EDITORIAL

Progress in Stem Cell Frontier

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Human life starts when a sperm combines with an ovum and forms a fertilised egg. This cell and its immediate descendents, are called "totipotent stem cells". During first 8 weeks of human life, embryonic stage, the embryo is made of specialised "embryonic stem cells" also called "pluripotent stem cells" that can form just about every cell except the placenta. In the course of human development a single fertilised egg, ultimately gives rise to more than 200 cell types (blood cells, neural (brain) cells, liver cells etc) which make up the human body. This process, whereby less specialised cells turn into more specialised cell types, is called "differentiation". As almost all cells in the body have the same genes, differentiation occurs, in large part, by switching on or switching off different subsets of these genes. Thus, differentiated cell types express different subsets of genes. For example, red blood cells express the gene making haemoglobin but neural cells do not. In general as cells become more specialised the subset of genes that they can express becomes more restricted "committed stem cells".

Stem cells have the capacity to undergo an asymmetric division such that one of the two "daughter" cells retains the properties of the stem cell while the other begins to "differentiate" into a more specialised cell type.

With the advent of DNA technology in 1980's, adult stem cells have been grown in the laboratory using appropriate culture conditions and a cocktail of growth factors. This enabled us to purify specific cell-type stimulating factors i.e. cardiac stem cells, brain cells, liver cells, ova and sperm etc. The focus then shifted to use embryonic and adult stem cells to repair damaged tissues / diseased organs. Embryonic stem cells are pluripotent and can be directed to make any organ of the body under appropriate conditions. Adult stem cells are specialist cells which have the (genetic information) memory of most bodily structure and functions but can regain the properties of embryonic stem cells partially under normal physiological or pathological environment.

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Using adult stem cells to repair damaged organ has been hampered by their limited capacity to re-differentiate into any other cell type. Haematopoietic stem cells obtained from bone marrow or peripheral blood are the most commonly used cells for this purpose because of the ease and quantity in which they can be obtained. They cant be transferred or implanted at the site of disease / damage in a particular organ. Using patients own stem cells abrogate the risk of rejection.

Advantages. Embryonic stem cells are:

- Immortal: One cell line could supply endless amounts of cells with carefully defined characteristics. Like an endless fountain, the cell line itself would remain intact.
- Flexible: They can make any body cell.
- Available: Human embryos remaining after in-vitro fertilization are routinely destroyed by fertility clinics.

Disadvantages. Embryonic stem cells are:

- Hard to control: They may pass through several intermediate stages before becoming the cell type needed to treat a particular disease; this process is controlled by complex chemical cues.
- Ethically controversial: Many who believe life begins at conception say that the informed consent by patient donors does not remove the ethical stigma of doing research on human embryos.
- Rejected by the immune system: The immune profile of the specialized cells would differ from that of the recipient. The problem might be overcome by creating cell lines with generalized compatibility, perhaps through genetic engineering.

Advantages. Adult stem cells are:

- Immune to immune attack: If patients receive the products of their own stem cells, they will not mount an immune response.
- Available: Some types, like blood stem cells, are easy to find.
- Partly specialized: That reduces the amount of outside direction needed to create specialized cells.
- Flexible: Adult stem cells may form other tissue types. Last fall, scientists reported that skin and blood

stem cells both produced cells that look like neurons - in the lab.

Disadvantages. Adult stem cells are:

- Scarce: Not all types of adult stem cells have been found yet.
- Unavailable. They can be dangerous to extract
- Vanishing: They don't live as long as embryonic cells in culture.
- Rare: Adult stem cells are never very common, and grow more scarce as we age, when the cells might be needed most. Like the following problem, this is relevant for self-transplants of a patient's stem cells.
- Questionable quality: Genetic defects may occur after exposure to sunlight or toxins. Or the disease being treated may be present in the stem-cell genes.

Beyond replacing parts - stem cell research has other theoretical advantages. For one thing, stable populations of human cells would be a boon to the pharmaceutical industry, which could test new drugs on real, live and fairly normal human cells. Stem cells could increase the accuracy of early drug discovery tests while reducing costs and the need to use animals such as, well, guinea pigs. Second, knowing more about the change and specialization of cells could help in two diseases where such processes go awry - birth defects and cancer. In birth defects, some cells fail to become their intended tissue type, while in cancer, cells revert to a less-specialized form and lose the usual inhibition on endless multiplication. By studying the sequence of genes that turn on and off during specialization, we could learn to control and treat these diseases.

Research on adult stem cells is at a very early stage. Without a great deal of further research it will not be clear to what extent their therapeutic potential will be realised, or for what type and proportion of potential applications adult stem cells will be applicable. Most scientists believe that many of the published studies on stem cells are still open to multiple interpretations or require replication; and there are many crucial scientific issues to be resolved. Embryonic Stem Cells are needed for this purpose, partly because of the relative ease with which they can be isolated, maintained in culture and differentiated into other cell types; and partly because they are the only fully undifferentiated pluripotent cell type available for study. If scientists are to dedifferentiate adult stem cells to pluripotency, prior to redifferentiation into a new cell type for therapeutic purposes, they must know whether they have done this correctly and whether the process is safe.

So far consistent benefit of haematopoietic stem cells have been reported in the setting of myocardial regeneration. There have been large multi-centre controlled trials published in the literature. Kuswardhani RA et al in a meta-analysis reported that resulting meta-analysis concluded that bone marrow derived stem cell therapy consistently improves cardiac performance parameters (left ventricular ejection fraction, end systolic volume, and end diastolic volume) when compared to placebo, even after the establishment of primary intervention. It is also safe to use and prevents the development of recurrent myocardial infarction and heart failure.

There is a mushroom growth of stem cell therapy centers in many countries who claim to treat almost every disease using allogeneic umbilical cord blood stem cell and autologus stem cells. Their websites show video of patients' interview and other anecdotes. In Pakistan, human organ transplant authority (HOTA) is able to control such a situation and successful in organ trade and implemented ethical practices in organ transplantation.

Currently, stem cells are obtained from mobilised peripheral blood stem cells, bone marrow or human unblical cord blood for transplantation. Bone Marrow /Stem cell Transplantation is the only established treatment for leukaemia, b-thalassaemia major and aplastic anaemia and lymhpoma etc. There is "No Quantum Leap"; Effective stem-cell based therapies would be a gradual process over the next five to twenty years. This is a normal time-span for the development of any new treatment. Currently, multi-million dollar business interest guiding stem cell research to go leap and bound without going through conventional way of evolution for a particular treatment. There is a great deal of controversy over the ethics of embryonic stem cell research. Some say that life begins at conception and that the use of humans (even immature ones) for research purposes is immoral. Others claim that the embryos are only tiny amounts of undifferentiated tissue and since they are already scheduled for destruction, they should be used to help others. Regenerative medicine is a new area of stem cell research. It offers a lot of potential to understand many disease processes and cure many incurable diseases. It is still in its very early stage of development and by no means considered standard of care.

Suggested Reading:

1 Essentials of Stem Cell Biology: Edited by Robert Lanza, John Gearhart, Brigid Hogan. Elsevier Academic Press, San Diego, Calif., 2006.

2 Körbling M. and Estrov Z.N Adult stem cells for tissue repair –a new therapeutic concept? Engl J Med 2003; 349:570-582.

3 Okie S.N Stem-Cell Research - Signposts and Roadblocks. Engl J Med 2005; 353:1-5.

4 Kuswardhani RA. Bone marrow-derived stem cells as an adjunctive treatment for acute myocardial infarction: a systematic review and meta-analysis. Acta Med Indones. 2011 Jul;43(3):168-77.

5 Spar D. The Business of Stem Cells. N Engl J Med 2004; 351:211-213.