8. Stem cells: Basic aspects and possible therapeutic applications

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Stem cells’ abilities to self-renew and differentiate have captured the attention of both developmental biologist and medical practitioners. In this chapter, characteristics that define a stem cell are discussed, followed by description of different types of stem cells. In particular, embryonic stem cells are cited as an example of pluripotent cells that can be used to study human development, and also have possible future therapeutic applications. Two of the best characterized somatic stem cells, hematopoietic and neural, are then described. Hematopoiesis is dependent on stem cells throughout lifespan. Umbilical cord hematopoietic stem cells and those found in adults are critically discussed. The clinical applications of hematopoietic stem cells are recapitulated, since this cell type is already used in the treatment of a few specific hematological diseases. Fetal neural stem cells are essential to central nervous system assembly, but adult neurogenesis is restricted to specific areas in the adult brain. Even though anatomical evidence indicates integration of newborn neurons in the mature brain, the functional significance of this phenomenon has not been clarified. Throughout these pages, we analyze published evidence to speculate on manipulation of stem cells that might make them competent in the treatment of human diseases.

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Introduction

As in many scientific disciplines, several concepts in developmental biology have changed in a profound manner during the last decade. This has been due to the implementation of new experimental techniques that have contributed to our understanding of complex biological mechanisms, the discovery of molecular elements that play key roles in the formation and development of cells and tissues, and to the characterization of a rare population of cells that act as “managing” cells, directing the organization and dynamics of the early embryo, as well as that of adult tissues. These so-called stem cells, have caught the interest of the lay public, governments, biotechnology industry and scientists, to a point in which they have been included in forums and debates regarding not only science, but also economy, politics, ethics and religion.

In this chapter, we will present a brief overview on stem cell biology, including some general and basic concepts; and then will analyze in more detail particular stem cell types, such as those developed during early embryogenesis (embryonic stem cells), and those giving rise to blood cells (hematopoietic) and cells of the central nervous system (neural).

Definition and basic concepts

Stem cells (SC) are undifferentiated cells with a high capacity for self-renewal, that can give rise to one or more specialized cell types with specific functions in the body [1-3]. In other words, SC can give rise to daughter cells identical to their mother (self-renewal) and to progeny with a more restricted potential (differentiated cells). Proliferation is required for self-renewal of SC, but it is important to clearly state that not all proliferating cells are potential SC. Functional assays, ideally combined with phenotypic characterization, to demonstrate that daughter cells retain SC properties are therefore very important.

Throughout mammalian development, different types of SC are generated (Fig. 1). The fertilized egg, or zygote, is capable of producing both embryonic and extraembryonic tissues. Thus, it is referred to as a totipotent cell [4]. As development proceeds, the embryo reaches the blastocyst stage, where 2 types of cells are present. The outer layer is called trophoblast and will give rise to extraembryonic structures. The second cell type present in blastocysts is contained in the inner cell mass; these cells will differentiate into tissues that constitute the embryo itself, but do not contribute to extraembryonic tissue. If isolated and grown in culture, cells from the inner mass generate cell lines called embryonic stem cells (ESC). As expected from
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Figure 1. Origin of embryonic, hematopoietic and neural stem cells. The fertilized mammalian egg (zygote) starts dividing to generate embryos constituted by blastomeres (2- to 8-cells embryos). Embryonic development continues to the pre-implantation stage called blastocyst. From its inner cell mass, pluripotent embryonic stem cells (ESC) can be isolated and kept in culture. Top left picture shows a colony of ESC growing on a feeder layer of fibroblasts. Later on, the embryo gastrulates, which means that 3 germinal layers are formed: endo, meso and ectoderm. The central nervous system is ectoderm-derived and in its fetal state is a source of multipotent neural stem cells (NSC). The adult brain also contains NSC but only in two regions: i) the subventricular zone (black), that produce neuroblasts migrating to the olfactory bulb; ii) the subgranular zone in the hippocampus (white). NSC from fetal or adult brain can be grown in culture and differentiate to neurons, astrocytes and oligodendrocytes. Hematopoietic stem cells (HSC) can be isolated from the umbilical cord blood at birth, and also from the bone marrow of adult organisms. Multipotent HSC can differentiate to all lineages present on circulating blood. Schemes and pictures are not to scale.

its early origin, these cells have the potential to form any fully differentiated cell of the body, and therefore they are referred to as pluripotent SC [5, 6]. Interestingly, under specific culture conditions, they can be induced to unlimited proliferation without differentiation [7]. Cells of blastocyst’s inner mass will produce different tissue-specific multipotent somatic SC as development proceeds, including those that give rise to central nervous
system, peripheral nerves, blood, liver, pancreas, muscle, etc. Yet, a different type of non-somatic SC is produced during development: the germline SC, which migrate to the developing gonads (genital ridges) and eventually give rise to the gametes [8].

Stem cells possess no morphological features that could be used for their identification. Thus, current ways to recognize these cells involve both immunophenotypic analysis and functional in vivo and in vitro assays. As we shall see later in this chapter, these observations are true for both embryonic and somatic SC. In any given somatic tissue, the frequency of SC is very low (0.01% - 5% of the cells present in the tissue; 3). This fact, evidently, gives studies on SC biology a particular degree of difficulty and complexity.

According to their definition, SC are capable of giving rise to different cell types. There are two ways by which stem cells generate differentiated progeny. On the one hand, stem cells may undergo asymmetric divisions, in which two different daughter cells are produced every time a stem cell divides, i.e., one is a stem cell and the other one a progenitor cell, capable of differentiating into mature cells; examples of this mechanism abound in invertebrates [9]. Asymmetry may result from the differential distribution, in the two daughter cells, of particular molecules, either cytoplasmic or integrated into the cell membrane (divisional asymmetry); alternatively, asymmetry may be due to the differential influence of particular elements from the surrounding microenvironment (environmental asymmetry).

On the other hand, stem cells may give rise to two similar daughter cells (symmetric division) that have a finite probability of being either stem cells or committed progenitors. At steady state, each stem cell division gives rise, on average, to one stem and one committed daughter, but asymmetry is achieved on a population basis rather than at the level of individual cell divisions [10].

Stem cell viability, self-renewal, proliferation, commitment and differentiation depend on both intrinsic and extrinsic elements. The former include a variety of regulatory molecules present in a cell, according to the specific tissue or lineage to which the cell belongs; the latter, on the other hand, include all the different cell types and cell products that form part of the microenvironment in which the cell develops. In other words, stem cell function ultimately depends on intrinsic cell regulators which are modulated by external signals [1].

Embryonic stem cells

ESC are the best studied pluripotent cells [11]. Although Embryonic Carcinoma (EC) cells were described before [12] than ESC, their neoplastic
origin has precluded its use. The third type of pluripotent cells are Embryonic Germ (EG) cells, which are derived from the Primordial Germ cells in the developing gonad [13, 14]. These cells are diploid and chromosomally stable, but there are not many available cell lines. We therefore will focus on ESC. The derivation of mouse cells was reported independently by 2 groups more than 25 years ago [15, 16]. The gold standard to prove pluripotency is the formation of chimeric rodents. Mouse ESC can be injected into the inner cell mass of same-species blastocysts; if these mice are allowed to proceed, ESC will contribute to both somatic and germline lineages. This remarkable property has been used to perform gene targeting of ESC, introduce modified ESC to early embryos and obtain mice that preserve such genetic manipulation in their gametes, allowing the generation of Knock-out technology [17]. These experiments are difficult to carry out and consequently, some simpler alternatives have been devised to test pluripotency in vivo: subcutaneous implantation of ESC in immuno-deficient adult mice results in teratoma formation. Teratomas are non-invasive tumors that contain differentiated cells derived from the three embryonic layers (endoderm, mesoderm and ectoderm). The third test for pluripotency is in vitro differentiation of ESC. Theoretically, ESC in culture can produce all differentiated cell type in the body. As we will discuss later, many cell types have been produced from ESC under culture conditions, opening the possibility of therapeutic use of their differentiated progeny in the long term.

Human ES cells have been derived from supernumerary frozen embryos donated from parents that received fertility aid and agreed to the terms of a consent donor form [18]. Currently, derivation of ESC implicates the interruption of embryo’s development, but this could change in the next few years. Attempts have been made to separate one blastomere of a 8-cell mouse embryo and allow the remaining 7 cells to develop normally, whereas the single blastomere will produce ESC [19]; a similar approach has been reported for human 8-cell blastulas, but using more than one blastomere per embryo and without further embryo development, with 2 human ESC lines established [20]. Other possibilities to produce human ESC are oocyte parthenogenesis to produce female embryos, a procedure already achieved in non-human primate cells [21], and somatic cell nuclear transfer, which has been possible in various species including non-human primate species [22-24]. Two other procedures already working in human tissue are i) cell fusion of somatic cells with ESC to produce heterokaryons (tetraploid cells with 4 sets of chromosomes instead of the normal number of 2) that preserve pluripotent properties [25] with the obvious complication of having extra genetic information, and ii) reprogramming of somatic cells to an embryonic state by expressing central genes for this process [26-28]. These cells are
called induced pluripotent stem (iPS) cells and are so far indistinguishable from ESC. Human ESC are similar in many aspects to mouse ESC, but also present differences that could be relevant for their function. Common characteristics of murine and human ESC include the presence of transcription factors that regulate pluripotency, principally Oct-4, Nanog and Sox-2. In fact, these genes constitute a core regulatory circuit for maintaining pluripotency in human ESC [29]. Among the most prominent differences, are the growth factors required to preserve pluripotency in cultured ESC: mouse cells require Leukemia Inhibitory Factor and human cells depend on Fibroblast Growth Factor 2. Human ESC pluripotency has been tested only in vitro and in teratoma formation, due to the ethical barriers inherent to form early chimeras of human cells with experimental species.

In vitro differentiation of mouse or human ESC reveals the same plasticity to differentiate to a wide variety of cells types including neuronal [30-33], hematopoietic [34, 35], pancreatic [36], cardiac [37] and germline lineages [38, 39]. Differentiation of human ESC to produce high amounts of specific cell phenotypes can be used for in vitro drug testing at large scale to promote differentiation or to prevent cell death. Furthermore, if reprogramming of somatic cells to embryonic state can proceed routinely in human cells, it would be interesting to use biopsies of patients suffering diseases where the pathogenesis mechanisms are unknown (Parkinson disease for example). Such cells would then differentiate to the affected cell type (in this example dopaminergic neurons) to study in detail what are the factors contributing to neurodegeneration of human dopamine neurons.

The production of terminally differentiated cells from ESC has opened the possibility of using this progeny for cell therapy treatments. So far, only experimental species have received ESC-derived cells. Experimental models that resemble human diseases have been employed to establish proof of principle that in vitro-generated cells can indeed be used to treat deficits in a particular tissue. Both mouse and human ESC have been used for this purpose. For example, rodents treated with streptozotocin develop hyperglycemia due to death of beta cells in the pancreas, a model for type I diabetes. Transplantation of insulin-producing cells caused normoglycemia [40-42]. In other series of studies, heart infarcts were induced and ESC-derived cardiomyocytes were grafted; functional recovery was observed by independent groups [43-45]. Among the most complex diseases are those affecting the central nervous system. Parkinson disease is due to the selective degeneration of dopaminergic neurons in the substantia nigra. Dopaminergic neurons produced by ESC differentiation were tested in animal models of this disease. So far, mouse [46-49], monkey [50] and human ESC [51] have been effective in alleviating motor signs in experimental animals. Furthermore,
even mouse ESC derived from somatic cell nuclear transfer (cloning) promoted recovery in parkinsonian mice [52]. One cause of paralysis of lower limbs is degeneration of motor neurons in the spinal cord. Using a model of motor neuron damage by viral infection, it has been shown that ESC-derived motor neurons caused recovery from paralysis in rats [53]. Finally, production of hematopoietic precursors from mouse nuclear transfer ESC that received gene therapy, were transplanted to cause recovery in immunodeficient mice [54].

**Hematopoietic stem cells**

Hematopoietic SC (HSC) have been defined as primitive, undifferentiated cells capable of both, self-renewal and differentiation into all blood cell types [55, 56]. The vast majority of them reside in the bone marrow (Fig. 1), where they represent 0.005% of the total cells in that tissue. HSC possess an extremely high proliferation potential. It is estimated that in normal humans there are approximately 50 million HSC, some of which can generate up to $10^{13}$ mature blood cells over a normal life span [55]. These cells can be identified and quantified by using *in vivo* assays in which their capacity to repopulate the hematopoietic system of immunodeficient, Non-Obese Diabetic (NOD) – Severe Combined ImmunoDeficiency (SCID) mice is assessed; accordingly, they are also known as SCID-repopulating cells (SRC; [55]). It has been shown that a single HSC can regenerate and maintain the entire hematopoietic system following transplantation into an immunodeficient host [55]. Their immediate progeny, referred to as hematopoietic progenitor cells (HPC), comprise cells with a limited capacity to self-renew, and the ability to form hematopoietic colonies in semisolid cultures (thus, they are also known as colony-forming cells or CFC; [55, 56]). HPC represent 0.1% of the total cells in the marrow, and include cells with multilineage potential, as well as cells committed to individual lineages.

Most HSC and HPC express the CD34 antigen, an integral membrane glycoprotein of 90 – 120 kDa that functions as a regulator of hematopoietic cell adhesion to stromal cells of the hematopoietic microenvironment [57, 58]. Antigens such as CD90, CD117 and CD133 are also expressed by HSC [59, 60]. In keeping with their immaturity, HSC do not express CD38, CD45RA, CD71, HLA-DR or any other lineage-specific antigen; thus, they are referred to as lineage-negative cells (Lin⁻ cells; [59, 60]). Interestingly, some reports indicate that a small subpopulation of HSC does not express the CD34 antigen, that is to say, they are CD34⁻ CD38⁻ Lin⁻ cells, and there is evidence that these latter cells give rise to HSC expressing CD34 [61-63].
The functioning of hematopoietic stem and progenitor cells depends on intrinsic regulators (including nuclear transcription factors, as well as molecules involved in signal transduction and cell cycle; [64, 65]) which are modulated by external signals. The latter are provided by molecules (cytokines and extracellular matrix) produced by stromal and accessory cells. Together, stromal and accessory cells, and their products, constitute an intricate structural and functional network known as the hematopoietic microenvironment (HM; [66, 67]). In postnatal life, more than 90% of the hematopoietic activity takes place in the bone marrow, where HSC and HPC develop under the influence of the different elements of the HM. Such a microenvironment is crucial in hematopoiesis, and alterations in the structure and/or function of some of its components may contribute to the development of hematological disorders [68, 69].

To date, more than 20 hematopoietic cytokines have been identified. These molecules regulate, both in a positive and a negative manner, stem cell survival, proliferation and differentiation [70, 71]. Cytokines can be presented to their target cells as soluble or as membrane-bound molecules, and exert their effects via specific receptors on the cell membrane [72]. In some cases, cell-to-cell interactions between cytokine-producing and cytokine receptor-bearing cells must take place, so the specific cytokine can act efficiently on its target.

It is clear that cell death and cell division are processes controlled by cytokines [10]; in contrast, the role of cytokines in lineage commitment is still a controversial issue [73-75]. Indeed, some studies suggest that cytokines play an inductive role on HSC, directing them into a particular lineage of differentiation; others suggest that cytokines play a permissive role, allowing the progression of a particular cell lineage, without influencing the decision of a stem cell to commit into such a lineage.

The interactions of hematopoietic cells with microenvironment cells, as well as with extracellular matrix molecules, are mediated by cell adhesion molecules (CAMs; [76, 77]). Three groups of CAMs have been recognized: The Immunoglobulin superfamily of adhesion receptors (that includes CD2, CD54, CD58, VCAM-2, etc); Integrins (LFA-1, Mac1, VLA-1, VLA-2, VLA-4, VLA-5, etc) and the Selectin/LEC CAMs (including L-selectins, E-selectins and P-selectins). Together, CAMs play a crucial role in homing, attachment and localization of HSC and HPC within the medullary cavity.

It is interesting the fact that the distribution of HSC and HPC within the medullary cavity is not random. Most HSC are located within the endosteal region, whereas lineage-committed progenitors and mature cells are distributed away from this region, predominantly in the central marrow area, in close proximity to the central marrow vessels [78-80]. Thus, it seems
evident that there is a spatial organization of the hematopoietic system within the marrow that allows the controlled egress of hematopoietic cells from the bone marrow to the blood.

**HSC from umbilical cord blood**

Although the vast majority of HSC and HPC are localized in bone marrow, a small proportion of such cells are present in circulation [56]. This occurs not only in adult subjects, but also during fetal development and at the moment of birth. Accordingly, HSC and HPC are also found in umbilical cord blood (UCB; Fig. 1). This was first reported by Knudtzon in 1974, who described the presence of relatively mature myeloid progenitors in UCB [81]. About ten years later, Ogawa and colleagues documented the presence of more primitive hematopoietic cells [82], and in the late 1980s, Broxmeyer et al. showed that UCB contains vast amounts of both primitive and mature hematopoietic cells [83]. To date, UCB is recognized as a major source of HSC and HPC both for research and clinical application [84, 85].

When comparing the relative levels of stem and progenitor cells in UCB and bone marrow, it has been found that no significant differences exist in the values of total progenitors; however, important differences in the frequency of particular HPC subpopulations have been observed. That is to say, whereas the levels of relatively mature progenitors are similar in both sources, the frequency of primitive progenitors, including multipotent, erythroid and bipotent granulo-monocytic, is significantly higher in UCB than in marrow [86-91]. The frequency of stem cells also seems to be significantly higher in UCB than in adult bone marrow [92, 93].

Important functional differences between adult and neonatal HSC/HPC have been described [56]. Both proliferation and expansion potentials from UCB cells are significantly higher than those from adult subjects [94, 95]. The reason for this is not totally clear, however, some studies indicate that such functional differences are the result of differences in telomere length and biology, cell cycle regulators and expression of particular “master” genes and signal pathways [96-98].

**HSC plasticity**

A general concept in somatic stem cell biology has been that such cells are restricted in their differentiation potential to an individual organ system. Accordingly, HSC would produce blood cells only; neural stem cells would give rise solely to neurons, astrocytes and olygodendrocytes; satellite cells of muscle to muscle cells only, and so on. However, during the last decade, a
great deal of evidence has been generated from in vivo studies, mainly in mice, indicating that this concept may not be true. Although it is still a controversial issue and the evidence is not conclusive, it seems that somatic stem cell differentiation plasticity is actually wider than previously envisioned [99]. Indeed, growing evidence has emerged indicating that HSC can also differentiate into non-hematopoietic cells [100]. The actual mechanisms for plasticity are not completely understood; however, some possible mechanisms have already been suggested: One possibility is that a stem cell “de-differentiates” into a more primitive and plastic state and then “re-differentiates”. A second possibility is that a stem cell “trans-differentiates”, that is to say, a stem cell from a particular tissue directly takes on another differentiation path, without going into intermediate stages. Any of these processes could involve or not cell division [1]. In spite of the mounting evidence, stem cell plasticity, strictly defined, has yet to be rigorously proven.

Neural stem cells

The neuroepithelium has an ectodermal origin and is responsible of neural tube formation to generate the central nervous system. Somatic SC, isolated from developing or adult central nervous system, are called neural SC (NSC; Fig. 1) [4, 101]. These multipotent cells normally differentiate to different types of neurons, and glial cells (astrocytes and oligodendrocytes). Neurons are responsible for the transmission of information in the brain, whereas astrocytes were believed for a long time to provide mechanical support and trophic factors to neurons, but as we will see, this view radically changed in recent years. Oligodendrocytes produce myelin that isolate the electrical impulse traveling along the neuronal axon. One of the most used markers to identify NSC in vitro and in vivo is the filamentous protein Nestin [102]. NSC, similar to HSC, can be grown in culture for restricted periods of time. There are 2 forms of keeping them in vitro: 1) neurospheres are floating aggregates of neural cells [103]. 2) monolayers [104] with the aid of extracellular matrix proteins such as fibronectin or laminin to promote attachment to the culture dish [105]. In both cases, NSC respond proliferating to application of either Fibroblast Growth Factor-2 or Epidermal Growth Factor. With neurospheres is easy to test for self-renewal, because the amount of secondary or tertiary neurospheres can be quantified upon mechanical desegregation of primary spheres. If dissociated cells contain SC, new neurospheres will form. Differentiation is normally achieved with growth factor withdrawal and cells will start expressing proteins characteristic of neuronal, astrocytic or oligodendrocytic phenotypes.
NSC during development of the central nervous system

During development, all central nervous system regions contain abundant SC in early stages and later on, precursor cells are the dominating cell population. These two cell types can be isolated and grown in culture from cerebral cortex [106], midbrain [107], hippocampus [105] and the spinal cord [108]. In vivo, NSC originate neurons first, followed by astrocytogenesis and finally oligodendrocyte differentiation. This temporal program is recapitulated by cultured NSC, because early passage cells are neurogenic and older NSC are gliogenic [109, 110]. Also, NSC respond to specific growth factors by differentiating to neurons, astrocytes or oligodendrocytes [105].

Neurogenesis in the developing cerebral cortex

The development of cerebral cortex is one of the best in vivo studied regions of the brain. Cortices are formed from multipotent NSC that divide initially in the ventricular zone (VZ) and later in the subventricular zone (SVZ), a region that is though to be preserved in the adult brain as we shall discuss later. The cerebrocortical epithelium is constituted by asynchronously dividing NSC that produce migrating neuroblasts that radially migrate to the cortical plate, where they differentiate in 6 distinct layers of neurons. Along the cortical plate there are glial fibrillary acidic protein (GFAP)-positive cells called radial glia (RG), that span the thickness of this structure from the VZ to the cortical plate, and serve as scaffolds for dorsal migration of neurons to the corresponding cortical layer [111]. Recently, a portion of RG cells have been identified as the neural stem cells in cerebral cortex [112]. NSC were though to be immature and therefore devoid of receptors for neurotransmitters. This turned out to be false, since neuroactive substances such as glutamate [113], gamma-amino-butyric acid [114] can regulate proliferation and differentiation of these multipotent cells.

NSC in the adult brain

One of the central dogmas in Neurobiology during the 20th century was that the number of neurons in the adult brain was fixed and no neurons were generated after the newborn period. This view started to change slowly after the seminal work of Joseph Altman, who reported some neurons labeled with radioactive thymidine given in adult life, suggesting adult neurogenesis (reviewed by Kempermann [115]). This dogma is no longer valid in this new
century, since newborn neurons are produced in discrete regions of the adult brain in several species, including humans. As the reader might realize, adult neurogenesis is a phenomenon that stimulates the idea of brain plasticity (the ability to modify existing neural circuits), and the possibility for brain repair in diseased or aged central nervous system. We next review some data on characterization of the two main neurogenic regions in adult mammalian forebrain.

**Subventricular zone**

Brain lateral ventricles are used for cerebrospinal fluid circulation. Very close to ventricles is located the SVZ, which is the region that contains the largest population of SC in adult rodent brain [116, 117]. This area contains GFAP-expressing multipotent NSC [118], though to originate from the embryonic ventricular zone [119]. Structural and functional studies have provided a detailed picture of the SVZ. Neural stem cells (called B cells) are in close apposition with ependymal cells (ciliated cells facing directly the ventricles). These B cells divide and generate transit amplifying (C) cells that differentiate into migratory neuroblasts (A cells) that reach olfactory bulbs through the rostral migratory stream; once arriving to this target region, neuroblasts differentiate to GABAergic and dopaminergic interneurons. Recently, a similar germinal region has been described in humans [120]. The functional role, if any, of SVZ neurogenesis remains to be conclusively established.

**Subgranular zone in the hippocampus**

The hippocampus is a cerebral structure closely related to learning and memory tasks. Hippocampal SC express GFAP and Nestin [121, 122]. They are found in the SGZ of the dentate gyrus, at the hilus / granule cell layer interphase. NSC are also called type-1 cells and divide slowly to generate a highly dividing population (type-2 cells, D cells) that migrate a short distance to integrate as neurons into the granule cell layer of the dentate gyrus. Hippocampal neurogenesis in humans was reported ten years ago [123]. In rats, newborn neurons decline with age; however, lowering of corticosteroid levels can reverse this process [124]. There are many other factors positively regulating this phenomenon, such as living in an enriched environment [125], running [126], stroke [127], and non-coding double-stranded RNA [128]. The possibility that adult hippocampal neurogenesis could play a physiological role during learning and/or remembering has been suggested [129, 130].
Concluding remarks

Stem cell biology has emerged as a scientific field with a two-fold relevance. On one hand, it has helped to our understanding of complex cellular processes, such as proliferation and differentiation, as well as tissue development, renewal and repair. On the other hand, it may have significant impact on the treatment of a variety of human diseases, such as cancer, diabetes, cardiac, and neural disorders. There is still a long way to go in the characterization of these “master” cells, and genomics and proteomics will surely play key roles in our understanding of the way SC function.

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