Stem Cells: A Dormant Volcano Within Our Body?

Devaveena Dey and Annapoorni Rangarajan

Stem cells constitute an important class of cells in the body that have the ability to perpetuate themselves and remain in an uncommitted state by a process of self-renewal as well as to specialize into new cell types. Their ability to differentiate into multiple cell types marks the tremendous potential of stem cells for tissue repair and organ regeneration. Realization of this potential is rapidly opening up unexplored avenues for curing several ailments including diabetes and neurodegenerative diseases. However, very little is understood about the basic biology of stem cells. For example, what are the biochemical tags that allow us to identify stem cell? Which are the signaling pathways that regulate their function? How does the environment (niche) influence major decisions made by stem cell? Is stem cell therapy the end to all woes, or is there a flip side to the story? This article aims to give an overview of the current status of stem cell research and raises some alarming issues related to stem cell-based therapies.

The life of a multi-cellular organism begins from a single cell – the fertilized egg or zygote. The zygote and the cells resulting from its first couple of cell divisions are totipotent, that is, they have the potential to give rise to all the three germ layers (the ectoderm, endoderm and mesoderm) and produce the extra-embryonic membranes (such as the placenta) which together can give rise to an entire organism. As the zygote starts its further chain of divisions, there is a slow and steady transition from a solid ball of cells, the morula, to a hollow cellular ball, the blastula. Within the blastula is a group of cells, the inner cell mass, from which are derived the *embryonic stem cells* (*Figure* 1). These cells are pluripotent, that is, they have the potential to give rise to all the three germ layers of an adult organism, but not the extra-embryonic material. Therefore, they cannot give rise to a whole organism [1].

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Keywords
Stem cells, self-renewal, pluripotency, niche, differentiation.

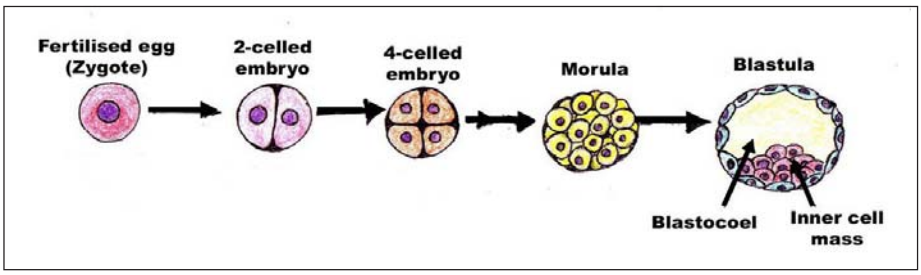

Figure 1. Beginning of Life: From a single cell to the blastula.

One of the inherent and fascinating characteristics of multicellular organisms is the existence of tissue homeostasis, that is, maintenance of cell number and types in any given tissue during the lifespan of the organism in the face of constant attrition and injury. Nature has devised diverse mechanisms to sustain this homeostasis. For example, amphibians and some reptiles can reverse 'specialized cells' back to a more 'primitive' stage (de-differentiation), which then recapitulates the developmental processes to form a new organ. Unlike amphibians, mammals cannot regenerate an entire organ. However, they possess a small sub population of cells in many tissues which, unlike the bulk of cells, have the potential to give rise to the specialized cells of the given tissue type [2]. These are called the ***adult stem cells.*** Adult stem cells, also termed as 'somatic stem cells', are multipotent, that is, they can give rise to cells of the same lineage, but not that of other lineages. Thus, haematopoietic stem cells give rise to all the cell types of the blood lineage, mammary stem cells give rise the three cell types found in the mammary epithelium, and so on. Such adult stem cells have so far been identified in the blood, muscle, breast, brain, skin, liver, lungs, pancreas, intestine, and quite recently in the dental pulp [3–11].

Two Hallmarks of Stem Cells

Stem cells are endowed with two fundamental properties: self renewal and multi-lineage differentiation potential.

Stem cells are endowed with two fundamental properties: self renewal and multi-lineage differentiation potential (*Figure* 2). Typically, a stem cell divides by mitosis to make one daughter cell which is a complete replica of itself, such that it also inherits the dual capacity of self-renewal and differentiation. This property of a stem cell to make more of its own kind is referred to

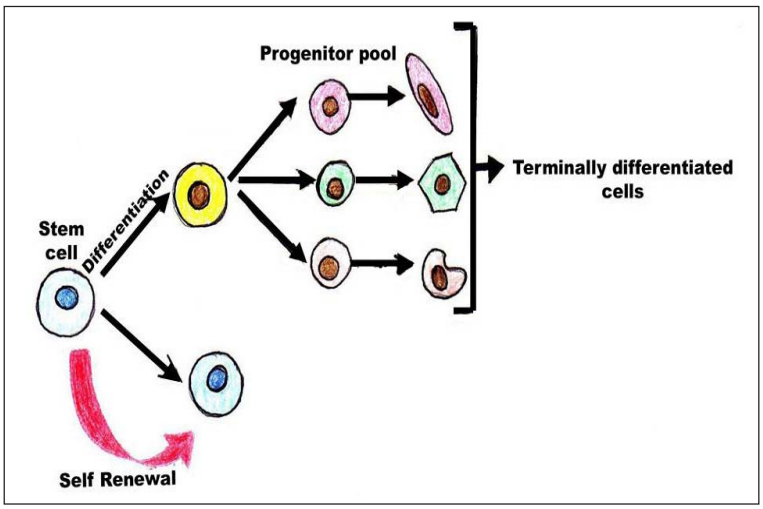

Figure 2. A stem cell has the dual property of self renewal and differentiation. It differentiates to give rise to the terminally differentiated cells via a pool of progenitor cells. These differentiated cells constitute the tissue.

as self-renewal. The other daughter cell undergoes a few rounds of rapid division, thereby generating a progenitor pool, which finally culminates in differentiation to generate the specialized (differentiated) cells (*Figure* 2). While the embryonic stem cells can give rise to all the three lineages, the adult stem cells are usually restricted to their tissue of origin. Accordingly, adult stem cells are also referred to as tissue-specific stem cells. It is this ability to give rise to different cell types that makes stem cell research a hotly pursued area of research today for cell-based therapies which aim to replace the existing non-functional cells with new cells.

A Twist in the Rule

One of the hallmark features of multi-potent adult stem cell, as just discussed, is its ability to differentiate into the cell types seen within the tissue of its residence. In the past few years, however, exciting findings [12] indicate a much broader differentiation potential of adult stem cells – a phenomenon known as *trans-differentiation* (*Figure* 3). This is the plasticity of a tissue specific stem cell, its ability to 'switch' its lineage to that of some other tissue when given suitable conditions. Thus, bone marrow cells have been observed to trans-differentiate into skeletal muscle, smooth muscle and neuronal cells [13].

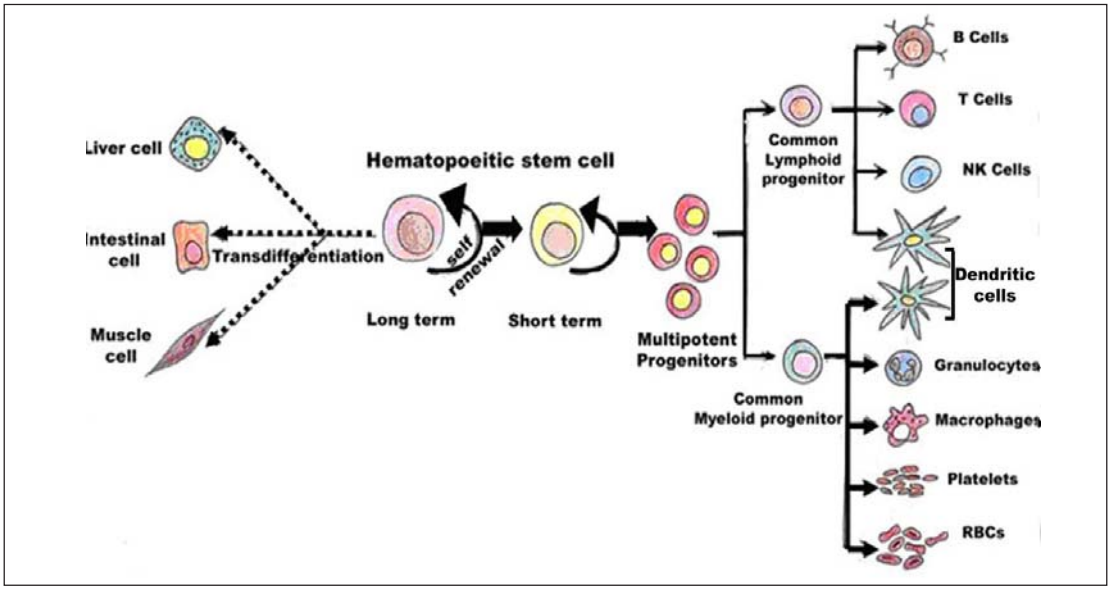

Figure 3. The haematopoietic stem cell gives rise to all cells of the blood lineage.

The Stem Cell 'Niche': Environment Matters!

In spite of their unique potential to self renew and differentiate, the adult stem cells remain in a 'quiescent' state through most of their lifetime [2]. They spring into action, that is divide and differentiate, only in response to certain cues (extrinsic factors) from their surrounding environment. This environment includes the stroma and other differentiated support cells. The stroma has in it fibroblasts, macrophages, neutrophils and endothelial cells. This surrounding microenvironment of a stem cell is known as the ***stem cell niche.*** The concept of a stem cell niche came from the observation that different signaling microenvironments can direct daughter cells to adopt different fates. According to the niche hypothesis, signals from the local microenvironment specify stem cell self renewal. Adhesion between stem cells and either an underlying basement membrane or the support cells themselves appears to play an important role in holding the stem cells within the niche, close to the self renewal signals. In addition, the niche could also provide polarity cues to orient stem cells within the niche so that upon division, one cell is displaced outside the niche into an alternative environment that encourages differentiation. Thus, stem cell number, division, self renewal and differentiation

are all likely to be regulated by the integration of extrinsic cues provided by the niche and the intrinsic factors within the stem cell itself.

One of the most distinguishing features of a stem cell is its marker profile. Markers refer to molecules which are unique to a given cell type.

How do Stem Cells Look?

In some tissues like the mammary gland, it has been reported that the stem cells are smaller compared to other cells around them and appear lightly stained when observed under an electron microscope [14]. Such a difference has not been reported for all tissue-specific stem cells. So, what is it that sets apart this unique cell population from the rest? One of the most distinguishing features of a stem cell is its marker profile [15]. Markers refer to molecules which are unique to a given cell type. They can include cell surface proteins, trans-membrane receptors, or cell adhesion molecules. Researchers have shown the expression of specific markers on different tissue specific stem cells, for example, c-kit and Sca1 on haematopoeitic stem cells, nestin and GFAP on neural stem cells, and so on. For many tissues, such as the breast tissue, no single specific marker has been found as yet [14]. Such markers have been and are being extensively used to isolate and purify stem cells from different tissues. Isolation and enrichment of stem cells from a tissue is the first step towards understanding the properties of this unique cell population. This understanding is the critical stepping stone towards harnessing the potential of adult stem cells for tissue replacement.

Towards a Molecular Analysis of Stem Cells

'Stemness' refers to the common molecular process underlying the core stem cell properties of self renewal and generation of differentiated progeny. Although stem cells in different tissues with different cellular niches will, by necessity, have different physiological demands and thus distinct molecular programs, there are likely to be certain genetic characteristics specific to and shared by all stem cells. By observing their total transcription profiles, many of the genes whose expression is enriched in different adult stem cells have been identified [15,16]. By

correlating and networking the information obtained through such studies, it may be possible to develop a molecular fingerprint of expressed genes for stem cells. This fingerprint could be used to help identify and isolate new stem cells.

The transcriptional profiling of stem cells has suggested that they share several distinct molecular characteristics [15, 16]. Stem cells appear to have the capacity to sense a broad range of growth factors and signaling molecules and to express many of the downstream signal transduction components. Signal transduction pathways present and perhaps active in stem cells include Notch, TGF β, Wnt, BMP, Hedgehog and Jak/Stat family members [17]. Adult stem cells also express many components involved in establishing their specialized cell cycle related to maintaining cell cycle arrest in G1 and hence establishing the 'quiescent' state [18]. Most stem cells also express molecules involved in telomere[1] maintenance and display elevated levels of telomerase activity [19]. There is also considerable evidence that stem cells have significantly remodeled chromatin, acted upon by DNA methylases or transcriptional repressors of histone deacetylase.

[1] Telomere is the structure found at the terminals of chromosomes and telomerase is the enzyme that maintains the integrity of the telomere during successive divisions.

Stem Cell Therapies

Stem cells, due to their pluripotency, can be directed to differentiate into specific cell types. This has made them highly preferred candidates for cell-based therapy, wherein, introduction of these cells can replenish cells of any damaged organ, thus enabling complete repair of the tissue or organ in question. Some of the diseases for which stem cell therapy holds promise are – Parkinson's disease, Alzheimer's diseases, spinal cord injury, stroke, burns, heart disease, diabetes, and arthritis. Even though currently much of the stem cell therapies are at experimental stages, many believe that it is only short time before it will become available in the clinic.

All this is not without a price. The idea of derivation of embryonic stem cells from the inner cell mass has stirred a grave ethical war in the world. According to some, isolating these stem cells at the

blastula stage would mean terminating a life. This issue has had severe impact on embryonic stem cell research worldwide, with several countries taking drastic steps like banning research on embryonic stem cells. In India, the scientific ethical bodies have taken a middle path, respecting the sanctity of Life as well as scientific research, by allowing derivation of embryonic stem cells from excess, defective or dead embryos from *in vitro* fertilization clinics.

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While adult stem cells are not surrounded by controversy, they are much limited in number and difficult to get hold of. There is much more need to understand how to isolate and enrich these type of stem cell before harnessing their true potential.

A Word of Caution: Can the Good Become the Bad?

It is today beyond doubt that adult stem cells hold a strong potential in successful tissue replacement and repair. There is also a grave side to the story of adult stem cells which is coming up strongly, based on emerging experimental evidences. This is about the possibility and potential of a normal adult stem cell to become a cancer cell.

Normal stem cells and cancer cells share many key properties, some of them being a high proliferation potential, ability to give rise to multiple cell types, migration, expression of telomerase, similar signaling pathways operating within them, like the Notch, Wnt and Hedgehog and common marker expression profiles. Given the striking similarities between normal stem cells and cancer cells, there is a strong possibility that cancer arises in a normal stem cell since many cellular mechanisms which are found active in cancer cells are already active in stem cells, albeit in a controlled fashion. Multiple mutations need to come together in a single cell for the cell to become cancerous. Considering the fact that the stem cells are the longest living cells within the body, it is possible that a normal stem cell acquires multiple mutations over a period of time and becomes cancerous, as predicted by the 'stem cell hypothesis' of origin of cancer [17]. Indeed, evidence

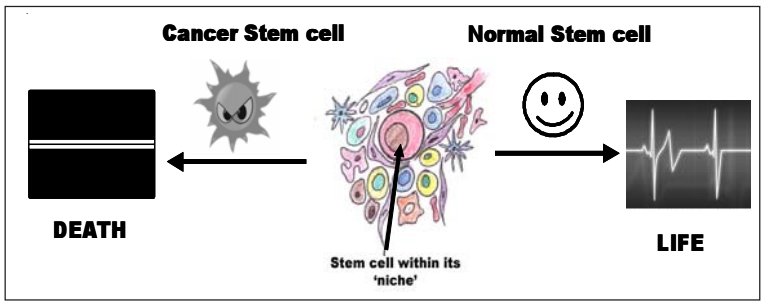

Figure 4. Stem cells in a tissue is thus, like a dormant volcano, a tremendous potential existing quietly unless provoked.

is building up for the stem cell origin for some leukemias [20].

In the face of these two opposing fates of stem cell biology (*Figure* 4), it is difficult to confidently state what will happen when a population of stem cells is injected into the human body – will it remain the "good" stem cell, adding vitality to the damaged tissue or will it 'transform' into the "bad" cancer cell ? The small population of stem cells in a tissue is thus like a dormant volcano – a tremendous potential existing quietly unless provoked.

Suggested Reading

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