REVIEW PROF-620

STEM CELLS

DR. ABDUL HAGUE
National Institute for Biotechnology and Genetic Engineering (NIBGE)
P 0 Box 577 Jhang Road Faisalabad.

Stem cells is the most current topic of medical importance these days. The reason why they have become focus of attention is their miraculous potential for treatment of diseases and rather controversial origin of the main type, the embryonic stem (ES) cells.

Stem cells are the most primitive type of cells. These cells are defined as cells that have a capacity of unlimited or prolonged self renewal and can produce at least one type of highly differentiated descendent. There are two main types, embryonic stem (ES) cells and adult stem cells.

The egg of a female is haploid. Other half of chromosomes is provided by the sperm. Union of egg and sperm results in formation of fertilized egg. This egg , a single cell, has the potential to form any part of the body, or in other words, its potential is total. So it is called totipotent. By the fourth day, the number of cells has increased to about a hundred. At this stage, they are in th form of a ball called blastocyst.

There is an outer layer, the placental layer and an inner group of cells. These are termed inner mass cells or embryonic stem cells. They are pluripotent. It means that they can form almost all types of cells but not all. An obvious exception is the placental layer. As the time passes these cells specialize further into different type of stem cells. These cells have limited potential and are multi potent in nature. They remain throughout the adult life and are responsible for repair and growth of respective organs. These are termed as adult stem cells. The major differences between ES cells and adult stem cells are given in table I.

In animals, especially mice, the scientists have been working on stem cells for last 20 years. They successfully isolated the ES cells and found ways to transform these cells into various types of specialized cells. These transformed cells were used to replace damaged cells and cure many diseases.

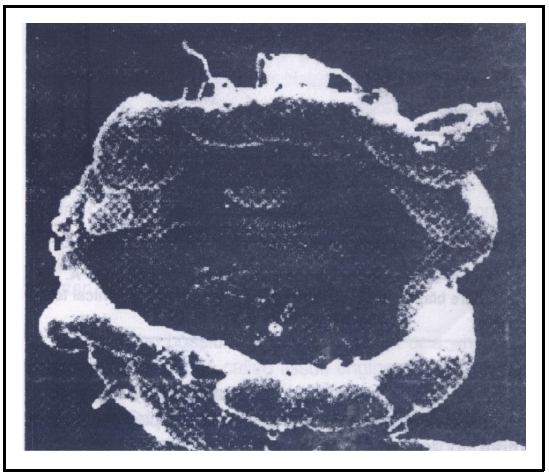

Figure-1. Electron Micrograph of a blastocyst opened upto reveal inner cell mass

However, the real breakthrough came in 1998 . Dr.

J. Thomson of University of Wisconsin, USA isolated human ES cells from embryos obtained from IVF (in vitro fertility) clinics. At IVF clinics, female eggs are fertilized with male sperms and the best match is placed in the womb of the mother. Rest of these fertilized eggs are destroyed. Embryos developed from these eggs were used by Dr. Thomson. He showed that ES ells obtained from these embryos could be transformed into other cells. At about the same time, similar results were reported by Dr. Gaerhart of John Hopkins Institute though his source was fetal tissue obtained from terminated pregnancies.

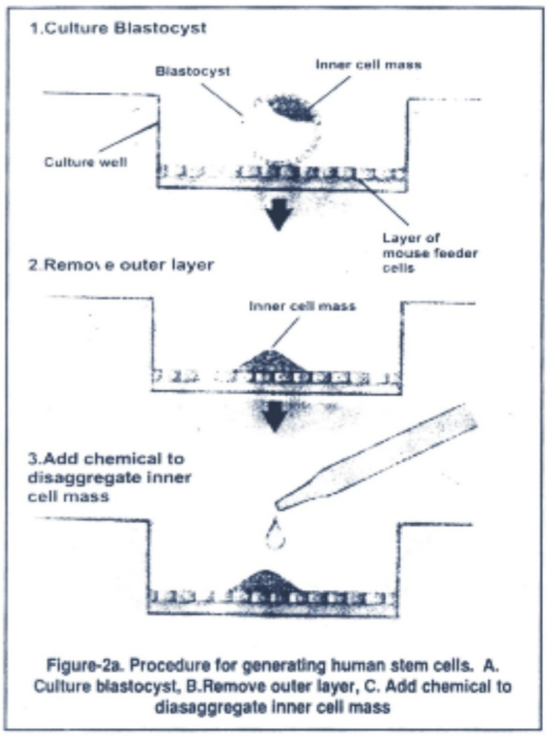

Figure-2a. Procedure for generating human stem cells. A. Culture blastocyst, B.Remove outer layer, C. Add chemical to diasaggregate inner cell mass

The blastocyst are removed from embryos by use of MRI (magnetic resonance imaging) and laparoscopic examination. Three to four blastocysts are placed on a mitotically inactivated mice embryonic fibroblast feeder layer. The placental layer is removed by using pronate. The inner mass cells or ES cells are disaggregated and a culture medium (Dulbecco's modified Eagle's medium) is added.

After a week, clumps of cells are transferred to a new well. After another week, when colony formation has taken place, the cells are distributed into different culture vessels and treated with selected differentiation factor to form different types of stem cells.

It has been estimated that replicating human ES cells can differentiate into 210 types of tissue specific cells. By July 2001 transformation of ES cells into 110 types of cells has been achieved including liver, heart, bone, cartilage, pancreatic cells and brain cells. This means that ES cells have the potential of eliminating a major part of human illnesses including heart, liver and kidney diseases, diabetes, Parkinson's disease, Alzheimer's disease, osteoarthritis, rheumatoid arthritis and perhaps blindness.

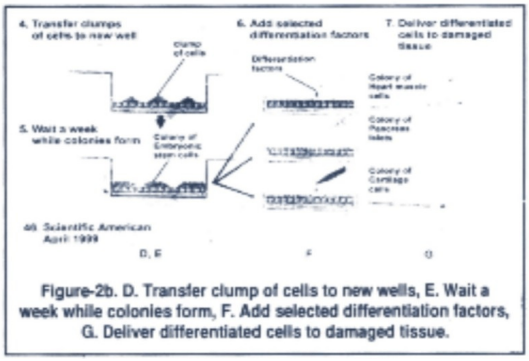

Figure-2b. D. Transfer clump of cells to new wells, E. Wait a week while colonies form, F. Add selected differentiation factors, G. Deliver differentiated cells to damaged tissue.

But there are some stumbling blocks. Most important is the ethical debate attached with these cells. The removal of ES cells from an embryo, that results in its death, has been equated with abortion. This has resulted in restricted research areas in USA, Germany, Canada and Japan. Recently President Bush has allowed work on 64 existing cell lines, forbidding creation of new cell lines. Ironically, many of these cell lines are not considered suitable for research even by scientists

who developed them.

However in Britain and Israel there is no restriction. A council of Muslim religious leaders in USA has declared that this research is acceptable.

Other problems associated with ES cell research are scientific. Most important is the so-called "immune rejection" which means the treatment of these cells as foreign by the body and reaction against them. Somatic cell nuclear transfer (SCNT) which was originally used for cloning has been suggested as an alternative. A nucleus from any cell of a patient's body will be taken and placed in a donated egg that has been deprived of its own nucleus.

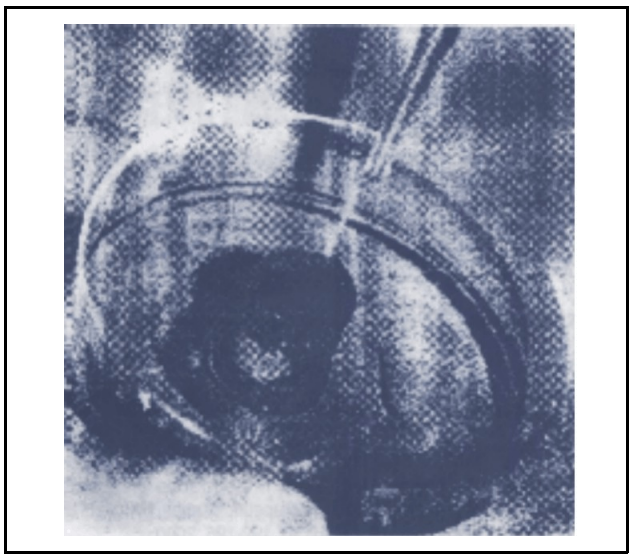

Figure-3. Bioartificial heart valve made of biodegradable plastic is "seeded" with cells from the linings of sheep blood vessels

A blastocyst developed from this egg will provide ES cells acceptable for the patient's body. This has been termed therapeutic cloning. But success rate of such unions is very low, roughly 1 in 280. An alternative called trans-specific nuclear transfer (TSNT), in which an animal's egg instead of human egg is used, has been suggested but it has glaring disadvantages centered around incompatibility.

Only realistic approach is the development of "universal donor" ES cells by use of genetic engineering. The proteins which displayed on the cell surface to label it as foreign may be suppressed so that it is bypassed by the immune system.

Although ES cells have distinct advantages, the ethical and scientific problems associated with them forced the scientists to give importance to adult stem cells as well. Although these cells are not as versatile as ES cells and their number is very minute (one in 1 billion blood cells is a stem cell), these are controversy free and bypass immune rejection as well.

Umbilical cord blood is rich in adult stem cells. Its use is replacing bone marrow transplants and many patients of leukemia (blood cancer) and other blood diseases have been successfully treated. This technique, termed stem cell transplant, has also been used for the treatment of breast cancer, multiple sclerosis and Scleroderma. Promising work is also going on for the treatment of prostrate and kidney cancers.

Initially it was thought that adult stem cells could not be transformed. But recently scientists have achieved success in giving even adult stem cells a career switch. Moreover, adult stem cells have been found in organs thought to be devoid of them e.g. brain. These have been successfully transformed into blood stem cells and muscle cells.

Conversely, human bone marrow cells have been changed into neuronal cells. Like brain, retina was also considered to be devoid of stem cells. Recent discoveries have shown that birds and fish have these cells. This discovery may one day lead to treatment of blindness.

What can be expected to come out of stem cell research in future?. Most importantly, it will help to

identify factors involved in cellular "decision making" process that results in cell specialization. Understanding of genes involved and what turns them on or off, will help resolve some most serious medical conditions such as cancer and birth defects.

Stem cell research will also have profound effect on drug development. These cells can form the first testing platform before moving on to laboratory animals (if required) and human subjects.

It may also be possible to generate a part or a whole new organ by a technique called tissue engineering. The critical challenge of development of blood vessels has been overcome. Some chemical substances such as growth factors have been identified that can direct stem cells to move into desired area and start forming the required tissue. This can be done in a more stable form by transfer of relevant genes instead of proteins.

In animals, biodegradable polymers have been used to form three dimensional scaffolds which are placed in an injured area. These are seeded with stem cells. As the new tissue takes shape, polymers are slowly degraded. Finally a completely new organ or a neo-organ is formed. This technology can easily be applied for humans.

Table-I. Comparison of ES and adult stem cells

	ES Cells	Adult stem cells
Potential	Pluripotent	Multi potent
Growth in culture	Unlimited	Restricted
Immune rejection	Significant	Negligible
Tumor formation	Significant	Negligible
Genetic abnormalities	Negligible	Significant
Ethical status	Debatable	Controversy free

In fact, the stem cell research is moving so fast that in many cases, future is already here. In the beginning of August, 200, a group of lsraeli scientists succeeded in converging human ES cells into heart cells. Just three weeks later, news broke that in a German hospital, a 46 years old heart patient was injected with heart stem cells and he recovered in ten weeks.

It can be concluded that if stem cell research is allowed to proceed without inhibition and its potentials are fully realized, it will be the greatest success story of medical science even surpassing the development of vaccines and antibiotics.

REFERENCES

1. Marshal, E. Bioethics panel urges broader oversight. Science. 292:1466-1467, 2001.
2. Vogel G. NIH pulls plug on ethics review. Science. 292: 415-416,2001.
3. Reubinoff BE, MF Pera . C Fong, A Trounson and A Bongso. Embryonic stem cell lines from human blastocysts. somatic differentiation in virto, Nat. Biotech. 18:399-404,2000.
4. Vogel G. Fetal cell transplant trial draws fire. Science 291: 2060-2061,2001. j
5. Shamblott M. May. Stem cells, a primer. NIH Bulletin p 1-4, 2000.
6. Colman A and a Kind. Therapeutic cloning, concepts and practicalities. TIBTECH. 18: 192-196, 2000. .
7. Mooney D J, and AG Mikos. Growing new organs Scientific Amereican. p 30-43, Apr 1999.
8. Jasefone D. Stem cells: medicine, new frontiers. Mayo clinic health letter, p 1 -4, July 2001.
9. Vogel G. Stem cells are coaxed to produce insulin. Science 292: 615-617, 2001.