Future of stem cell implications in critically ill patients

An essay

Submitted for Partial Fulfillment of Master Degree in

critical care medicine

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(2009)

مستقبل تطبيقات العلاج بالخلايا الجذعية في المرضى ذوى الحالات الحرجة

بحث

توطئة للحصول على درجة الماجستير في طب الحالات الحرجة والرعاية المركزة

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(٢٠٠٩)

Aim of the work

The aim of the essay is to study stem cells what they are, their different types and the characteristics of each type and to elucidate their potential to radically change the treatment of human disease of critically ill nature , e.g. strokes (hemorrhage, infarction) ,burn patients , patients with bed sores ,spinal cord injuries, cancer, diabetes mellitus ,critically ill hepatic, cardiac patients and others, spotting light on where we are and where we are going and to what extent can such category of patients get benefit !!!

Introduction

Stem cells are primal cells found in all multicellular organisms that retain the ability to renew themselves through mitotic cell division and can differentiate into a wide range of specialized cell types ***(Beckers F et al., 2007)***. The rigorous definition of a stem cell requires that it possesses two properties:-

- **Self-renewal:** the ability to go through numerous cycles of cell division while maintaining the undifferentiated state.
- **Unlimited potency:** the capacity to differentiate into any mature cell type. In a strict sense, this makes stem cells either totipotent or pluripotent, although some multipotent and/or unipotent progenitor cells are sometimes referred to as stem cells.

potency of differentiation:-

Potency specifies the differentiation potential (the potential to differentiate into different cell types of the stem cell).

(Siminiovitch J et al., 2005*) *fig no:(1)

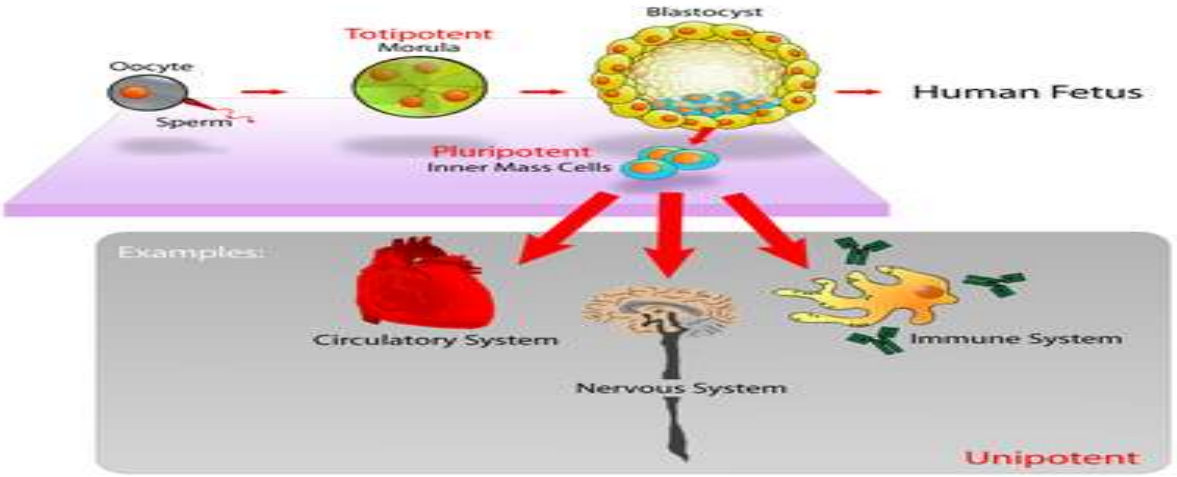


***fig no:(1) potency of stem to differentiate into multiple cell types (Siminiovitch J et al., 2005*)**

- **Totipotent** stem cells are produced from the fusion of an egg and sperm cell. Cells produced by the first few divisions of the fertilized egg are also totipotent. These cells can differentiate into embryonic and extraembryonic cell types.
- **Pluripotent** stem cells are the descendants of totipotent cells and can differentiate into cells derived from the three germ layers.
- **Multipotent** stem cells can produce only cells of a closely related family of cells (e.g. hematopoietic stem cells differentiate into red blood cells, white blood cells, platelets, etc.). ***(Lennard F et al., 2000)***.
- **Unipotent** cells can produce only one cell type, but have the property of self-renewal which distinguishes them from non-stem cells.***(Friedenstein S et al., 2000)***

Lineage:-

To ensure self-renewal, stem cells undergo two types of cell division. Symmetric division that gives rise to two identical daughter cells both endowed with stem cell properties. Asymmetric division, on the other hand, produces only one stem cell and a progenitor cell with limited self-renewal potential. Progenitors can go through several rounds of cell division before terminally differentiating into a mature cell. It is possible that the molecular distinction between symmetric and asymmetric divisions lies in differential segregation of cell membrane proteins (such as receptors) between the daughter cells. However, there is no evidence for this mechanism. ***(Song P and Xie J 2003).***

An alternative theory is that stem cells remain undifferentiated from environmental cues in their particular niche. Stem cells differentiate when they leave that niche or no longer receive those signals. ***(SongP and Xie H 2003).***

Medical researchers believe that stem cell therapy has the potential to radically change the treatment of human disease. A number of adult stem cell therapies already exist, particularly bone marrow transplants that are used to treat leukemia ***(Gahrton B et al , 2003)***.

In the future, medical researchers anticipate being able to use technologies derived from stem cell research to treat a wider variety of diseases including cancer, Parkinson's disease, spinal cord injuries, and muscle damage, amongst a number of other impairments and conditions ***(Lindvall J, 2003)***

In 2009 Goldman has reported the historical back ground of stem cell research of considerable effects since 1960s as follows :-

- **1960s** - ***Joseph Altman and Gopal Das*** presented an evidence of adult neurogenesis, ongoing stem cell activity in the brain; their reports contradicted ***Cajal's*** "no new neurons" dogma and were largely ignored **.*(Goldman P et al 2006)***
- **1963** - ***McCulloch and Till*** illustrated the presence of self-renewing cells in mouse bone marrow
- **1968** - Bone marrow transplant between two siblings had successfully treated Severe combined immunodeficiency disease (SCID) **.**
- **1978** – Haematoppoietic stem cells were discovered in human cord blood . ***(Friedenstein S et al., 2000)***
- **1981** - Mouse embryonic stem cells were derived from the inner cell mass**.** ***(Friedenstein S et al., 2000)***
- **1997** - Leukemia was shown to originate from a haematopoietic stem cell, the first direct evidence for cancer stem cells

- **1998** - ***James Thomson and coworkers*** have derived the first human embryonic stem cell line at the University of Wisconsin-Madison***. (Mitalipov J et al ,2000)***
- **2003** - ***Dr. Songtao Shi*** of NIH has discovered new source of adult stem cells in children's primary teeth ***(Shostak, I 2006)***.
- **07 January, 2007** - Scientists at Wake Forest University led by ***Dr. Anthony Atala*** and Harvard University report discovery of a new type of stem cell in amniotic fluid **.**This may potentially provide an alternative to embryonic stem cells for use in research and therapy ***(Calif in Stem Cell Grants Associated Press, 2007)***.

- **October 2007** - ***Mario Capecchi, Martin Evans, and Oliver Smithies*** won the 2007 Nobel Prize for Physiology or Medicine for their work on embryonic stem cells from mice using gene targeting strategies producing genetically engineered mice (known as knockout mice) for gene research***. (Takahashi B ,2007)***
- ***In 2007 Takahashi,k and coworkers*** claimed that It has been possible to produce a stem cell from almost any other human cell instead of using embryos as needed previously, albeit the risk of tumorigenesis due to c-myc and retroviral gene transfer remains to be determined***. (Yu V et al 2007)***
- **January 2008** - ***Robert Lanza and his colleagues*** at Advanced Cell Technology created the first human embryonic stem cells without destruction of the embryo ***.(French S, et al 2008)***
- **30 October 2008** - Embryonic-like stem cells were derived from a single human hair. ***.(French S, et al 2008)***

Contents

(Iv)Umblical cord blood cells:-

Use of umbilical cord stem cells has been increasing, as the cells have been recognized as a useful source for hematopoietic transplants similar to bone marrow stem cell transplants, included for treatment of sickle cell anemia .Cord blood shows decreased graft-versus-host reaction compared to bone marrow, perhaps due to high interleukin-10 levels produced by these cells ***(Rainsford B et al , 2002)***.

Another possibility for the decreased rejection seen with cord blood stem cell transplants is decreased expression of the beta-2-microglobulin on human cord blood stem cells. ***(Broxmeyer et al., 2003***)

Cord blood can be cryopreserved for over 15 years and retain significant functional potency ***(Broxmeyer S et al., 2003)***.

Cord blood stem cells also show similarities with bone marrow stem cells in terms of their potential to differentiate into other tissue types. Human cord blood stem cells have shown expression of neural markers *in vitro* ***(Sanchez B et al., 2001),*** and intravenous administration of cord blood to animal models of stroke has produced functional recovery in the animals. Infusion of human cord blood stem cells has also produced therapeutic benefit in a mouse model of amyotrophic lateral sclerosis (ALS) ***(Garbuzova B et al., 2003)*** and in rats with spinal cord injury ***(Saporta B et al., 2003)***.

A more recent report noted establishment of a neural stem/progenitor cell line derived from human cord blood that has been maintained in culture over two years without loss of differentiation ability. Several reports also noted the production of functional liver cells from human cord blood stem cells. Additional differentiative properties of human umbilical cord blood stem cells are likely to be discovered as more investigation proceeds on this source of stem cells ***(Kakinuma B et al., 2003)***.

Umbilical cord mesenchyme (Wharton's jelly):fig (8)

While most of the focus regarding umbilical cord stem cells has focused on the cord blood, there are also reports that the matrix cells from umbilical cord contain potentially useful stem cells. Using pigs, this matrix from umbilical cord, termed Wharton's jelly, has been a source for isolation of mesenchymal stem cells. ***(Weiss F et al., 2003).***

The cells express typical stem cell markers such as c-kit and high telomerase activity, have been propagated in culture for over 80 population doublings, and can be induced to form neurons in vitro ***(Mitchell J et al., 2003)***. When transplanted into rats, the cells expressed neuronal markers and integrated into the rat brain, additionally without any evidence of rejection ***(Weiss F et al., 2003).***

Amniotic stem cells:

Amniotic fluid has also been found to contain stem cells that can take on neuronal properties when injected into brain. These stem cells were recently isolated from human amniotic fluid, and were found to express Oct-4, a gene typically associated with expression in pluripotent stem cells ***(Prusa S et al., 2003)***.

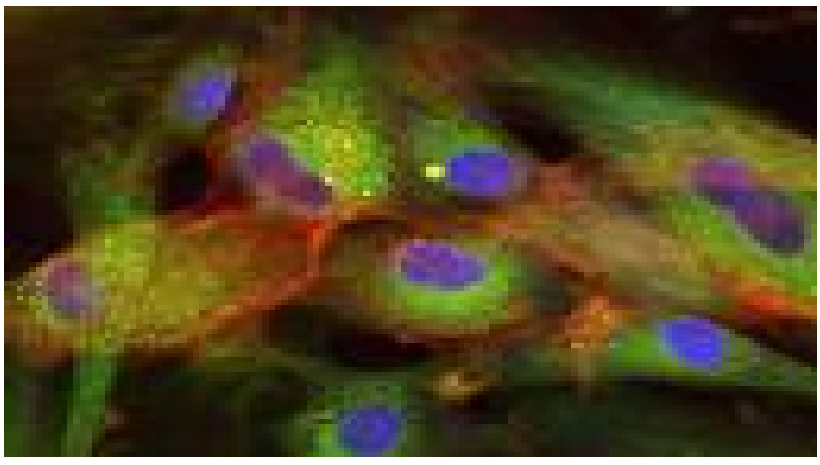


fig (8)Umbilical cord mesenchyme (Wharton's jelly): (Rainsford B et al , 2002)

CHAPTER (1)

Classification of stem cells

The three broad categories of mammalian stem cells are: embryonic stem cells, derived from blastocysts, adult stem cells, which are found in adult tissues, and cord blood stem cells, which are found in the umbilical cord :- ***(Tuch V, 2006)***

(i) Embryonic stem cells;-

Human embryonic stem (ES) cells capture the imagination because they are immortal and have an almost unlimited developmental potential after many months of growth in culture dishes. The proliferative and developmental potential of human ES cells promises an essentially unlimited supply of specific cell types for basic research and for transplantation therapies for diseases ranging from heart disease ,Parkinson's disease to leukemia (***Trounson S et al., 2003)***.

Embryonic stem cells are derived from embryos at a developmental stage before the time that implantation would normally occur in the uterus. (***Trounson S et al., 2003)***. The first differentiation event in humans occurs at approximately five days of development, when an outer layer of cells committed to becoming part of the placenta (the trophectoderm) separates from the inner cell mass (ICM).***fig(2)***

Figure (2): Human blastocyst showing inner cell mass a trophectoderm (Reubinoff F et al., 2000).

Defining Properties of an Embryonic Stem Cell: *fig (3)*

The ICM cells have the potential to generate any cell type of the body, but after implantation, they are quickly depleted as they differentiate to other cell types with more limited developmental potential ***(Martin B etal, 2003)***

ES cells are pluripotent, This means they are able to differentiate into all derivatives of the three primary germ layers: ectoderm, endoderm, and mesoderm. These include each of the more than 220 cell types in the adult body. Pluripotency distinguishes ES cells from multipotent progenitor cells found in the adult; these only form a limited number of cell types. When given no stimuli for differentiation, (i.e. when grown *in vitro*), ES cells maintain pluripotency through multiple cell divisions ***(Andrews O et al., 2005)***.

The first study that describes successful separation of human inner cell mass (ICM) cells and their continued culture for at least two passages in vitro was in 1994. The authors demonstrated that separated ICM cells either differentiate or produce cells with typical HES-cell-like morphology positive for alkaline phosphatase staining and with normal karyotype ***(Bongso P et al., 2004)***.

- Derived from the inner cell mass/epiblast of the blastocyst.
- Capable of undergoing an unlimited number of symmetrical divisions without differentiating (long-term self-renewal).
- Exhibit and maintain a stable, full (diploid), normal complement of chromosomes (karyotype). ***(Odorico E et al., 2001)***.

Pluripotent ES cells can give rise to differentiated cell types that are derived from all three primary germ layers of the embryo (endoderm, mesoderm, and ectoderm).

- Capable of integrating into all fetal tissues during development. (Mouse ES cells maintained in culture for long periods can still generate any

tissue when they are reintroduced into an embryo to generate a chimeric animal.)

- Capable of colonizing the germ line and giving rise to egg or sperm cells. ***(Odorico E et al., 2001)***.
- Clonogenic that is a single ES cell can give rise to a colony of genetically identical cells, or clones, which have the same properties as the original cell.

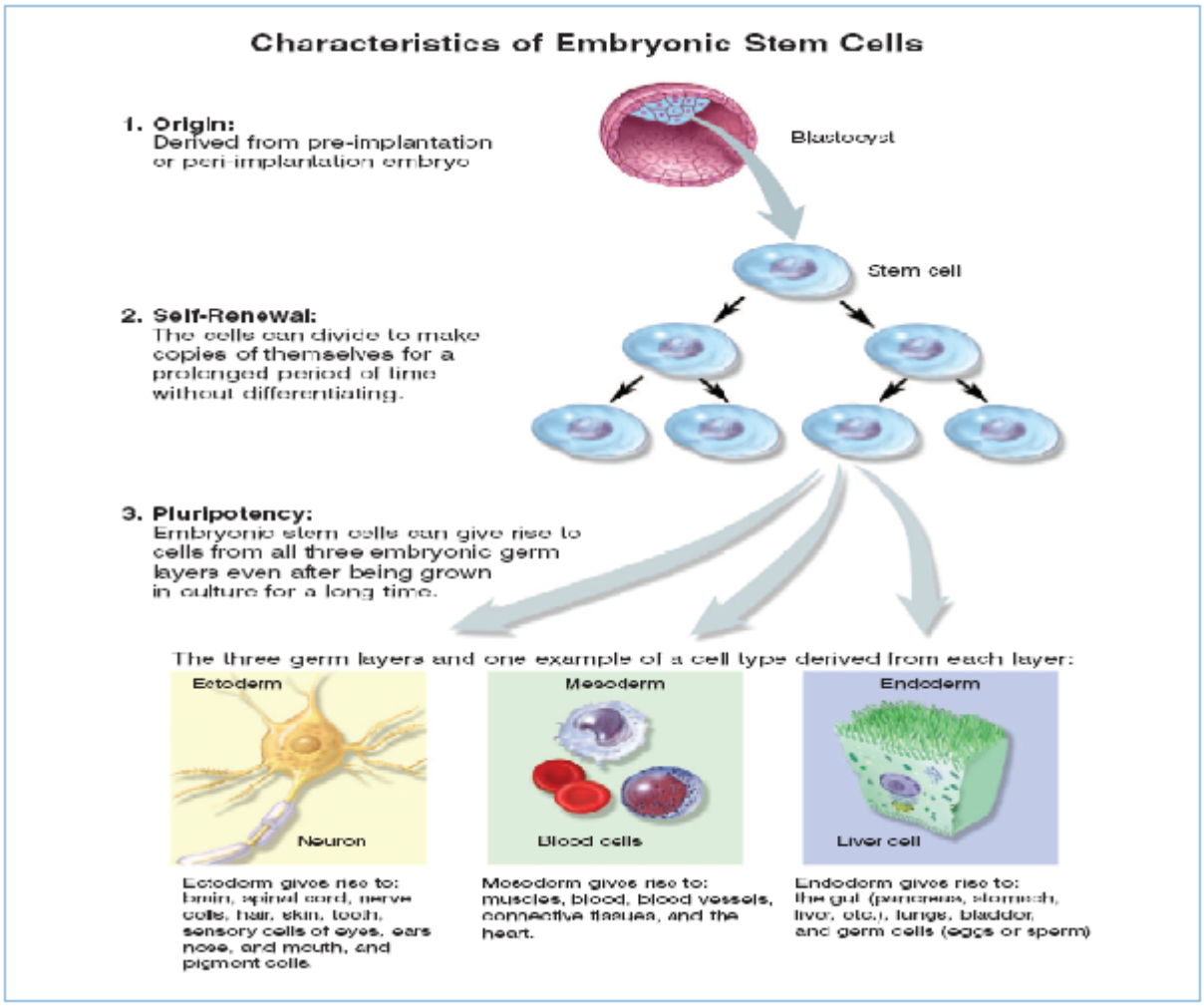


Fig (3) Characteristics of Embryonic stem cells (Odorico E et al 2001)

Derivation of human embryonic Stem cells *fig (4)*

Nearly all described hES cell lines have been efficiently derived using the immuno surgery procedure, however mechanical isolation is advantageous since there is no contact of blastocysts with animal antibodies. On the other hand, there is a risk that not all of the trophectoderm (TE) cells may be removed during mechanical isolation and these may subsequently overgrow and inhibit the growth of ICM cells ***(Pickering J et al., 2003)***.

Success rate in deriving hES cell lines is highly dependant on the quality of recovered blastocysts, isolation conditions and experience of the group ***(Mitalipova J et al., 2003)***.

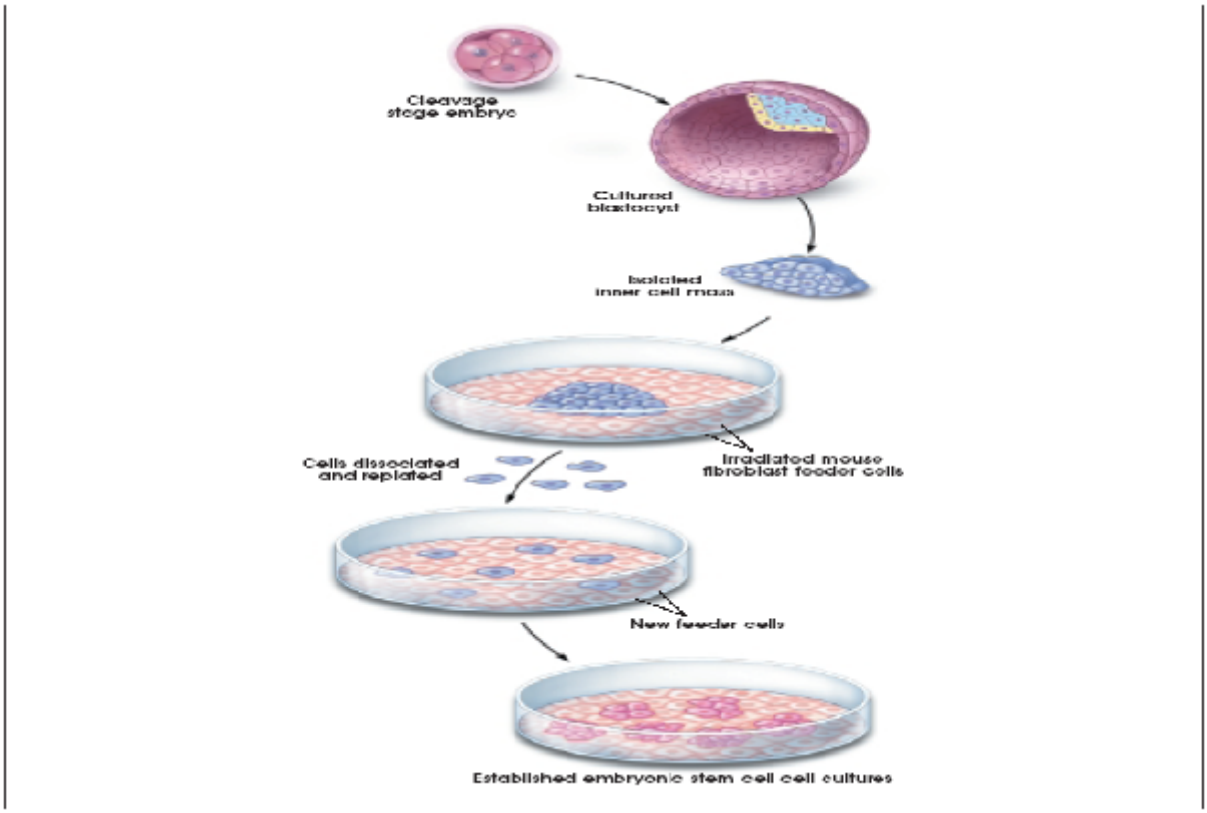
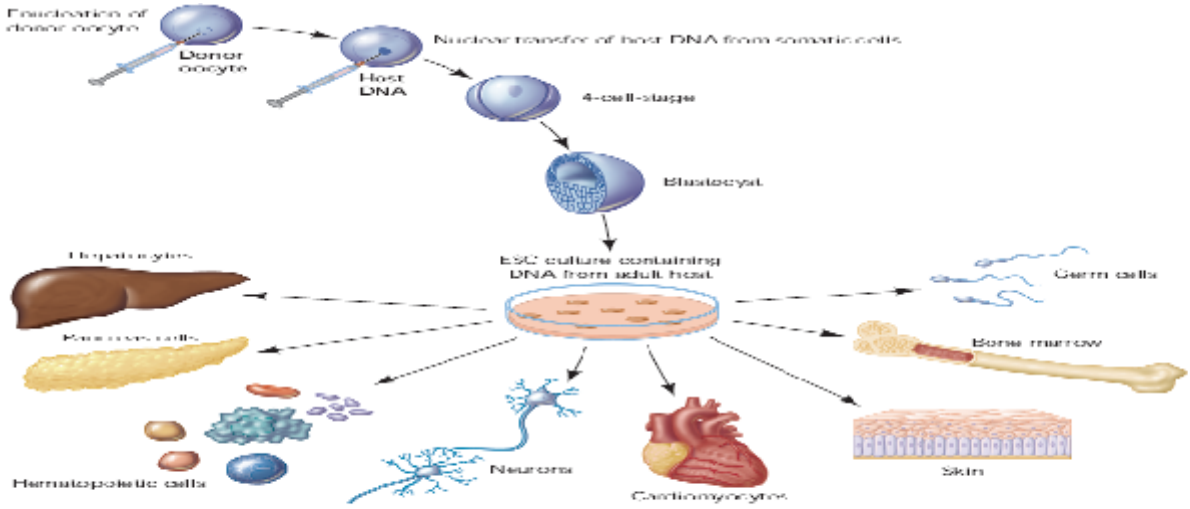


Figure (4)Derivation of embryonic stem cells(Hwang X et al ,2004)

Differentiation Potential of human embryonic stem cell (ESC) into functional tissues: *Fig(5)*

Despite the well-recognized pluripotency of hESC, it has proven rather challenging to direct the differentiation of hESC into specific lineages. However, an ESC based strategy could permit the generation of an unlimited supply of desirable, fully functional cell types from an abundant, renewable, and readily accessible source. ***(Sudhanshu V et al., 2006)***.

Induced differentiation of hES cells into cardiomyocytes which are electrophysiologically comparable with normal human cardiomyocytes and fetal ventricular myocytes has been reported by ***Mummery and his coworkers (2003)*** and induced neuronal cell differentiation of hES cells has been achieved using retinoic acid and nerve growth factor ***(Schuldiner D et al., 2001)***.



Fig(5): Nuclear transfer and directed differentiation (Sudhanshu D et al., (2006)