TAP-deficient tumor cells from natural killer cell-mediated rejection *in vivo*. J Immunol, 2003; 171: 1715
110. Kofidis T, Debruin JL, Tanaka M et al: They are not stealthy in the heart: embryonic stem cells trigger cell infiltration, humoral and T-lymphocyte-based host immune response. Eur J Cardiothorac Surg, 2005; 28: 461–66
111. Stamm C, Westphal B, Kleine HD et al: Autologous bone-marrow stem-cell transplantation for myocardial regeneration. Lancet, 2003; 361: 45

112. Cohen Y, Nagler A: Umbilical cord blood transplantation – how, when and for whom? Blood Rev, 2004; 18: 167

113. Perin EC, Dohmann HF, Borojevic R et al: Improved exercise capacity and ischemia 6 and 12 months after transendocardial injection of autologous bone marrow mononuclear cells for ischemic cardiomyopathy. Circulation, 2004; 110: II213

114. McGuckin CP, Forraz, N, Baradez M-O et al: Production of stem cells with embryonic characteristics from human umbilical cord blood. Cell Prolif, 2005; 38: 245–55

115. Marx J: Mutant Stem Cells May Seed Cancer. Science, 2003; 301: 1308–10

116. Kamel-Reid S, Dick JE, Greaves A et al: Differential kinetics of engraftment and induction of CD10 on human pre-B leukemia cell lines in immune deficient scid mice. Leukemia, 1992; 6: 8–17

117. Lapidot T, Pflumio F, Doedens M et al: Cytokine stimulation of multilineage hematopoiesis from immature human cells engrafted in SCID mice. Science, 1992; 255: 1137–41

118. Bonnet D, Warren EH, Greenberg PD et al: CD8(+) minor histocompatibility antigen-specific cytotoxic T lymphocyte clones eliminate human acute myeloid leukemia stem cells. Proc Natl Acad Sci USA, 1999; 96: 8639–44

119. Liu S, Dontu G, Wicha MS: Mammary stem cells, self-renewal pathways, and carcinogenesis. Breast Cancer Res, 2005; 7: 86–95

120. Park IK, Qian D, Kiel M et al: Bmi-1 is required for maintenance of adult self-renewing haematopoietic stem cells. Nature, 2003; 423: 302–5

121. Lessard J, Sauvageau G: Bmi-1 determines the proliferative capacity of normal and leukaemic stem cells. Nature, 2003; 423: 255–60

122. Kroon E, Krosl J, Thorsteinsdottir U et al: Hoxa9 transforms primary bone marrow cells through specific collaboration with Meis1a but not Pbx1b. EMBO J, 2003; 17: 3714–25

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