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Stem Cells in Perspective

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Abstract: The essence of a stem cell is that it is an unspecialized cell and therefore has the unique properties of retaining the ability to renew itself as well as being able to undergo multilineage differentiation. The transition between a stem cell and its progeny involves a number of steps with several intermediate cells known as transit amplifier cells which have a lesser ability to undergo self-renewal but are more likely to differentiate. Stem cells all give rise to differentiated cells. However, their degree of potency varies. In this study, an overview of the different types of cells is given, ranging from unipotent to totipotent cells. Each of the three main properties of stem cells is discussed in detail as are the different types of stem cells, namely embryonic, umbilical cord and adult stem cells. The new concept that adult stem cells are not lineage restricted is introduced, leading to adult stem cell plasticity. Finally, the stem cell niche has also been discussed.

Key words: Stem cells, multipotent, pluripotent, embryonic, umbilical

INTRODUCTION

The basic definition of a stem cell which demarcates it from other types of cells is that a stem cell is an unspecialized cell which is able to renew itself and has the capacity for multilineage differentiation. Thus, the properties that give stem cells their uniqueness are self-renewal (which is crucial for maintaining the initial stem cell pool) and the ability to give rise to progeny with more restricted potential since they have differentiated. Differentiation is the process by which the cell acquires specific morphological, phenotypic and functional features and hence the cell becomes adapted to perform one particular function in preference to the others (Verfaillie, 2006).

It is believed that there is a gradation between the stage of a stem cell and its final differentiated progeny. The transition between the stem cell and its progeny is not clear-cut but there are numerous intermediate cells with increasing commitment (Preston *et al*., 2003). These are the so-called transit amplifier cells which exhibit a lower degree of capacity for self-renewal but show more likelihood of undergoing differentiation. This progression from the stem cell to its progeny is depicted in Fig. 1. (http://www.stemcellresearchfoundation.org/WhatsNew/Multipotent.htm) (http://www.stemcellresearchfoundation.org/WhatsNew/Pluripotent.htm)

Although all stem cells are able to give rise to differentiated cells, their degree of potency varies and in fact there exists a spectrum of potencies. At one end of this spectrum there are the unipotent cells which have the capability to give rise to only one type of differentiated cell and thus are very limited. At the other extreme end, there are the totipotent cells which have been called by some the 'master cells' of the body since this type of stem cells gives rise to all of the cells in the body. These are

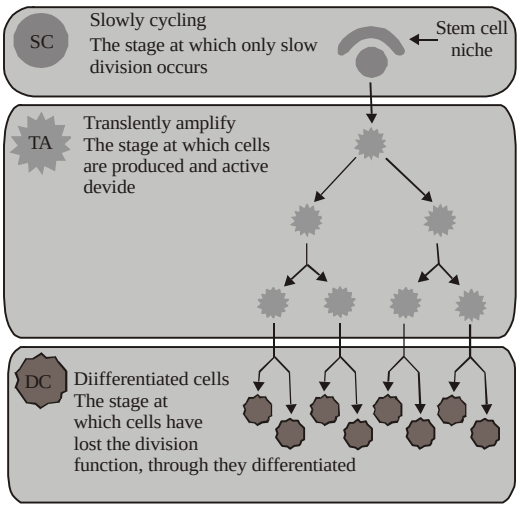

Fig. 1a: The process of how a stem cell becomes differentiated (Preston *et al*., 2003)

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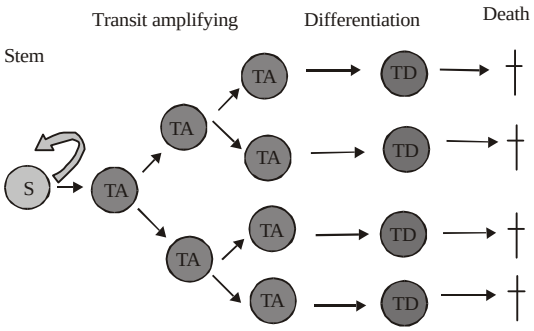

Fig. 1 b: A hierarchy of stem cell potential. Stem cell(s) can divide asymmetrically to maintain their number while giving rise to Transit Amplifying cells (TA), whose functional capacity evolves concomitantly with a reduction in division potential. Eventually, TA cells become Terminally Differentiated (TD) and are programmed to die in a tissue specific manner (Preston *et al*., 2003)

found before the third day of intra-uterine life. In between these ends of the spectrum, there are multipotent cells which can give rise to multiple differentiated cell types within a specific tissue such as blood and pluripotent cells which can produce a wide range of differentiated cells as illustrated in Fig. 2 (Stem Cell Research Foundation, 2006).

THE ABILITY OF STEM CELLS TO REMAIN UNSPECIALIZED FOR A LONG TIME

Due to the fact that stem cells are unspecialized cells, they lack any morphological structures that adapt them to perform a specific function as compared to red blood cells, for example, which have adapted for oxygen transport by getting rid of their nucleus and mitochondria and storing haemoglobin. The actual factors that can make it possible for stem cells to remain unspecialized for such a long time has greatly baffled scientists. Questions such as: What is this signal that causes the onset of specialization or Is this signal intrinsic such as in the genome of the cell or is it extrinsic such as via chemicals or is it perhaps both? have been and are still the target questions which scientists long to answer (The National Institutes of Health resource for stem cell research, 2006). Needless to say, such answers are crucial for allowing scientists to culture stem cells and retain them in the unspecialized stage for a reasonable period of time.

Self-renewal: Our body is constantly facing continued insult and injury. This may range from simple skin shedding to xenobiotic and ischeamic injury. Cells such as

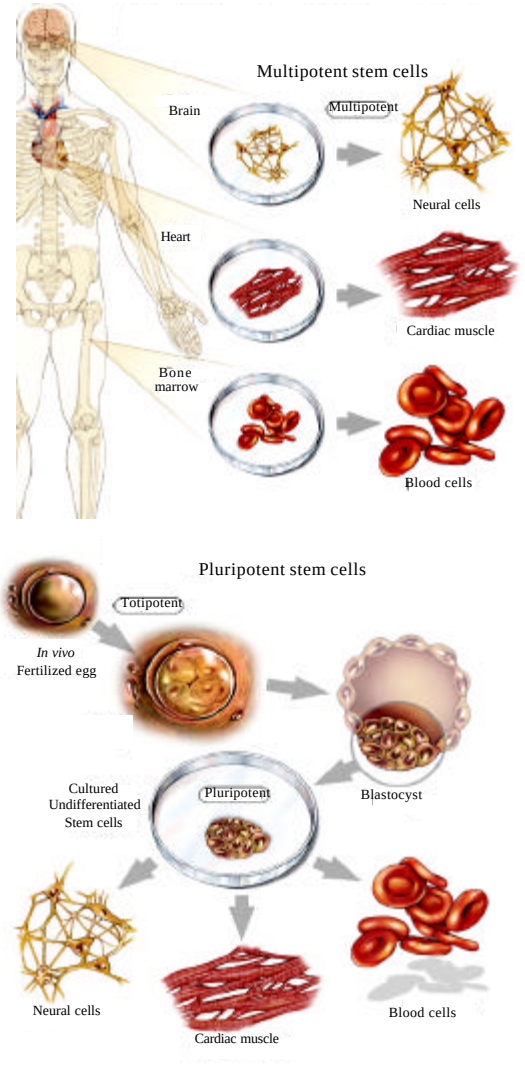

Fig. 2: The properties of Multipotent and Pluripotent stem cells (Stem Cell Research Foundation, 2006)

skin cells and gastrointestinal cells have a high turn-over rate. It does follows that quite a number of stem cells are required to suffice the lifetime of an animal so that the latter keeps up with the loss of older cells (Preston *et al*., 2003).

How can stem cells manage to maintain the balance between renewing themselves and giving rise to differentiated progeny? This tuning must be very fine because if the self-renewal process exceeds the differentiation, the damaged cells may not be entirely replaced by new cells. Similarly, if differentiation overrides self renewal, the stem cell pool will eventually dwindle. The factors behind this balance are still not quite fully answered.

Differentiation: Another criterion that must be met for a stem cell is the ability to give rise to differentiated progeny. The process of differentiation is a highly complex one and it is obviously triggered by intrinsic and extrinsic factors. An interesting question to speculate is whether these signals are universal, that is applying for all stem cells or whether they are specific for different types of stem cells.

When discussing differentiation, one must keep in mind the different degrees of potency already alluded to. It must be borne in mind that there is a gradation of potencies.

It is debatable whether a cell that is able to renew itself but give rise to only one type of differentiated cell is nevertheless a stem cell. To avoid this misnomer, unipotent cells are defined as being the descendants of stem cells, that is, the final product of stem cells also referred to as progenitors (Cowen and Melton, 2006).

Although the basic definition discussed above serves to delineate stem cells in a group that is different from other cells, there exist different types of stem cells, these being embryonic, umbilical cord and adult stem cells.

THE DIFFERENT TYPES OF STEM CELLS

Embryonic stem cells: Before the third day of life, the embryo is called a morula (ball of cells) and is capable of unlimited proliferation in vitro, retaining its unspecialized state. These early cells are thus totipotent, able to give rise to all the cells of the body. Between the third and the fourteenth day of intra-uterine life, that is, before gastrulation, embryonic cells are pluripotent. This means that they have lost their ability to give rise to all types of body cells but still retain their potential to produce a wide range of types of tissues.

Embryonic stem cells are derived from embryos formed as a result of *in vitro* fertilization. Culturing embryonic stem cells in the laboratory involves the transfer of the inner cell mass onto a culture medium which has the necessary nutrients for the cells to proliferate. In order to provide an adhesive background onto which these cells adhere, the culture dish is often coated with mouse embryonic skin cells known as the feeder layer. Advances in stem cell research has made it possible to grow embryonic stem cells emitting the feeder layer, thus ruling out the possibility of the transfer of viruses from the mouse stem cells. This is seen in Fig. 3.

Within several days, the embryonic stem cells aggregate via repeated cell divisions. They are then removed and replated onto other dishes, a process known as subculturing. This process is repeated over and over again and in a matter of months, the initial few cells multiply to millions of cells. In the process of subculturing, scientists carry out various tests to confirm that the cells are still in an undifferentiated state. One of the ways in which this can be done is by testing for the presence of cell surface markers present solely in undifferentiated cells (The National Institutes of Health resource for stem cell research, 2006).

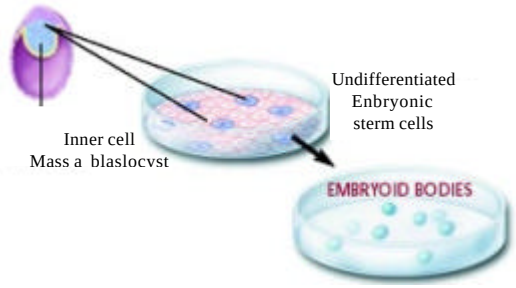

Fig. 3: Culturing embryonic stem cells in the laboratory (The National Institutes of Health resource for stem cell research, 2006). (http://stemcells.nih.gov/info/basics/basics 4.asp)

Umbilical cord stem cells: It is now a well-known fact the umbilical cord of neonates can harbor in it a collection of pluripotent or multipotent cells which can differentiate into several different types of tissues. After the baby is born, the umbilical cord is more often than not disposed of. However, the realization that the umbilical cord is a rich source of hematopoietic stem cells is gradually altering this practice. The fact that the umbilical cord contains hematopoietic stem cells implies that it can be used as a treatment to disorders affecting blood and the immune system ranging from aplastic anemias to leukemias as an alternative to bone marrow transplants. Not only are umbilical cord stem cells an alternative to bone marrow transplant but they have several advantages over the latter. The most obvious advantage is that bone marrow transplant involves an invasive procedure with the intervention of surgery. Moreover, in bone marrow transplant, compatibility is a crucial factor in order to avoid rejection whereas umbilical cord stem cells tolerate a greater variety of recipients. Thus, there is a much wider probability of rejection in bone marrow transplants than in transfer of umbilical cord stem cells. Duration is another vital element that must not be left unconsidered. In fact, another important advantage is that umbilical cord stem cells solve the problem of having a never-ending waiting list. While some patients are lucky and manage to find a

suitable donor within months, many others have to wait for years. This may be fatal for those patients diagnosed with severe blood diseases such as leukemia with a bad prognosis not to mention the difficulty encountered by ethnic people who have a lesser chance of finding compatible tissue. On the other hand, umbilical cord stem cells provide a readily available source of cells. Moreover, the risk of the blood being contaminated by pathogenic organisms and infectious agents such as viruses is much lower than in bone marrow transplantation (March of Dimes, 2006).

However, this merely gives an assessment rather than the exact picture and it is totally in the parents' hands to weigh the pros and cons of such an issue and evaluate whether the process is financially viable.

Adult stem cells: Adult stem cells are found residing in post natal organs such as skin, liver, skeletal muscle, the eye and pancreas amongst others. These possess the potential to differentiate and give rise to specialized cells of that organ in circumstances of organ damage. Thus, adult stem cells are part of the protective mechanism of the body as regards repair. Adult stem cells are nowadays also being referred to as somatic stem cells (The National Institutes of Health resource for stem cell research, 2006).

An important recent milestone in the relatively short history of stem cells is the realization that adult stem cells may actually be able to traverse lineage boundaries. The most important implication of this realization is that this clears the clouds posed by ethical issues regarding embryonic stem cells.

Bone marrow cells portray a classical example of making use of these flexible cells for transplants. However, we are now being faced with the cognition that other regions in the human body contain stem cells that can give rise to differentiated cells of other organs as well. In fact, it has been unraveled that skeletal muscle, liver, skin, the lining of the gastrointestinal tract, the eye and pancreas all contain stem cells. However, it is crucial to emphasize that the number of stem cells within each organ mentioned is not abundant but relatively minute (The National Institutes of Health resource for stem cell research, 2006).

The new goal that worldwide scientists are aspiring to achieve is culturing viable adult stem cells in the laboratory which will have important implications in regenerative medicine. This includes substitution of the dopamine-producing cells in the brain of patients suffering from Parkinson's disease or treating osteoporosis, diabetes and congestive heart failure (Richards, 2000).

ADULT STEM CELL PLASTICITY

The new concept that adult stem cells are not actually lineage restricted as previously thought, leads us to the concept of stem cell plasticity or transdifferentiation. Besides the fact that adult stem cells differentiate into the tissues making up the organ into which they reside as occurs in response to cell injury, stem cells can surprisingly give rise to specialized cells of other organs.

Figure 4 below portrays the typical pathways followed by adult stem cells in the process of differentiation into the cells of the organ they are harboring in. As can be seen in the diagrammatic representation, the main stem cells found in organs such as bone marrow, brain, gut epithelium and skin amongst others generate several different types of cells but which are all found in the organ itself. For example, stem cells in gut epithelium generate Paneth cells, goblet cells, enteroendocrine and absorptive cells all found within the gut. Similarly stem cells in the brain have trilineage ability and can give rise to both glial cells and nerve cells. Apart from these several organs, stem cells in blood are also capable of generating all types of blood cells ranging from erythrocytes to all types of lymphocytes (The National Institutes of Health resource for stem cell research, 2006).

(The National Institutes of Health resource for stem cell research, 2006). (http://stemcells.nih.gov/info/basics/basics4.asp).

Besides the multipotency exhibited by adult stem cells, several experimental results indicate that adult stem cells exhibit pluripotency. Thus, adult stem cells may be even more malleable than previously thought. Even more interesting is the fact that there can be links between the liver and pancreas because of their similar embryonic development (Preston *et al.*, 2003).

Dilemmas that must be dissolved include speculating whether all stem cells in the adult body irrespective of their organ of origin transdifferentiate via the same process. Other potential questions are: Is the trigger for this transdifferentiation the same for all types of stem cells? What may stimulate one type of stem cell to differentiate may not stimulate others. For example, ischeamia may trigger bone marrow cells to develop into cardiac myocytes but liver cells may not be activated by ischemia to give rise to cardiomyocytes but require a different stimulus. Moreover, the same stimulus can activate two different types of stem cells to develop into different types of cells.

Finding ways to culture adult stem cells outside the body is a high priority of stem cell research.

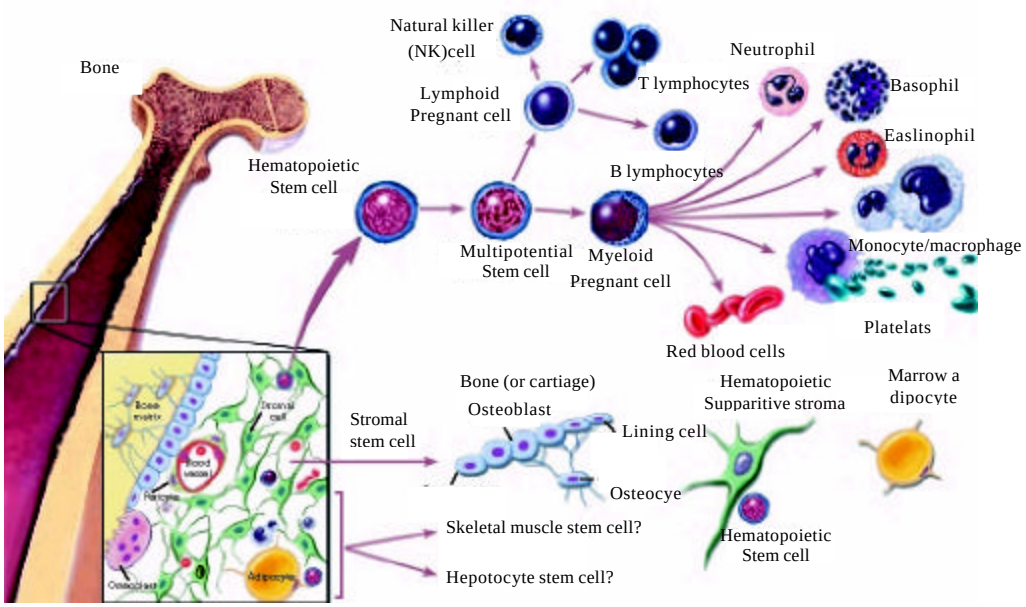

Fig. 4: Hematopoietic and stromal stem cell differentiation

The stem cell niche: Just as a living organism is defined by a niche which explains its ecological relations in the habitat in which it lives, the stem cell niche is the environment surrounding a stem cell. The niche embodies both cells and substrates which encourage the stem cell in vivo to remain in the undifferentiated state.

Not only does the surrounding environment support the stem cell by, for example, nourishing it, but it is crucial for determining self-renewal and differentiation processes. $1 integrin which plays an important part in adhesion and migration of all types of cells was found to have a vital 'glue' effect. In fact, in its absence, cells exit their niche and either differentiate or apoptose (Preston *et al*., 2003).

Conclusions from experiments by Alan C. Spradling have shown that if a stem cell is removed, another nearby cell which had already differentiated becomes a stem cell to replace the lost one. According to Spradling, it is essential to have a pair of stem cells within a given niche so that "they can back each other up". In Spradling's opinion, a lot of interest have been given to the stem cell itself. In actual fact, however, the cells surrounding the stem cell can be even more crucial to the maintenance of the stem cell pool (Howard Hughes Medical Institute, 2000). The exact role of the niche in the processes that dominate the stem cells is not yet deduced but advances are being made and it may not be a surprise if scientists find that the stem cell niche's importance has been underestimated.

CONCLUSION

The biology of stem cells is a topic in science that still has to be unraveled. We are already on our way of doing so, but there is still a lot more to uncover. There are also important hurdles that must be overcome such as finding ways to culture adult stem cells outside the body. However, stem cells promise a revolution in science and in the practice of clinical medicine.

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