(Review Article)

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A Review on Embryonic Stem cell Information

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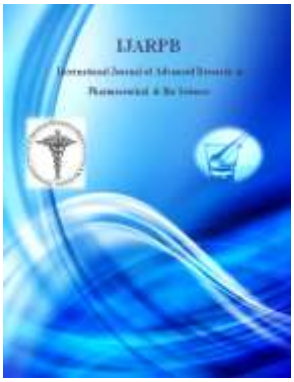

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ABSTRACT

Most tissues in complex metazoans contain a rare subset of cells that, at the single-cell level, can self-renew and also give rise to mature daughter cells. Such stem cells likely in development build tissues and are retained in adult life to regenerate them. Cancers and leukemias are apparently not an exception: rare leukemia stem cells and cancer stem cells have been isolated that contain all of the tumorigenicity of the whole tumor, and it is their properties that will guide future therapies. None of this was apparent just 20 years ago, yet this kind of stem cell thinking already provides new perspectives in medical science and could user in new therapies. Today, political, religious, and ethical issues surround embryonic stem cell and patient-specific pluripotent stem cell research and are center stage in the attempts by governments to ban these fields for discovery and potential therapies. These interventions require physicians and physician-scientists to determine for themselves whether patient welfare or personal ethics will dominate in their practices, and whether all aspects of stem cell research can be pursued in a safe and regulated fashion.

KEY WORDS: Embryonic stem cells, Haematopoiesis, mesenchymal cell.

(Review Article)

INTRODUCTION

Embryonic stem cells are pluripotent cells derived from the inner cell mass of the early mammalian embryo. Pluripotency distinguishes ES cells from multipotent progenitor cells (also known as adult stem cells), which persist throughout life; these cells are capable of giving rise to a tissue-specific, limited number of cell types.

The term "embryonic stem cell" was first introduced in 1981 to distinguish embryo-derived from teratocarcinoma derived pluripotent cells and was stated to define a cell with the following essential characteristics: 1) derivation from the pre- or periimplantation embryo; 2) ability to undergo prolonged, undifferentiated proliferation; and 3) potential to form derivatives of all 3 embryonic germ layers, even after prolonged culture. A fourth essential characteristic as defined for the mouse ES cell the ability to integrate into an embryonic chimera is considered beyond the ethical bounds of testing in primates[1]. Seventeen years later, Thomson et al[2]. Reported the first successful creation of a hens cell line that was formed using cells derived from the inner cell mass of donated embryos that had been generated for in vitro fertilization. Because of their plasticity and potentially unlimited capacity for self-renewal, ES cells generated tremendous interest both as models for developmental biology and as possible tools for regenerative medicine. This excitement has been attenuated, however, by scientific, political, and ethical considerations.

Stem cells are biological cells found in all multicellular organisms, that can divide (through mitosis) and differentiate into diverse specialized cell types and can self-renew to produce more stem cells. In mammals, there are two broad types of stem cells: embryonic stem cells, which are isolated from the inner cell mass of blastocysts, and adult stem cells, which are found in various tissues. In adult organisms, stem cells and progenitor cells act as a repair system for the body, replenishing adult tissues. In a developing embryo, stem cells can differentiate into all the specialized cells (these are called pluripotent cells), but also maintain the normal turnover of regenerative organs, such as blood, skin, or intestinal tissues.

There are three sources of autologous adult stem cells: 1) Bone marrow, which requires extraction by harvesting, that is, drilling into bone (typically the femur or iliac crest), 2) Adipose tissue (lipid cells), which requires extraction by liposuction, and 3) Blood, which requires extraction through pheresis, wherein blood is drawn from the donor (similar to a blood donation), passed through a machine that extracts the stem cells and returns other portions of the blood to the donor. Stem cells can also be taken from umbilical cord blood. Of all stem cell types, autologous harvesting involves the least risk. By definition, autologous cells are obtained from one's own body, just as one may bank his or her own blood for elective surgical procedures. Highly plastic adult stem cells are routinely used in medical therapies, for example bone marrow transplantation. Stem cells can now be artificially grown and transformed (differentiated) into specialized cell types with characteristics consistent with cells of various tissues such as muscles or nerves through cell culture. Embryonic cell lines and autologous embryonic stem cells generated through therapeutic cloning have also been proposed as promising candidates for future therapies[3].

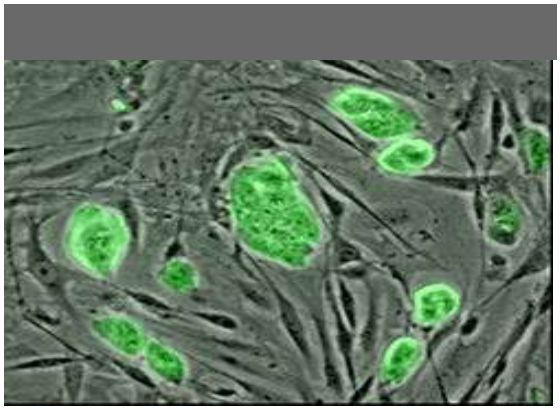

Figure1: Mouse embryonic stem cells with fluorescent marker

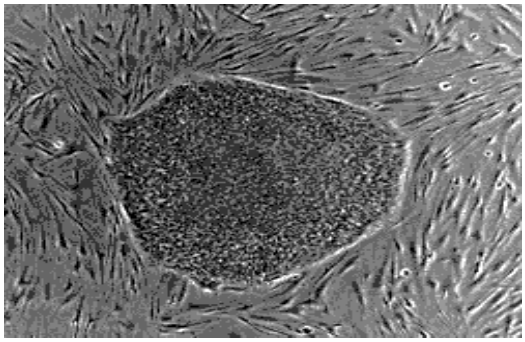

Figure2: Human embryonic stem cell colony on mouse embryonic fibroblast feeder layer

Properties

The classical definition of a stem cell requires that it possess two properties:

- *Self-renewal*: the ability to go through numerous cycles of cell division while maintaining the undifferentiated state.
- *Potency*: the capacity to differentiate into specialized cell types. In the strictest sense, this requires stem cells to be either totipotent or pluripotent to be able to give rise to any mature cell type, although multipotent or unipotent progenitor cells are sometimes referred to as stem cells. Apart from this it is said that stem cell function is regulated in a feedback mechanism.

Self-renewal

Two mechanisms to ensure that a stem cell

Population is maintained exist:

- Obligatory asymmetric replication: a stem cell divides into one father cell that is identical to the original stem cell, and another daughter cell that is differentiated
- Stochastic differentiation: when one stem cell develops into two differentiated daughter cells, another stem cell undergoes mitosis and produces two stem cells identical to the original.

Potency definitions

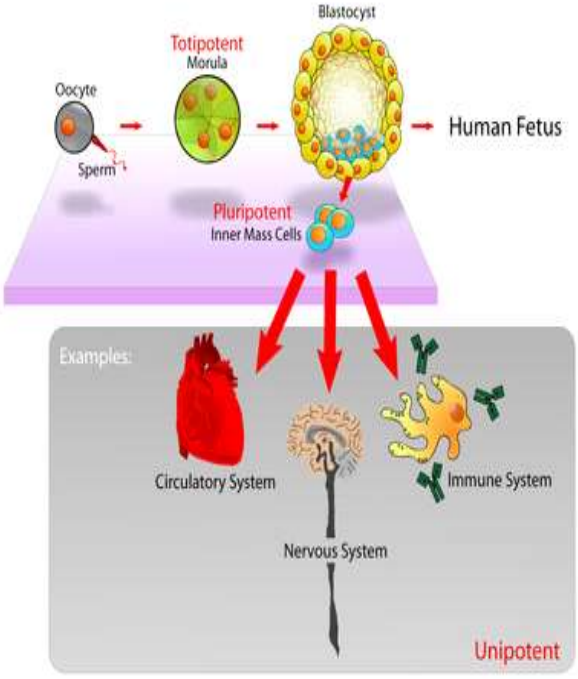

Figure3: Pluripotent, embryonic stem cells originate as inner cell mass (ICM) cells

Pluripotent, embryonic stem cells originate as inner cell mass (ICM) cells within a blastocyst. These stem cells can become any tissue in the body, excluding a placenta. Only cells from an

earlier stage of the embryo, known as the morula, are totipotent, able to become all tissues in the body and the extraembryonic placenta.

CLASSIFICATION

Stem cells are a class of undifferentiated cells that is able to differentiate into specialized cell types. Commonly, stem cells come from two main sources:

- Embryos formed during the blastocyst phase of embryological development (embryonic stem cells) and
- Adult tissue (adult stem cells).

Both types are generally characterized by their potency, or potential to differentiate into different cell types (such as skin, muscle, bone, etc.).

Adult stem cells

Adult or somatic stem cells exist throughout the body after embryonic development and are found inside of different types of tissue. These stem cells have been found in tissues such as the brain, bone marrow, blood, blood vessels, skeletal muscles, skin, and the liver. They remain in a quiescent or non-dividing state for years until activated by disease or tissue injury[4].

Adult stem cells can divide or self-renew indefinitely, enabling them to generate a range of cell types from the originating organ or even regenerates the entire original organ. It is generally thought that adult stem cells are limited in their ability to differentiate based on their tissue of origin, but there is some evidence to suggest that they can differentiate to become other cell types.

Embryonic stem cells

Embryonic stem cells are derived from a four- or five-day-old human embryo that is in the blastocyst phase of development. The embryos are usually extras that have been created in IVF (in vitro fertilization) clinics where several eggs are fertilized in a test tube, but only one is implanted into a woman.

Sexual reproduction begins when a male's sperm fertilizes a female's ovum (egg) to form a single cell called a zygote. The single zygote cell then begins a series of divisions, forming 2, 4, 8, 16 cells, etc. After four to six days - before implantation in the uterus - this mass of cells is called a blastocyst. The blastocyst consists of an inner cell mass (embryoblast) and an outer cell mass (trophoblast). The outer cell mass becomes part of the placenta, and the inner cell mass is the group of cells that will differentiate to become all the structures of an adult organism. This latter mass is the source of embryonic stem cells - totipotent cells (cells with total potential to develop into any cell in the body).

Figure4: 9-week Human Embryo from Ectopic Pregnancy creative commons license

In a normal pregnancy, the blastocyst stage continues until implantation of the embryo in the uterus, at which point the embryo is referred to as a fetus. This usually occurs by the end of the 10th week of gestation after all major organs of the body have been created[5].

However, when extracting embryonic stem cells, the blastocyst stage signals when to isolate stem

cells by placing the "inner cell mass" of the blastocyst into a culture dish containing a nutrient-rich broth. Lacking the necessary stimulation to differentiate, they begin to divide and replicate while maintaining their ability to become any cell type in the human body. Eventually, these undifferentiated cells can be stimulated to create specialized cells.

Stem cell cultures

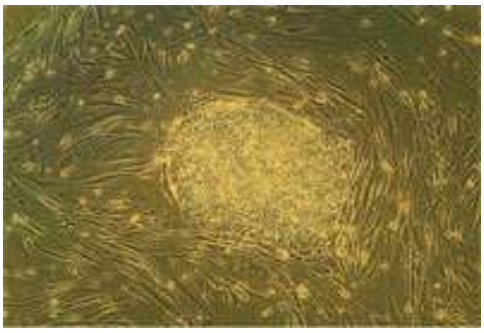

Figure4: Human embryonic stem cell colony

Stem cells are either extracted from adult tissue or from a dividing zygote in a culture dish. Once extracted, scientists place the cells in a controlled culture that prohibits them from further specializing or differentiating but usually allows them to divide and replicate. The process of growing large numbers of embryonic stem cells has been easier than growing large numbers of adult stem cells, but progress is being made for both cell types[6].

Stem cell lines

Once stem cells have been allowed to divide and propagate in a controlled culture, the collection of healthy, dividing, and undifferentiated cells is called a stem cell line. These stem cell lines are subsequently managed and shared among researchers. Once under control, the stem cells can be stimulated to specialize as directed by a researcher a process known as directed differentiation. Embryonic stem cells are able to differentiate into more cell types than adult stem cells.

Potency

Stem cells are categorized by their potential to differentiate into other types of cells. Embryonic stem cells are the most potent since they must become every type of cell in the body. The full classification includes:

- Totipotent - the ability to differentiate into all possible cell types. Examples are the zygote formed at egg fertilization and the first few cells that result from the division of the zygote.
- Pluripotent - the ability to differentiate into almost all cell types. Examples include embryonic stem cells and cells that are derived from the mesoderm, endoderm, and ectoderm germ layers that are formed in the beginning stages of embryonic stem cell differentiation.
- Multipotent - the ability to differentiate into a closely related family of cells. Examples include hematopoietic (adult) stem cells that can become red and white blood cells or platelets.
- Oligopotent - the ability to differentiate into a few cells. Examples include (adult) lymphoid or myeloid stem cells.
- Unipotent - the ability to only produce cells of their own type, but have the property of self-renewal required to be labeled a stem cell. Examples include (adult) muscle stem cells.

Embryonic stem cells are considered pluripotent instead of totipotent because they do not have the ability to become part of the extra-embryonic membranes or the placenta.

IDENTIFICATION OF STEM CELLS

Although there is not complete agreement among scientists of how to identify stem cells, most tests are based on making sure that stem cells are undifferentiated and capable of self-renewal. Tests are often conducted in the laboratory to check for these properties.

One way to identify stem cells in a lab, and the standard procedure for testing bone marrow or hematopoietic stem cell (HSC), is by transplanting one cell to save an individual without HSCs. If the stem cell produces new blood and immune cells, it demonstrates its potency[7].

Clonogenic assays (a laboratory procedure) can also be employed in vitro to test whether single cells can differentiate and self-renew. Researchers may also inspect cells under a microscope to see if they are healthy and undifferentiated or they may examine chromosomes.

To test whether human embryonic stem cells are pluripotent, scientists allow the cells to differentiate spontaneously in cell culture, manipulate the cells so they will differentiate to form specific cell types, or inject the cells into an immunosuppressed mouse to test for the formation of a teratoma (a benign tumor containing a mixture of differentiated cells).

Stem cells from this point of view are from one of three main types also known as germ layers: 1) ectoderm, 2) mesoderm, or 3) endoderm. In autism, the patients generally get all three stem types but the concentration may vary from patient to patient. The rationale is related to the need for brain, gut and immune healing. The graphic below can help to guide you through the cell types.

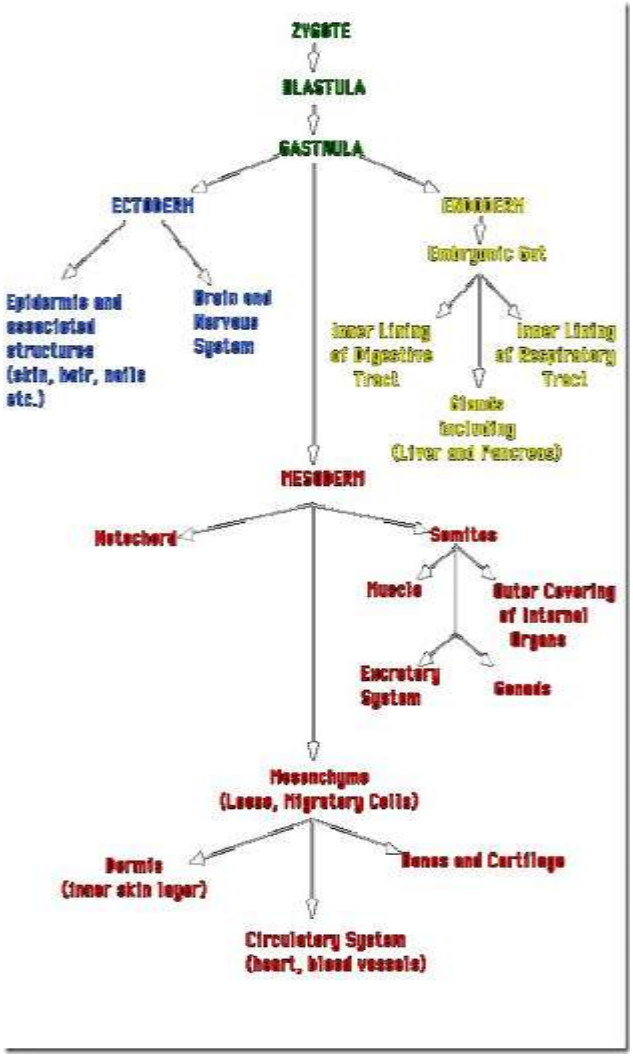

Figure5: Classification of cell.

And to further help you see this process in stem cell development see this graphic.

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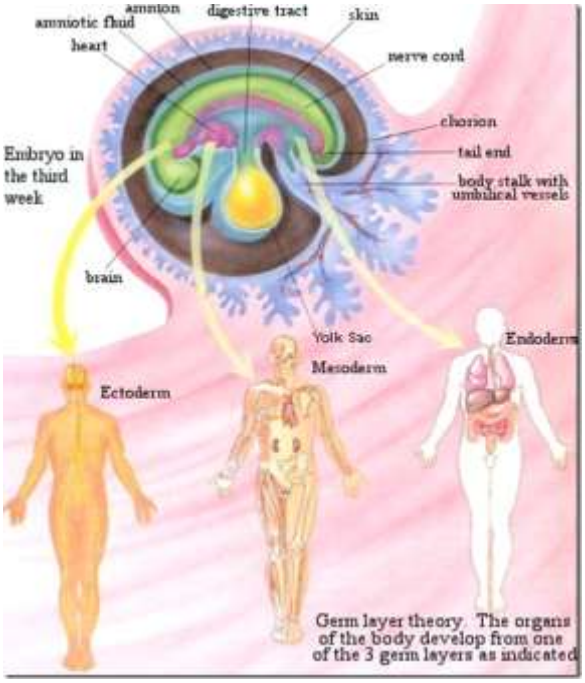

Figure6: Stem cell development

One of the philosophies expressed by Prof Karpenko goes like this: stem cells from designer laboratory creations and embryonic cells created by artificial fertilization have no history of regulated function as healthy human cells. By contrast, fetal derived stem cells have been taught by the system how they should behave. This just means they have been given their regulatory instructions on how to act like a team player. He believes this is important and I tend to agree with him on this.

Immediate effects of stem cell transplantation

The doctors at the clinic informed me we would most likely see immediate effects which could last up to 10 days. These effects are thought to foreshadow future more permanent changes to come. This is an intriguing observation. My take is that these effects are largely mediated by cell signaling chemicals in the suspension of the stem cells rather than by the direct action of stem cells. This would be especially true for the brain effects.

I was able to observe an immediate decrease in self-stimulation and hyperactivity in my step-son with his treatments. It was so profound that on the day we were supposed to get the second application (and it is nearly always a 2 day process separated by a day between) he actually asked to go to the clinic to see the doctors to get his shot. The physicians at EmCell claim they see this routinely where the children act much differently within 2 days. As hard as that is to accept, I was able to observe it firsthand. Another immediate effect is improved appetite and energy. Also observed within these first few days in improved sensory integration and functioning – especially for touch and auditory dysfunctions. Exactly how this happens so fast is hard to understand but it may have a lot to do with anti-inflammatory effects or other cell mediators.

Stem cell treatments

Stem cell treatments are a type of intervention strategy that introduces new cells into damaged tissue in order to treat disease or injury. Many medical researchers believe that stem cell treatments have the potential to change the face of human disease and alleviate suffering[8]. The ability of stem cells to self-renew and give rise to subsequent generations with variable degrees of differentiation capacities[9], offers significant potential for generation of tissues that can potentially replace diseased and damaged areas in the body, with minimal risk of rejection and side effects.

A number of stem cell therapies exist, but most are at experimental stages or costly, with the notable exception of bone marrow transplantation. Medical researchers anticipate that adult and embryonic stem cells will soon be able to treat cancer, Type 1 diabetes mellitus, Parkinson's disease, Huntington's disease, Celiac Disease, cardiac failure, muscle damage and neurological disorders, and many others.[3] Nevertheless, before stem cell therapeutics can be applied in the

clinical setting, more research is necessary to understand stem cell behavior upon transplantation as well as the mechanisms of stem cell interaction with the diseased/injured microenvironment[10].

Current treatments

Further information: Hematopoietic stem cell transplantation For over 30 years, bone marrows, and more recently, umbilical cord blood stem cells, have been used to treat cancer patients with conditions such as leukemia and lymphoma[11]. During chemotherapy, most growing cells are killed by the cytotoxic agents. These agents, however, cannot discriminate between the leukemia or neoplastic cells, and the hematopoietic stem cells within the bone marrow. It is this side effect of conventional chemotherapy strategies that the stem cell transplant attempts to reverse; a donor's healthy bone marrow reintroduces functional stem cells to replace the cells lost in the host's body during treatment.

Potential treatments

Brain damage

Stroke and traumatic brain injury lead to cell death, characterized by a loss of neurons and oligodendrocytes within the brain. Healthy adult brains contain neural stem cells which divide to maintain general stem cell numbers, or become progenitor cells. In healthy adult animals, progenitor cells migrate within the brain and function primarily to maintain neuron populations for olfaction (the sense of smell). Interestingly, in pregnancy and after injury, this system appears to be regulated by growth factors and can increase the rate at which new brain matter is formed. Although the reparative process appears to initiate following trauma to the brain, substantial recovery is rarely observed in adults, suggesting a lack of robustness.

Stem cells may also be used to treat brain degeneration, such as in Parkinson's and Alzheimer's disease[12].

Cancer

The development of gene therapy strategies for treatment of intra-cranial tumors offers much promise, and has shown to be successful in the treatment of some dogs; although research in this area is still at an early stage. Using conventional techniques, brain cancer is difficult to treat because it spreads so rapidly. Researchers at the Harvard Medical School transplanted human neural stem cells into the brain of rodents that received intracranial tumors. Within days, the cells migrated into the cancerous area and produced cytosine deaminase, an enzyme that converts a non-toxic pro-drug into a chemotherapeutic agent. As a result, the injected substance was able to reduce the tumor mass by 81 percent. The stem cells neither differentiated nor turned tumorigenic.[8] Some researchers believe that the key to finding a cure for cancer is to inhibit proliferation of cancer stem cells. Accordingly, current cancer treatments are designed to kill cancer cells. However, conventional chemotherapy treatments cannot discriminate between cancerous cells and others. Stem cell therapies may serve as potential treatments for cancer.[9] Research on treating Lymphoma using adult stem cells is underway and has had human trials. Essentially, chemotherapy is used to completely destroy the patient’s own lymphocytes, and stem cells injected, eventually replacing the immune system of the patient with that of the healthy donor.

Spinal cord injury

A team of Korean researchers reported on November 25, 2003, that they had transplanted multipotent adult stem cells from umbilical cord

blood to a patient suffering from a spinal cord injury and that following the procedure; she could walk on her own, without difficulty. The patient had not been able to stand up for roughly 19 years. For the unprecedented clinical test, the scientists isolated adult stem cells from umbilical cord blood and then injected them into the damaged part of the spinal cord.

According to the October 7, 2005 issue of The Week, University of California, Irvine researchers transplanted multipotent human fetal-derived neural stem cells into paralyzed mice, resulting in locomotor improvements four months later. The observed recovery was associated with differentiation of transplanted cells into new neurons and oligodendrocytes- the latter of which forms the myelin sheath around axons of the central nervous system, thus insulating neural impulses and facilitating communication with the brain.

In January 2005, researchers at the University of Wisconsin–Madison differentiated human blastocyst stem cells into neural stem cells, then into pre-mature motor neurons, and finally into spinal motor neurons, the cell type that, in the human body, transmits messages from the brain to the spinal cord and subsequently mediates motor function in the periphery. The newly generated motor neurons exhibited electrical activity, the signature action of neurons. Lead researcher Su-Chun Zhang described the process as "[teaching] the blastocyst stem cells to change step by step, where each step has different conditions and a strict window of time."

Transformation of blastocyst stem cells into motor neurons had eluded researchers for decades. While Zhang's findings were a significant contribution to the field, the ability of transplanted neural cells to establish communication with neighboring cells remains unclear. Accordingly, studies using chicken embryos as a model organism can be an effective proof-of-concept experiment. If functional, the new cells could be used to treat diseases like Lou Gehrig's disease, muscular dystrophy, and spinal cord injuries.

Heart damage

Several clinical trials targeting heart disease have shown that adult stem cell therapy is safe, effective, and equally efficient in treating old and recent infarcts.[13] Adult stem cell therapy for treating heart disease was commercially available in at least five continents at the last count (2007).

Possible mechanisms of recovery include:

- Generation of heart muscle cells
- Stimulation of growth of new blood vessels to repopulate damaged heart tissue
- Secretion of growth factors
- Assistance via some other mechanism

It may be possible to have adult bone marrow cells differentiate into heart muscle cells[13].

Haematopoiesis (blood cell formation)

The specificity of the human immune cell repertoire is what allows the human body to defend itself from rapidly adapting antigens. However, the immune system is vulnerable to degradation upon the pathogenesis of disease, and because of the critical role that it plays in overall defense; its degradation is often fatal to the organism as a whole. Diseases of hematopoietic cells are called hematopathology. The specificity of the immune cells is what allows recognition of foreign antigens, causing further challenges in the treatment of immune disease. Identical matches between donor and recipient must be made for successful transplantation treatments, but matches are uncommon, even between first-degree relatives. Research using both hematopoietic adult stem cells and embryonic stem cells has provided insight into the possible mechanisms and methods of treatment for many of these ailments.

Fully mature human red blood cells may be generated ex vivo by hematopoietic stem cells (HSCs), which are precursors of red blood cells. In this process, HSCs are grown together with stromal cells, creating an environment that mimics the conditions of bone marrow, the natural site of red blood cell growth. Erythropoietin, a growth factor, is added, coaxing the stem cells to complete terminal differentiation into red blood cells. Further research into this technique should have potential benefits to gene therapy, blood transfusion, and topical medicine.

Baldness

Hair follicles also contain stem cells, and some researchers predict research on these follicle stem cells may lead to successes in treating baldness through an activation of the stem cells progenitor cells. This treatment is expected to work by activating already existing stem cells on the scalp. Later treatments may be able to simply signal follicle stem cells to give off chemical signals to nearby follicle cells which have shrunk during the aging process, which in turn respond to these signals by regenerating and once again making healthy hair. Most recently, Dr. Aeron Potter of the University of California has claimed that stem cell therapy led to a significant and visible improvement in follicular hair growth. Results from his experiments are under review by the journal Science (journal).

Missing teeth

In 2004, scientists at King's College London discovered a way to cultivate a complete tooth in mice and were able to grow them stand-alone in the laboratory. Researchers are confident that this technology can be used to grow live teeth in human patients.

In theory, stem cells taken from the patient could be coaxed in the lab into turning into a tooth bud which, when implanted in the gums, will give rise to a new tooth, and would be expected to grow within two months. It will fuse with the jawbone and release chemicals that encourage nerves and blood vessels to connect with it. The process is similar to what happens when humans grow their original adult teeth.

Many challenges remain, however, before stem cells could be a choice for the replacement of missing teeth in the future.

Deafness

Heller has reported success in re-growing cochlea hair cells with the use of embryonic stem cells[13].

Blindness and vision impairment

Since 2003, researchers have successfully transplanted corneal stem cells into damaged eyes to restore vision. "Sheets of retinal cells used by the team are harvested from aborted fetuses, which some people find objectionable." When these sheets are transplanted over the damaged cornea, the stem cells stimulate renewed repair, eventually restore vision. The latest such development was in June 2005, when researchers at the Queen Victoria Hospital of Sussex, England were able to restore the sight of forty patients using the same technique. The group, led by Dr. Sheraz Daya, was able to successfully use adult stem cells obtained from the patient, a relative, or even a cadaver. Further rounds of trials are ongoing.

In April 2005, doctors in the UK transplanted corneal stem cells from an organ donor to the cornea of Deborah Catlyn, a woman who was blinded in one eye when acid was thrown in her eye at a nightclub. The cornea, which is the transparent window of the eye, is a particularly suitable site for transplants. In fact, the first successful human transplant was a cornea transplant. The absence of blood vessels within the cornea makes this area a relatively easy target for transplantation. The majority of corneal

transplants carried out today are due to a degenerative disease called keratoconus.

The University Hospital of New Jersey reports that the success rate for growth of new cells from transplanted stem cells varies from 25 percent to 70 percent.

In 2009, researchers at the University of Pittsburgh Medical center demonstrated that stem cells collected from human corneas can restore transparency without provoking a rejection response in mice with corneal damage.[22]

In January 2012, The Lancet published a paper[23] by Dr. Steven Schwartz, at UCLA's Jules Stein Eye Institute, reporting two women who had gone legally blind from macular degeneration had dramatic improvements in their vision after retinal injections of human embryonic stem cells.

Amyotrophic lateral sclerosis

Stem cells have resulted in significant locomotor improvements in rats with an Amyotrophic lateral sclerosis-like disease. In a rodent model that closely mimics the human form of ALS, animals were injected with a virus to kill the spinal cord motor nerves which mediate movement. Animals subsequently received stem cells in the spinal cord. Transplanted cells migrated to the sites of injury, contributed to regeneration of the ablated nerve cells, and restored locomotor function.

Graft vs. host disease and Crohn's disease

Phase III clinical trials expected to end in second-quarter 2008 were conducted by Osiris Therapeutics using their in-development product Prochymal, derived from adult bone marrow. The target disorders of this therapeutic are graft-versus-host disease and Crohn's disease.

Neural and behavioral birth defects

A team of researchers led by Prof. Joseph Yanai were able to reverse learning deficits in the offspring of pregnant mice who were exposed to heroin and the pesticide organophosphate. This was done by direct neural stem cell transplantation into the brains of the offspring. The recovery was almost 100 percent, as shown both in behavioral tests and objective brain chemistry tests. Behavioral tests and learning scores of the treated mice showed rapid improvement after treatment, providing results that rivaled non-treated mice. On the molecular level, brain chemistry of the treated animals was also restored to normal. Through the work, which was supported by the US National Institutes of Health, the US-Israel Binational Science Foundation and the Israel anti-drug authorities, the researchers discovered that the stem cells worked even in cases where most of the cells died out in the host brain.

The scientists found that before they die the neural stem cells succeed in inducing the host brain to produce large numbers of stem cells which repair the damage. These findings, which answered a major question in the stem cell research community, were published in January 2008 in the leading journal, Molecular Psychiatry. Scientists are now developing procedures to administer the neural stem cells in the least invasive way possible - probably via blood vessels, making therapy practical and clinically feasible. Researchers also plan to work on developing methods to take cells from the patient's own body, turn them into stem cells, and then transplant them back into the patient's blood via the blood stream. Aside from decreasing the chances of immunological rejection, the approach will also eliminate the controversial ethical issues involved in the use of stem cells from human embryos.

Diabetes

Diabetes patients lose the function of insulin-producing beta cells within the pancreas. Human embryonic stem cells may be grown in cell culture and stimulated to form insulin-producing cells that can be transplanted into the patient.

However, clinical success is highly dependent on the development of the following procedures:

- Transplanted cells should proliferate
- Transplanted cells should differentiate in a site-specific manner
- Transplanted cells should survive in the recipient (prevention of transplant rejection)
- Transplanted cells should integrate within the targeted tissue
- Transplanted cells should integrate into the host circuitry and restore function

Orthopaedics

Clinical case reports in the treatment of orthopaedic conditions have been reported. To date, the focus in the literature for musculoskeletal care appears to be on mesenchymal stem cells. Centeno et al. have published MRI evidence of increased cartilage and meniscus volume in individual human subjects. The results of trials that include a large number of subjects, are yet to be published. However, a published safety study conducted in a group of 227 patients over a 3-4 year period shows adequate safety and minimal complications associated with mesenchymal cell transplantation.

Wakitani has also published a small case series of nine defects in five knees involving surgical transplantation of mesenchymal stem cells with coverage of the treated chondral defects.

Wound healing

Stem cells can also be used to stimulate the growth of human tissues. In an adult, wounded tissue is most often replaced by scar tissue, which is characterized in the skin by disorganized collagen structure, loss of hair follicles and irregular vascular structure. In the case of wounded fetal tissue, however, wounded tissue is replaced with normal tissue through the activity of stem cells. A possible method for tissue regeneration in adults is to place adult stem cell "seeds" inside a tissue bed "soil" in a wound bed and allow the stem cells to stimulate differentiation in the tissue bed cells. This method elicits a regenerative response more similar to fetal wound-healing than adult scar tissue formation. Researchers are still investigating different aspects of the "soil" tissue that are conducive to regeneration[14].

Infertility

Culture of human embryonic stem cells in mitotically inactivated porcine ovarian fibroblasts (POF) causes differentiation into germ cells (precursor cells of oocytes and spermatozoa), as evidenced by gene expression analysis.[34]

Human embryonic stem cells have been stimulated to form Spermatozoon-like cells, yet still slightly damaged or malformed[13]. It could potentially treat azoospermia.

Clinical Trials

On January 23, 2009, the US Food and Drug Administration gave clearance to Geron Corporation for the initiation of the first clinical trial of an embryonic stem cell-based therapy on humans. The trials aimed evaluate the drug GRNOPC1, embryonic stem cell-derived oligodendrocyte progenitor cells, on patients with acute spinal cord injury. The trial was dicontinued

in November 2011 so that the company could focus on therapies in the "current environment of capital scarcity and uncertain economic conditions".

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