Stem Cell Therapy – A Panacea for all Ills?

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Recently, a team of South Korean scientists has enabled a paraplegic of 19 years to walk after injecting stem cells derived from a cloned embryo into the site of spinal cord injury. It has been shown in an adult mouse with myocardial infarction that bone marrow stem cells are able to differentiate into cardiac myocytes, endothelial cells and vascular smooth muscle cells. Intracoronary infusion of autologous bone marrow stem cells in patients with acute myocardial infarction has been shown to decrease the functional myocardial defect and increase the left ventricular ejection fraction. Allogenic mesenchymal stem cell grafts are seen to regenerate bone in dogs without the need for immunosuppressive therapy. Apart from these, stem cell therapy seems to hold promise in a variety of conditions like Type I diabetes, Parkinson’s disease, amyotrophic lateral sclerosis, hepatic degeneration, corneal surface defects and much more – so much so that it has spawned a new speciality of medical practice “Regenerative Medicine.”

Stem cell therapy has been in vogue in the form of bone marrow transplantation for several years now. What has given an impetus to this field is the isolation of human embryonic stem cells from the inner cell mass of blastocyst by James Thomson in 1998. Stem cells are broadly categorized into Embryonic Stem Cells (ESCs) and Adult or Somatic Stem Cells (SSCs). ESCs can be derived in two ways: from embryo formed by the fusion of sperm and ovum and as of now such embryos are available as excess embryos from in-vitro fertility (IVF) clinics. The second method is through therapeutic cloning using Somatic Cell Nuclear Transfer (SCNT) technique, wherein the nucleus of a somatic cell is injected into an enucleated ovum, which then starts dividing like an embryo. This was the technique used by the South Korean scientists.

Adult stem cells are found in the mature, terminally differentiated tissues and are of two types: Haematopoietic Stem Cells (HSCs) and Mesenchymal Stem Cells (MSCs). Haematopoietic stem cells in the bone marrow are the oldest known variety of stem cells. HSCs are also found in the peripheral blood, umbilical cord blood and fetal hematopoietic system. MSCs are found in the bone marrow (as stromal cells), umbilical cord matrix (as perivascular cells of Wharton’s jelly), placental tissue, fetal tissue, fat and muscle. A sub-population of MSCs known as Multipotent Adult Progenitor Cells are also identified in the bone marrow. Multipotent adult stem cells, also known as basal cells, have been known to exist in the basal layer of epidermis of skin and in the lining epithelium of gastrointestinal tract and respiratory tract and in the epithelium of the limbus (sclero-corneal junction). These cells usually regenerate and replace cells that are lost to maturation and senescence. More recently, the discovery of stem cells in the post-mitotic tissues, thought to be incapable of regeneration, like brain (in the hippocampus and in the subventricular zone), myocardium and skeletal muscle has opened up exciting new possibilities.

Embryonic Stem Cells Versus Adult Stem Cells

Both embryonic stem cells and adult stem cells are capable of indefinite self-renewal; are capable of differentiation into specific functional cells and tissues and are capable of homing to areas of inflammation and injury. Their capacity to replicate indefinitely both in vivo and in vitro is a boon to regenerative medicine. Adult stem cells in skin, GIT, limbus etc. while differentiating into specified functional cells, replicate to protect their number, thereby maintaining a constant pool. Stem cell turnover and differentiation should always be in balance. If replication is not adequate, it may lead to stem cell deficiency at these sites.

ESCs are pluripotent and are capable of differentiating into tissues derived from any of the germ layers i.e. ectoderm or mesoderm or endoderm. This ‘Proteus’ like quality of ESCs can be used to manipulate them using tissue engineering techniques to develop new organs. MSCs also show pluripotency by differentiating into many tissues and also into tissues totally different from that of their origin. This capacity of transdifferentiation of MSCs into adipocytes, chondrocytes, myocytes, osteocytes, glial cells and neural cells makes them ideal for stem cell therapy. Maintenance of MSCs and their differentiation are controlled by their particular micro-environment, where chemical cues may be playing a role. Stem cells exhibit different markers on their surface which helps in distinguishing their type.

The Scope of Stem Cell therapy

The homing of stem cells to areas of tissue injury or inflammation may occur via a chemical route. This characteristic of stem cells can be used to treat tissue defects. Tissue necrosis releases certain chemical factors or signals that cause chemo-
taxis and mobilize stem cells to the site of injury. Based on the same principle MSCs have been used as gene carriers by introducing exogenous DNA into them. Viral transduction using adenoviruses in stem cells can generate stable clones and may be used in gene therapy. Stem cells can similarly be used in drug delivery systems.[7,11]

In yet another application of stem cells, multipotent adult progenitor cells may be turned into pluripotent stem cells similar to ESCs. This is developmental backtracking or rewinding known as ‘dedifferentiation’ and these pluripotent stem cells may then be used in therapy.[12] Another remarkable aspect of stem cell therapy is the immunoprivilege enjoyed by the ESCs. Allogenic ESCs do not evoke an immunological reaction after transplantation. In fact, they are said to induce immunological tolerance for organ transplantation and may obviate the need for immunosuppressive therapy.[13]

Ethical Dilemmas

The use of ESCs is however mired in the ethical controversy of destruction of the embryo while harvesting ESCs. Some argue that it is equivalent to killing a baby to take out the cells/ organs to save other people’s lives. Since they believe that ensoulment occurs at conception, they oppose embryonic stem cell therapy. Yet, there are people like Sandel who believe otherwise. He compares human embryo to an acorn; acorns grow into oak trees. He says, in spite of the developmental continuance, acorns and oak trees are different structures. Similarly, non-sentient human embryo is different from sentient human being according to him.[14] There are yet others who argue that of the two sources of ESCs, a product of therapeutic cloning is just that – a product manufactured with the sole purpose of harvesting ESCs. McHugh calls such a product a ‘clonote’ as opposed to a ‘zygote’ formed by the fusion of sperm and ovum for reproductive purpose.[15] Use of allogenic or autologous MSCs or HSCs will circumvent this ethical controversy easily. But they have to be expanded (cultured) in numbers before use and their plasticity i.e. differentiation potential is less than that of ESCs. Another problem they face is that of immunogenicity because HSCs and MSCs are not as immunoprivileged as ESCs and hence use of allogenic MSCs and HSCs would require immunosuppression.

Apart from ethical problems, ESC therapy also faces some biological problems. ESCs have a tendency to form teratomas and also exhibit chromosomal abnormalities. If the ESCs are obtained from therapeutic clones, the problems faced by cloned mammals due to senility of cells will also plague this form of therapy.[16] To produce a therapeutically cloned embryo, the South Korean scientists had to waste 250 oocytes. Thus there is also the fear of dehumanizing practices like embryo farms, commercialization of oocyte donation etc.[17] Maintenance and expansion of ESCs are presently done on feeder cell layer like mouse embryonic fibroblast layer. Such exposure to animal cell lines carries a risk of contamination with retroviruses and other pathogens.[18] Many governments like European union, have now made it mandatory that isolation and expansion of stem cell lines are done according to proper guidelines and in concurrence with Good Manufacturing Practices.[19]

If we search the history of Medicine, we find that man has always tried to treat diseases with available materials starting from herbal plants, metals and metallic compounds and then antibiotics and anti-viral agents. While the former two treated the symptoms, the latter two tackled the causative agents. Where these did not have a scope, he resorted to manual intervention in the form of surgery. Having expanded his knowledge in molecular medicine and cell biology, it is only a correct step that he should resort to cell-based therapy trying to establish the original milieu by almost re-creating the original cells in lieu of the diseased ones. But while trying to play God, he cannot become God himself and hence the caution required in going ahead full steam with Stem Cell therapy.

Presently, the questions facing stem cell therapy are:

i. What type of stem cell to use? - ESC or HSC or MSC?

ii. When and by what route to administer? - After conventional treatment fails or concurrently? - Whether to inject intrasensionally or intravascularly?

iii. In what manner to use them? As basic stem cells or after transdifferentiation / tissue engineering?

The answers will not be immediately forthcoming. Still there is a lot of ground to be covered. Stem cell therapy has to be pursued with caution taking care of ethical concerns and inherent biological and logistical problems. Yet, stem cell therapy holds open one promising door where all else have been closed and it is hoped, a few years hence, stem cells will occupy a pride of place in the therapeutic armamentarium.

References


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