

An Introduction to Stem Cells

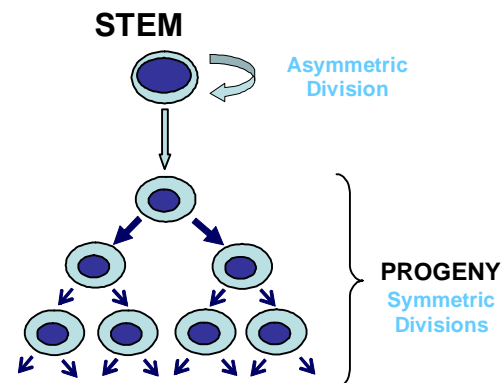
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Overview

Stem cells are cells that have the potential to replicate themselves for indefinite periods and to divide, producing one of themselves and one cell of a different type (**differentiation**). In humans, stem cells have been located in: the early stages of development after fertilization (around 5-6 days); the umbilical cord and placenta; and in several adult organs.

Regardless of their source all stem cells have two general properties:

- 1) *Stem cells are capable of dividing and renewing themselves for long periods.* Unlike muscle cells, blood cells, or nerve cells – which do not replicate themselves – stem cells can divide continuously and keep their innate properties.
- 2) *Stem cells are undifferentiated and can give rise to multiple cell-types.* Stem cells do not have any tissue-specific structures that allow them to perform specialized functions. They cannot carry molecules of oxygen through the bloodstream like red blood cells or release signals to other cells, such as permitting the body to move or speak, as nerve cells do. Although stem cells do not have any tissue-specific structures, they can give rise to differentiated cells, including red blood cells and nerve cells.



Stem Cell Division. The stem cell divides asymmetrically, generating one cell that repeats the feat indefinitely, and one cell that continues to divide symmetrically, dividing each time into two equal daughter cells. Reproduced with permission from the ISSCR.

Stem cells have varying abilities to differentiate into different cell-types. One type of stem cell can give rise to any other cell-type of a given organism (for example, an embryonic stem cell). Other stem cells can only give rise to cells of a given tissue type (for example, bone marrow can produce blood stem cells) or only give rise to a few cell-types in a given tissue.

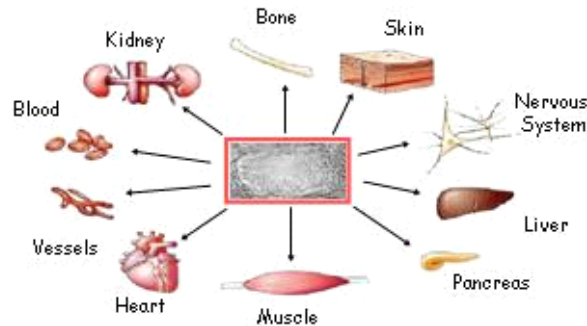
Scientists are just beginning to understand the **signals** in a body which can trigger cell differentiation. These signals can be created within a cell, triggered by a cell's genes, or by a neighboring cell that releases chemicals to promote differentiation in other cells. Determining what these signals are and what stem cells require to differentiate into different cell-types is an important research area necessary to utilize stem cells for therapies.

When cells differentiate, their abilities become more restricted. They often follow only a few prescribed pathways and can lose the capacity to replicate themselves. The ability of stem cells to replicate and remain unspecialized

until they are needed is an important area of research vital to understanding human development.

Stem cells offer a new look at old problems and diseases such as burns and diabetes. Although the field is relatively new, the impact of new discoveries could profoundly change medical research and therapy. Many of these new approaches involve the use of **somatic cell nuclear transfer** (sometimes known as **therapeutic cloning**) to produce recipient-specific tissue by creating embryonic stem cell lines.

This new area of research has great potential, but it is not without its controversies. Many ethical dilemmas are produced with the creation and destruction of human blastocysts as well as the potential to clone an entire human being (**reproductive cloning**). No matter where society designates the boundary to be for this research, or whether or not stem cells can live up to our high expectations, a great deal can be learned through careful and thoughtful studies.



Embryonic Stem Cells. The potential of human embryonic stem cell colonies shown in the middle could potentially be grown in culture to the illustrated organs and more. Reproduced with permission from the ISSCR.

Embryonic Stem Cells

Embryonic stem cells are derived exclusively from a fertilized egg that has been grown *in vitro* for 5 to 6 days to form a **blastocyst**. Within a blastocyst there is a small group of about 30 cells called the **inner cell mass**, which will give rise to the hundreds of highly specialized cells needed to make up an adult organism. Embryonic stem cells are obtained from this inner cell mass. For research purposes, embryonic stem cells are produced specifically from eggs that have been fertilized *in vitro*, or in a laboratory and not inside a woman's body, or ***in vivo***. Embryonic stem cells can come from a frozen fertilized egg or an egg which is fertilized *in vitro*.

Cell-Types Embryonic Stem Cells* Have Been Grown Into

Smooth Muscle
Heart Muscle
Nerves
Bone
Cartilage
Kidney
Red and White Blood Cells
Pancreas
Liver
Yolk Sac
Lymph Nodes
Endoderm

* Human

Embryonic stem cells can and do differentiate into all the specialized cells in the adult body. They could be induced to provide an unlimited source of specific and clinically important adult cells such as bone, muscle, liver or blood cells.

Adult Stem Cells

Adult stem cells are unspecialized or undifferentiated cells found among specialized cells in an adult tissue or organ. In some adult tissues, such as in bone marrow,

Cell-Types Adult Stem Cells* Have Been Grown Into
Red and White Blood Cells
Skin
Fat
Heart Muscle
Skeletal Muscle
Liver
Digestive Tract
Nerves
Cartilage
Pancreas
Cornea
* Human

muscle, or brain tissue, discrete populations of adult stem cells generate replacements for cells that are lost through disease, injury, or normal wear and tear. Adult stem cells are thought to reside in an area of each tissue where they may remain **quiescent**, or non-dividing, for many years until they are activated by disease or tissue injury. Where they are found, adult stem cells consist of a very small population of cells within each tissue.

Some adult stem cells retain the ability to form into specialized tissues other than the one from which they originated. For example, blood (**hematopoietic**) cells can differentiate into nerve, skeletal muscle, cardiac muscle, or liver cells. Brain stem cells can differentiate into blood or skeletal muscle cells.

However, adult stem cells have a limited number of tissues they can differentiate into and do not have the same potential as embryonic stem cells to become any cell-type.

The environment that adult stem cells grow in has an important, but poorly understood, effect on their fate. The relationship between the adult stem cell environment and its ability to differentiate into other cell-types has also not been fully explained.

Distinctions between Embryonic and Adult Stem Cells

Most importantly, adult and embryonic stem cells differ in the type of differentiated cells they can become. While embryonic stem cells can be induced to differentiate into any cell-type, adult stem cells cannot. Most adult cells can only differentiate into the types of cells found in their environment or their particular tissue or organ from which they reside. Therefore in many vital organs, adults do not have the stem cells necessary to regenerate damaged areas; thus scar tissue will develop instead.

Another key difference between embryonic and adult stem cells is the volume of cells one can isolate and grow *in vitro*. Large numbers of embryonic stem cells can be grown *in vitro* from a single blastocyst. On the contrary, adult stem cells are rare and methods of growing them still need to be perfected. In addition, due to their limited numbers, it is difficult to isolate a group of adult stem cells in pure form, without having them contaminated with differentiated cells.

Potential Uses of Stem Cells

Stem Cells

While stem cell research is in its infancy and many of its proposed uses are hypothetical, the research has generated excitement among many scientists for its potential. One of the vital components of ongoing work is understanding the very nature of these cells; that is, to determine the conditions necessary to maintain undifferentiated stem cells as well as differentiating them along specific pathways. In order to truly determine whether or not these cells can be used therapeutically, investment must be made to understand the nature of the cells.

Although we are only beginning to discover what stem cells are capable of doing, scientists have proposed several potential uses.

- 1) *Abnormal Cell Division.* Many serious medical conditions, such as cancer and birth defects, are due to abnormal cell divisions or the inability of cells to turn themselves on and off properly. Having a better understanding of stem cells and their genetic and molecular controls would yield information about diseases and potential strategies for therapies.
- 2) *Drug Testing.* Stem cells could be used to test new drugs or medications by differentiating them to the particular cell-types that the drugs are targeting. This would offer a short-cut for scientists to sort out chemicals that can be used to treat diseases. By testing new drugs on stem cell lines, we could perform rapid screening of hundreds of thousands of chemicals that now are tested by more time-consuming processes. This could also potentially decrease the time that it takes to get a drug to market.
- 3) *Cell-Based Therapies.* Stem cells could be used for **cell-based therapies**. Stem cells could be directed to differentiate to a specific cell-type that then could be used as a renewable source of replacement cells and tissues. In order to be useful for cell-based therapies, stem cells must be made to:

- *Differentiate into desired cell-types.* It is necessary for stem cell techniques to be improved until they can consistently and efficiently differentiate into a specific cell or type of cells without contamination by undifferentiated or improperly differentiated cells.
- *Proliferate extensively and generate sufficient quantities of tissue.* The protocols for differentiating stem cells need to be refined so that large quantities of tissue can be produced in a relatively efficient manner.
- *Survive in the recipient after the transplant.* Scientists must determine that the cells are healthy and viable after transplantation. They also should establish that the stem cells localized to the correct tissue in the recipient.
- *Function appropriately for the duration of the recipient's life.* Not only do the cells need to be localized and survive, but they must also behave like the original cells. Currently, there are not enough data showing that stem cells are functional in their new environment when they are transplanted into organs. For cell-based therapies to be successful, the new cells need to function properly and interact properly with the original tissue.

Stem Cell Research Could Potentially Help:

Parkinson's
Alzheimers
Spinal cord injury
Stroke
Burns
Heart disease
Diabetes
Osteoarthritis
Rheumatoid arthritis
Birth Defects
Infertility
Pregnancy Loss
Leukemia
Brain Cancer
Muscular Dystrophy
Sickle Cell Anemia
Brain Trauma/Damage
Liver Disease
Metabolic Disorders
Deafness
Macular Degeneration
Retinitis Pigmentosa
Organ donation

- *Avoid harming the patient in any way.* One concern about using undifferentiated cells or stem cells is the risk of the stem cells having genetic abnormalities which could cause them to be cancerous or to be rejected due to tissue immune incompatibility. Adequate testing is necessary to make sure the cells used are healthy.

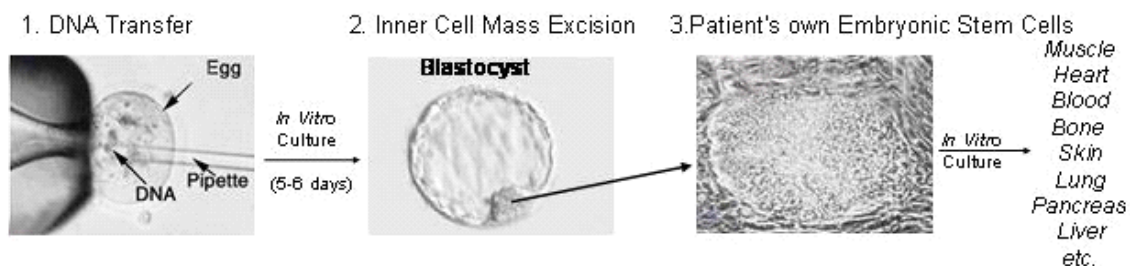
Embryonic Stem Cells

One of the most promising uses for embryonic stem cells is the study of the complex events that occur during human development. The earliest stages of human development have previously been difficult or impossible to study. By using embryonic stem cells, these studies can be performed with the goal of preventing or treating birth defects, infertility, and pregnancy loss.

The use of embryonic stem cells can also help scientists identify how undifferentiated cells become differentiated. Since these cells have the ability to become any type of cell in the adult body, they have a larger potential for medically viable tissues which can be derived and used in cell-based therapies.

Cloning

Somatic cell nuclear transfer is when the genetic material (**nucleus**) of an unfertilized egg is removed and replaced with the genetic material of a normal cell. The egg is then activated and allowed to grow. After it is allowed to grow into a blastocyst, embryonic stem cells are obtained from the inner cell mass. These embryonic stem cells can then be induced to become other differentiated cell-types.



Nuclear Transfer Procedure. Image 1: DNA is being introduced into an egg; Image 2: After 5-6 days the egg has developed into a blastocyst; Image 3: Cultured embryonic stem cells, obtained from the inner cell mass. Reproduced with permission from the ISSCR.

Much of the promise for embryonic stem cells lies in the potential of **deriving** or creating cell lines which are specific to a person. This technique can be used to create cell lines and study the development of different diseases (sometime call therapeutic cloning). For instance, by using a skin cell from a patient suffering with Parkinson's disease one could create a cell line that would show the researcher how the cell progressed from a normal to a diseased state. Not only could scientists study specific genetic diseases, but they could also create tissues that are compatible with the original donor.

Further, this technique can also be used to create tissues that are recipient-specific. In organ and tissue transplantation, a great concern is the rejection of transplanted tissue

by the recipients' immune system. If new cell lines were created to be identical to the recipient, this would no longer be a problem. Researchers from South Korea were the first to successfully clone human embryonic stem cell lines using somatic cell nuclear transfer. Their results were published in *Science* (Hwang et al, 2004).

Reproductive Cloning is when an egg undergoes somatic cell nuclear transfer and the resulting cell is allowed to grow to an infant that is an exact genetic copy of the somatic cell donor. Attempts at reproductive cloning have been error-prone and inefficient, resulting in the failure of most clones to develop. The most famous clone, Dolly (a sheep), was only created after multiple attempts and failures and then lived a shortened life (Wilmut et al, 1997).

Case Study: Juvenile Diabetes and Stem Cell Research

Juvenile diabetes, also known as type 1 diabetes, is essentially an **autoimmune** disease where one's own body starts attacking itself. In juvenile diabetes the body specifically destroys a pancreas cell, the **β -cell**, which produces **insulin**. Insulin is an important hormone that balances blood sugar levels. Unregulated sugar levels in the blood can lead to severe problems such as kidney failure, blindness, stroke, and even death. Patients with juvenile diabetes are required to take multiple injections of insulin daily or have a continuous infusion of insulin through a pump just to survive. Also, they must constantly monitor their food intake and daily activities.

Scientists have been working for years to find a cure and are extremely optimistic about the potential use of stem cells to replace destroyed β -cells. In a recently published study using mice, Harvard researchers determined that new β -cells in the pancreas are formed through the replication of pre-existing β -cells, rather than adult stem cells creating new β -cells. These are the very cells being attacked and therefore their numbers are limited. This result means that in order to cure juvenile diabetes, scientists must rely on another source of β -cells such as embryonic stem cells to generate new β -cells.

Glossary

adult stem cell - An unspecialized or undifferentiated cell found among specialized cells in a tissue or organ, which can renew itself and differentiate into a specialized cell.

autoimmune disease – A disease where ones own body starts attacking itself and destroying ones own cells.

β-cell – A cell in the pancreas which is responsible for the production and regulation of insulin.

blastocyst – A preimplanted embryo of 30-150 cells that is 5-6 days-old.

cell-based therapies –Treatment in which stem cells are induced to differentiate into the specific cell type required to repair damaged or depleted adult cell populations or tissues.

characterizing stem cells – Determining how a cell grows, where the cell came from, how it was derived, and if there are any chromosomal abnormalities.

cloning – In biology, it is the act of producing an exact copy of a sequence of DNA, cell, tissue, or organism.

Department of Human and Health Services (DHHS) - The United States government's principal agency for protecting the health of all Americans. It provides essential human services, especially for those who are least able to help themselves.

deriving – The creation of a cell line from one original cell or set of cells.

differentiation – The process of unspecialized cells transforming into specialized cells.

embryo – In humans, the developing organism from the time of fertilization until the end of the eight week, when it become known as a fetus.

embryonic stem cell - An unspecialized or undifferentiated cell found in the inner cell mass of a blastocyst, which can renew itself and differentiate into a specialized cell.

fetus – A developing human from the eighth week after fertilization to birth.

gamete – a mature sexual reproductive cell (sperm or egg) having a single set of unpaired chromosomes.

hematopoietic stem cell – An adult stem cell from which all white and red blood cells evolve.

Human Fertilisation and Embryology Authority (HFEA) – The governmental authority in the United Kingdom that regulates in vitro fertilization and embryo research.

inner cell mass – A small group of about 30 cells in a blastocyst which will gives rise to the hundreds of highly specialized cells needed to make up an adult organism; embryonic stem cells are derived from this group.

insulin – A hormone in the body that balances blood sugar levels.

in vitro – From the Latin for “in glass”; in a laboratory dish, test tube, or artificial environment.

in vitro fertilization (IVF) – An assisted reproduction technique in which fertilization is accomplished outside the body.

in vivo – In the living subject; the natural environment.

juvenile diabetes – Also known as type 1 diabetes, it is an autoimmune disease where the β-cells in the pancreas are destroy and therefore the individual loses some or all of their ability to regulate and produce insulin. Left untreated it can have severe side effects such as kidney failure, blindness, stroke and even death.

Medical Research Council (MRC) - The national organization in the United Kingdom that promotes research in all areas of medical and related science.

National Bioethics Advisory Council (NBAC) - A committee of experts during the Clinton administration that was formed in 1995 to provide advice and make recommendation to appropriate government entities related to bioethical issues. Their charter expired in October 2001.

National Institutes of Health (NIH) – An agency of the Department of Human and Health Services, its mission is the pursuit of knowledge about nature and behavior of living systems. It provides leadership and direction to programs designed to improve the health by conducting and supporting research: in the causes, diagnosis, prevention, and cure of human diseases; in the processes of human growth and development; in the biological effects of environmental contaminants; in the understanding of mental, addictive and physical disorders; in directing programs for the collection, dissemination, and exchange of information in medicine and health, including the development and support of medical libraries and the training of medical librarians and other health information specialists.

nucleus – A structure within a living cell that contains the cell's DNA and controls its metabolism, growth, and reproduction.

oocytes – A female cell that develops into an ovum (egg) after meiosis; an egg before maturation.

ovum (plural is ova) – The female reproductive cell or egg.

pluripotent – The ability of a single cell to develop into many different cell types of the body.

President's Council on Bioethics (PCB) - A committee of experts during the Bush administration that was formed in 2001 (after the NBAC was disbanded) to provide the President with advice on bioethical issues that may emerge as a result of biomedical science and technology.

proliferation – Expansion of a population of cells by the continuous division of single cells into two identical cells.

quiescent – A cell that does not divide or replicate.

reproductive cloning - When an egg undergoes somatic cell nuclear transfer and the resulting cell is allowed to grow to an infant that is an exact copy of the donor.

signals – Internal and external factors that control the changes in cell structure and function.

somatic cell – Any cell of a plant or animal other than the germ (sperm or egg) or germ precursor cell.

somatic cell nuclear transfer - When the genetic material (nucleus) of an egg is removed and replaced with the genetic material of a normal cell.

stem cell - An unspecialized cell that can replicate itself for indefinite periods through cell division and under certain conditions become a specialized cell.

therapeutic cloning - When embryonic stem cells created by somatic cell nuclear transfer are studied *in vitro* and used for cell-based therapies, but never are implanted in a female or grown past 14 days.

undifferentiated cell – A primitive cell that does not have any tissue-specific structures that allows it to perform specialized functions. Not having changed to become a specialized cell.

zygote – The cell (and the organism that develops from the cell) resulting from the union of an ovum and spermatozoon (also referred to as a fertilized ovum).

Further Suggested Readings

Introduction to Stem Cells

- (1) International Society for Stem Cell Research: www.isscr.org
- (2) NIH, Stem Cell Basics: <http://stemcells.nih.gov/info/basics/>
- (3) National Research Council and Institute of Medicine. (2002) Stem Cells and the Future of Regenerative Medicine. Washington D.C.: National Academy Press
- (4) Embryonic Stem Cell Research at the University of Wisconsin-Madison: <http://www.news.wisc.edu/packages/stemcells/facts.html#1>
- (5) National Parkinson Foundation: <http://www.parkinson.org/site/apps/s/content.asp?c=9dJFJLPwB&b=108269&ct=153765>
- (6) Juvenile Diabetes Research Foundation: www.jdrf.org
- (7) Hwang, W.S., et. al. (2004) Evidence of a Pluripotent Human Embryonic Stem Cell Line Derived from a Cloned Blastocyst. Science 303:1669-74.
- (8) Wilmut, I., et. al. (1997) Viable Offspring Derived from Fetal and Adult Mammalian Cells. Nature 385:810-13.