Stem cell biology is a new field, which is advancing at an incredible pace with new discoveries being reported from all over the globe.

Researchers have for years looked for ways to use stem cells to replace cells and tissues that are damaged or diseased. But it is only recently that stem cells have received much attention of the scientific and the public policies.

In 1998, James Thomson at the University of Wisconsin-Madison isolated cells from the blastocyst, and developed the first human embryonic stem cell lines. At the same time, John Gearhart at Johns Hopkins University reported the first derivation of human embryonic germ cells from the primordial germ cells.

Stem Cells are unspecialized cells, can divide and renew themselves for long periods of time and become specific specialized cell types of the body.

Pluripotent stem cells from embryos and fetal tissue possess the ability to repair or replace cells or tissues that are damaged or destroyed by many of our most devastating diseases and disabilities. Harvested stem cells from umbilical cord blood or embryos require proper cross matching and may lead to complications like graft versus host reaction. Also harvesting stem cells from embryos involves ethical issues, as life is considered by some to begin at conception so it may be considered criminal to sacrifice an embryo for experimental and research purposes. Embryonic Stem Cells are derived from embryos that develop from eggs that have been fertilized in vitro and then donated for research purposes with informed consent of the donors.

An adult stem cell is a multipotent cell, still capable of differentiating into only a few specialized cells. Evidence suggests that, given the right environment, some adult stem cells are capable of being “genetically reprogrammed” to generate specialized cells that are characteristic of different tissues. This phenomenon is termed adult stem cell plasticity or trans-differentiation. The origin of adult stem cells in mature tissues is unknown. Adult stem cells have been identified in brain particularly in the hippocampus, bone marrow, peripheral blood, blood vessels, skeletal muscle, epithelia of the skin and digestive system, cornea, dental pulp of the tooth, retina, liver, and pancreas. Thus, adult stem cells have been found in tissues that develop from all three embryonic germ layers.
Research Hurdles

In 1981, researchers reported methods for growing mouse embryonic stem cells in the laboratory, and it took nearly 20 years before similar achievements could be made with human embryonic stem cells. Most of the knowledge about embryonic stem cells has emerged from in vitro fertilization technologies and basic research on mouse embryology.

Hurdles in the stem cell research include the rare occurrence of adult stem cells among other differentiated cells, difficulties in isolating and identifying the cells (molecular “markers” are often used to identify adult stem cells), and in many cases, difficulties in growing stem cells in tissue culture.\(^5,6\)

Researchers in Philadelphia achieved a billion-fold increase in a few weeks from bone marrow stem cells in culture. Cultures of human pluripotent stem cells have active telomerase, which is an enzyme that maintains the length of telomeres and is important for cells to maintain their capacity to replicate.

Major concerns still remain that what prompts the stem cell to take up a specific function and what are the factors that would dictate to stop its multiplication once the aim is achieved. An uncontrolled proliferation may carry the risk of teratoma formation at any stage after stem cell therapy.

Clinical application

Umbilical cord blood stem cells have already been effectively used in the treatment of sickle cell, leukemia, non-Hodgkin’s lymphoma, other forms of cancer, life threatening anemias, and autoimmune diseases.\(^7-10\)

Stem cells may hold the key to replacing cells lost in many devastating diseases like Parkinson’s disease, Spinal cord injury, multiple sclerosis, Alzheimer’s disease, diabetes, chronic heart disease, end-stage kidney disease, liver failure and cancer.\(^11-19\) Lately stem cell use has been tried in the treatment of burns, infertility, lupus and deafness.\(^20-23\)

Another major area for research is the development of transplantable pancreatic tissues that can be used to treat diabetes. Researchers have recently shown that human embryonic stem cells can be directly differentiated into cells that produce insulin.\(^24,25\) Researchers are trying to devise ways to use specialized cells derived from stem cells to target specific cancerous cells and directly deliver treatments that will destroy or modify them.

In order to safely use stem cells or cells differentiated from them in tissues other than the tissue from which they were isolated, researchers will need purified populations (clonal lines) of adult stem cells. In addition, the potential for the recipient of a stem cell transplant to reject these tissues as foreign is very high. Modifications to the cells or the immune system, or both will be a major requirement for their use.

A scientific revolution that has direct impact on the future of fetal intervention is occurring in the field of stem cell biology. The fetus contains an increased frequency of stem cells that migrate, expand and differentiate in various tissue compartments. There is large percentage of stem cells in fetal tissues relative to adult tissues, allowing an opportunity for efficient genetic manipulation of stem cells with secondary correction of genetic abnormalities for the lifetime of the individual. This will open the door for prenatal therapy and safety of fetal gene therapy that need to be addressed prior to any clinical application of this approach. Stem cells are already being explored as a vehicle for delivering genes to specific tissues in the body.\(^26,27\)

Clinical Experience

After many years of isolating and characterizing stem cells, researchers are now just beginning to utilize these as discovery tools and a basis for potential clinical applications. Literature is still silent on the clinical application and the long-term effects of stem cell therapy in humans. Stem cell active research is going on in various centers in the world (Liverpool, Chicago, King’s College, London, University of California-San Francisco, and many more). No report is however, available of its use in newborns and children in the field of pediatric surgery.

The All India Institute of Medical Sciences (AIIMS), New Delhi has taken the global lead in using the autologous stem cells obtained from bone marrow (sternum, tibia) and using them for various disorders (cardiomyopathies, diabetes, bony disorders, biliary atresia and choledochal cyst (cirrhotic livers), spina bifida, cerebral palsy and muscular dystrophy). This has been possible following an extensive background research that has gone for more than 2 years before using the stem cells on the human beings. At AIIMS, stem cells have been used in more than 150 patients, including neonates and infants for various disorders.

Ethical issues for the autologous stem cell therapy

With the autologous infusion, there are no ethical issues involved with the stem cell therapy. However, being a new...
therapy with no definite known long term results, the detailed procedure of the stem cell therapy, its source, the route and the possible future impact is explained to each and every patient / parents and a special informed consent is obtained.

Source of Stem cells
The source to procure the stem cell, the amount to be infused, the route of infusion of the cells, the age of the patient at therapy and so also the concentration of stem cells being used, are all important considerations. However, very little knowledge is available to answer these issues. It is presumed that the newborns and more so the infants produce better quality and concentration of stem cells. Embryonic cells and the placental blood from the umbilicus at the time of birth are the best sources, if anticipated in advance or in mothers with high-risk pregnancy. Difficulty might arise to obtain sufficient amount for separating the stem cells for therapy from the bone marrow in the neonates. We have used 5 ml solution with a concentration of 4 million cells / ml stem cells. To achieve this, single puncture tibial bone marrow has been sufficient in most children. However, both tibias were used in the newborns with spina bifida to obtain 5 ml solute for infusion. Researchers have used various routes with the hope that the stem cells reach automatically at the site of the need or injury to develop, modify and repair the affected organ.[29] This would depend on the quality, concentration and the source of the stem cells.

To achieve higher level of concentration at the site of the target organ, the stem cells need to be either infused through the arterial supply or injected locally. The actual therapy to infuse would vary for various surgical conditions. To direct the stem cells to Liver in infants, we have used hepatic artery (20%) and the portal vein (80%). In cases with spina Bifida, we have injected stem cells in the epidural space and also directly in the defective spinal cord during surgical repair of the defect.

ORBO – AIIMS Central facility for storage
Facilities for storing of stem cells for future use are one of the important issues at present. In the European countries, apart from the initial storage cost (Euro 10.000/-), the monthly maintenance is around Euro 100/-. The ORBO – AIIMS Central facility for storage.

The AIMS has again taken the lead and is presently the third country after South Korea and England, establishing the Stem cell banking facility at the Organ Retrieval and Banking Organization (ORBO) at AIIMS. Samples would be preserved at around minus 186 degree Celsius in liquid nitrogen. Preservation of the embryonal cells for its possible future use is also in pipeline. The storage cost is expected to be very high and the demand is also extensive in India. The policy to store the umbilical cord/blood and whether it should be for general public or only for the ones with high-risk pregnancies, is yet to be defined.

Future scope
Future Applications include the exploration of the effects of chromosomal abnormalities in early development. This might include the ability to monitor the development of early childhood tumors, many of which are embryonic in origin. Another future use includes the testing of candidate therapeutic drugs. Stem cells are likely be used to develop specialized liver cells to evaluate drug detoxifying capabilities and represents a new type of early warning system to prevent adverse reactions.

Embryonic stem cells undoubtedly will be the key research tools for understanding fundamental events in embryonic development that may explain the causes of birth defects and approaches to correct or prevent them. Another important area of research that links developmental biology and stem cell biology is the understanding, the genes and molecules, such as growth factors and nutrients that function during the development of the embryo. So that these can be used to grow stem cells in the laboratory and direct their development into specialized cell types.

Evidence of structural, genetic, and functional cells characteristic of specialized cells developed from cultured human and mouse embryonic stem cells has been shown for:
- Pancreatic islet-cell like cells that secrete insulin (mouse and human)
- Cardiac muscle cells with contractile activity (mouse and human)
- Blood cells (human and mouse)
- Nerve cells that produce certain brain chemicals (mouse).

The clinical scope of the use of stem cell therapy could be endless. It may involve patients with liver cirrhosis due to biliary atresia and severe forms of choledochal cysts and sclerosing cholangitis.[29] Other fields include spina bifida, Hirschsprung’s disease, renal dysplasia (congenital dysplastic kidneys, bilateral multicystic kidney disease, polycystic disease of the kidney, severe hydronephrosis with renal insufficiency), residual tumors, pancreatic insufficiency due to diabetes, following surgical resection (nesidioblastosis, tumors), neurogenic bladder and bowel and the postoperative neurological deficits after surgery for anorectal malformations with sacral agenesis.[30,31] Research is going to take some more time before the an-
tibodies could be developed against the targeted disease, tissues and tumors, tagged with the stem cells and infused locally for achieving the maximal benefit. Hardware also needs to be developed to inject the stem cells direct to the smaller vessels in the infants and newborns, without the need for surgery for therapy.

During the coming years, embryonic stem cells and adult stem cells will be compared in terms of their ability to proliferate, differentiate, survive and function after transplant, and how can we avoid the immune rejection. The process of research is still ongoing and predicting the future of stem cell application is not possible at this stage. However, current challenges are to direct the differentiation of embryonic stem cells into specialized cell populations and also to devise ways to control their proliferation once placed in patients.

Only further research and its wider clinical application will solve many practical and theoretical queries related to the use of stem cells.

REFERENCES


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