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STEM CELLS-MODERN APPROACH IN MEDICINE

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Abstract

Stem cells have the remarkable potential to develop into many different cell types in the body during early life and growth. In addition, in many tissues they serve as a sort of internal repair system, dividing essentially without limit to replenish other cells as long as the person or animal is still alive. When a stem cell divides, each new cell has the potential either to remain a stem cell or become another type of cell with a more specialized function, such as a muscle cell, a red blood cell, or a brain cell. Stem cells are distinguished from other cell types by two important characteristics. Until recently, scientists primarily worked with two kinds of stem cells from animals and humans: embryonic stem cells and non-embryonic "somatic" or "adult" stem cells. The functions and characteristics of these cells will be explained in this document. Scientists discovered ways to derive embryonic stem cells from early mouse embryos nearly 30 years ago, in 1981. The detailed study of the biology of mouse stem cells led to the discovery, in 1998, of a method to derive stem cells from human embryos and grow the cells in the laboratory. These cells are called human embryonic stem cells. Stem cells are important for living organisms for many reasons. Given their unique regenerative abilities, stem cells offer new potentials for treating diseases such as diabetes, and heart disease. However, much work remains to be done in the laboratory and the clinic to understand how to use these cells for cell-based therapies to treat disease, which is also referred to as regenerative or reparative medicine. Laboratory studies of stem cells enable scientists to learn about the cells essential properties and what makes them different from specialized cell types. Scientists are already using stem cells in the laboratory to screen new drugs and to develop model systems to study normal growth and identify the causes of birth defects. Research on stem cells continues to advance knowledge about

how an organism develops from a single cell and how healthy cells replace damaged cells in adult organisms. Stem cell research is one of the most fascinating areas of contemporary biology, but, as with many expanding fields of scientific inquiry, research on stem cells raises scientific questions as rapidly as it generates new discoveries. This review focuses on these issues with illustrative and descriptive information.

Key Words: Stem cells, Embryonic stem cells, medicine, diseases.

Introduction:

Stem cells have the remarkable potential to develop into many different cell types in the body during early life and growth. In addition, in many tissues they serve as a sort of internal repair system, dividing essentially without limit to replenish other cells as long as the person or animal is still alive. When a stem cell divides, each new cell has the potential either to remain a stem cell or become another type of cell with a more specialized function, such as a muscle cell, a red blood cell, or a brain cell. Human embryonic stem cells burst into the headlines in 1998 and have made regular appearances ever since. Stem cells promise to be a powerful new technology that can't be ignored. Proponents say they will revolutionize medicine, while opponents call them Frankenstein technology.

Stem cells are distinguished from other cell types by two important characteristics. First, they are unspecialized cells capable of renewing themselves through cell division, sometimes after long periods of inactivity. Second, under certain physiologic or experimental conditions, they can be induced to become tissue- or organ-specific cells with special functions. In some organs, such as the gut and bone marrow, stem cells regularly divide to repair and replace worn out or damaged tissues. In other organs, however, such as the pancreas and the heart, stem cells only divide under special conditions.

Until recently, scientists primarily worked with two kinds of stem cells from animals and humans: embryonic stem cells and non-embryonic "somatic" or "adult" stem cells. The functions and characteristics of these cells will be explained in this document. Scientists discovered ways to derive embryonic stem cells from early mouse embryos nearly 30 years ago, in 1981. The detailed study of the biology of mouse stem cells led to the discovery, in 1998, of a method to derive stem cells from human embryos and grow the cells in the laboratory. These cells are called human embryonic stem cells. The embryos used in these studies were created for reproductive purposes through *in vitro* fertilization procedures. When they were no longer needed for that purpose, they were donated for research with the

informed consent of the donor. In 2006, researchers made another breakthrough by identifying conditions that would allow some specialized adult cells to be "reprogrammed" genetically to assume a stem cell-like state. This new type of stem cell, called induced pluripotent stem cells (iPSCs).

Stem cells are important for living organisms for many reasons. In the 3- to 5-day-old embryo, called a blastocyst, the inner cells give rise to the entire body of the organism, including all of the many specialized cell types and organs such as the heart, lung, skin, sperm, eggs and other tissues. In some adult tissues, such as bone marrow, muscle, and brain, discrete populations of adult stem cells generate replacements for cells that are lost through normal wear and tear, injury, or disease.

Given their unique regenerative abilities, stem cells offer new potentials for treating diseases such as diabetes, and heart disease. However, much work remains to be done in the laboratory and the clinic to understand how to use these cells for cell-based therapies to treat disease, which is also referred to as regenerative or reparative medicine. Laboratory studies of stem cells enable scientists to learn about the cells essential properties and what makes them different from specialized cell types. Scientists are already using stem cells in the laboratory to screen new drugs and to develop model systems to study normal growth and identify the causes of birth defects.

Research on stem cells continues to advance knowledge about how an organism develops from a single cell and how healthy cells replace damaged cells in adult organisms. Stem cell research is one of the most fascinating areas of contemporary biology, but, as with many expanding fields of scientific inquiry, research on stem cells raises scientific questions as rapidly as it generates new discoveries.

Embryonic stem cells

Embryonic stem cells, as their name suggests, are derived from embryos. Most embryonic stem cells are derived from embryos that develop from eggs that have been fertilized *in vitro*-in an *in vitro* fertilization clinic-and then donated for research purposes with informed consent of the donors. They are *not* derived from eggs fertilized in a woman's body. The embryos from which human embryonic stem cells are derived are typically four or five days old and are a hollow microscopic ball of cells called the blastocyst. The blastocyst includes three structures: the trophoblast, which is the layer of cells that surrounds the blastocoel, a hollow cavity inside the blastocyst; and the inner cell mass, which is a group of cells at one end of the blastocoel that develop into the embryo proper.

How are embryonic stem cells grown in the laboratory?

Growing cells in the laboratory is known as cell culture. Human embryonic stem cells are isolated by transferring the inner cell mass into a plastic laboratory culture dish that contains a nutrient broth known as culture medium. The cells divide and spread over the surface of the dish. The inner surface of the culture dish is typically coated with mouse embryonic skin cells that have been treated so they will not divide. This coating layer of cells is called a feeder layer. The mouse cells in the bottom of the culture dish provide the inner cell mass cells a sticky surface to which they can attach. Also, the feeder cells release nutrients into the culture medium. Researchers have devised ways to grow embryonic stem cells without mouse feeder cells. This is a significant scientific advance because of the risk that viruses or other macromolecules in the mouse cells may be transmitted to the human cells. The process of generating an embryonic stem cell line is somewhat inefficient, so lines are not produced each time an inner cell mass is placed into a culture dish. However, if the plated inner cell mass cells survive, divide and multiply enough to crowd the dish, they are removed gently and plated into several fresh culture dishes. The process of re-plating or sub culturing the cells is repeated many times and for many months. Each cycle of sub culturing the cells is referred to as a passage. Once the cell line is established, the original cells yield millions of embryonic stem cells. Embryonic stem cells that have proliferated in cell culture for six or more months without differentiating, are pluripotent, and appear genetically normal are referred to as an embryonic stem cell line. At any stage in the process, batches of cells can be frozen and shipped to other laboratories for further culture and experimentation.

How are embryonic stem cells stimulated to differentiate?

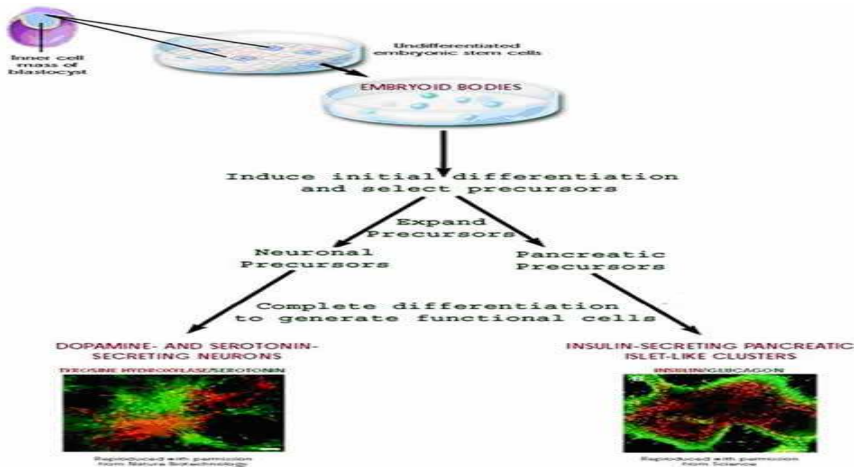

Figure-1: Directed differentiation of mouse embryonic stem cells (© 2001 Terese Winslow).

As long as the embryonic stem cells in culture are grown under appropriate conditions, they can remain undifferentiated (unspecialized). But if cells are allowed to clump together to form embryoid bodies, they begin to differentiate spontaneously. They can form muscle cells, nerve cells, and many other cell types. Although spontaneous differentiation is a good indication that a culture of embryonic stem cells is healthy, it is not an efficient way to produce cultures of specific cell types.

So, to generate cultures of specific types of differentiated cells-heart muscle cells, blood cells, or nerve cells, for example-scientists try to control the differentiation of embryonic stem cells. They change the chemical composition of the culture medium, alter the surface of the culture dish, or modify the cells by inserting specific genes. Through years of experimentation, scientists have established some basic protocols or "recipes" for the directed differentiation of embryonic stem cells into some specific cell types (Figure 1).

If scientists can reliably direct the differentiation of embryonic stem cells into specific cell types, they may be able to use the resulting, differentiated cells to treat certain diseases in the future. Diseases that might be treated by transplanting cells generated from human embryonic stem cells include Parkinson's disease, diabetes, traumatic spinal cord injury, Duchenne's muscular dystrophy, heart disease, and vision and hearing loss.

Adult stem cells

An adult stem cell is thought to be an undifferentiated cell, found among differentiated cells in a tissue or organ that can renew it and can differentiate to yield some or all of the major specialized cell types of the tissue or organ. The primary roles of adult stem cells in a living organism are to maintain and repair the tissue in which they are found. Scientists also use the term somatic stem cell instead of adult stem cell, where somatic refers to cells of the body (not the germ cells, sperm or eggs). Unlike embryonic stem cells, which are defined by their origin (the inner cell mass of the blastocyst), the origin of adult stem cells in some mature tissues is still under investigation.

Research on adult stem cells has generated a great deal of excitement. Scientists have found adult stem cells in many more tissues than they once thought possible. This finding has led researchers and clinicians to ask whether adult stem cells could be used for transplants. In fact, adult hematopoietic, or blood-forming, stem cells from bone marrow have been used in transplants for 40 years. Scientists now have evidence that stem cells exist in the brain and the heart. If the

differentiation of adult stem cells can be controlled in the laboratory, these cells may become the basis of transplantation-based therapies.

The history of research on adult stem cells began about 50 years ago. In the 1950's, researchers discovered that the bone marrow contains at least two kinds of stem cells. First population, called hematopoietic stem cells, forms all the types of blood cells in the body. Second population, called bone marrow stromal stem cells (also called mesenchymal stem cells, or skeletal stem cells by some), were discovered a few years later. These non-hematopoietic stem cells make up a small proportion of the stromal cell population in the bone marrow, and can generate bone, cartilage, fat, cells that support the formation of blood, and fibrous connective tissue (Figure 2). In the 1960's, scientists who were studying rats discovered two regions of the brain that contained dividing cells that ultimately become nerve cells. Despite these reports, most scientists believed that the adult brain could not generate new nerve cells. It was not until the 1990's that scientists agreed that the adult brain does contain stem cells that are able to generate the brain's three major cell types-astrocytes and oligodendrocytes, which are non-neuronal cells, and neurons, or nerve cells.

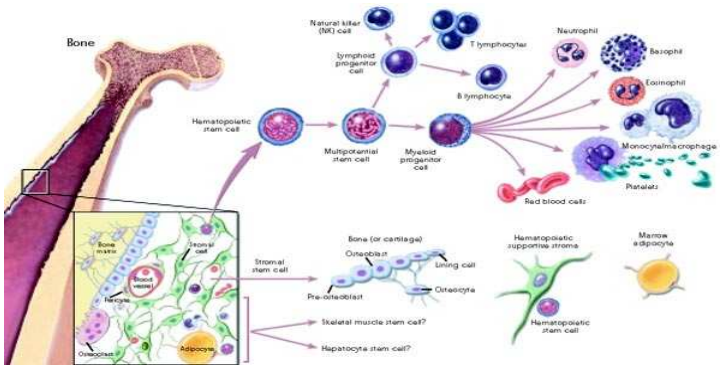

Figure 2.Hematopoietic and stromal stem cell differentiation. (© 2001 Terese Winslow).

Where are adult stem cells found, and what do they normally do?

Adult stem cells have been identified in many organs and tissues, including brain, bone marrow, peripheral blood, blood vessels, skeletal muscle, skin, teeth, heart, gut, liver, ovarian epithelium, and testis. They are thought to reside in a specific area of each tissue (called a "stem cell niche"). In many tissues, current evidence suggests that some types of stem cells are pericytes, cells that compose the outermost layer of small blood vessels. Stem cells may remain quiescent (non-dividing) for long periods of time until they are activated by a normal need for more cells to maintain tissues, or by disease or tissue injury.

Typically, there is a very small number of stem cells in each tissue, and once removed from the body, their capacity to divide is limited, making generation of large quantities of stem cells difficult. Scientists in many laboratories are trying to find better ways to grow large quantities of adult stem cells in cell culture and to manipulate them to generate specific cell types so they can be used to treat injury or disease. Some examples of potential treatments include regenerating bone using cells derived from bone marrow stroma, developing insulin-producing cells for Type-I diabetes, and repairing damaged heart muscle following a heart attack with cardiac muscle cells.

What is known about adult stem cell differentiation?

Stem Cells – Future Treatment of Heart Disease

Cardiovascular disease (CVD), which includes hypertension, coronary heart disease, stroke, and congestive heart failure, has ranked as the number one cause of death in the United States every year since 1900 except 1918, when the nation struggled with an influenza epidemic. Nearly 2600 Americans die of CVD each day, roughly one person every 34 seconds. Given the aging of the population and the relatively dramatic recent increases in the prevalence of cardiovascular risk factors such as obesity and Type-II diabetes, CVD will be a significant health concern well into the 21st century.

Cardiovascular disease can deprive heart tissue of oxygen, thereby killing cardiac muscle cells (cardiomyocytes). This loss triggers a cascade of detrimental events, including formation of scar tissue, an overload of blood flow and pressure capacity, the overstretching of viable cardiac cells attempting to sustain cardiac output, leading to heart failure, and eventual death. Restoring damaged heart muscle tissue, through repair or regeneration, is therefore a potentially new strategy to treat heart failure. The use of embryonic and adult-derived stem cells for cardiac repair is an active area of research. A number of stem cell types, including Embryonic Stem (ES) cells, cardiac stem cells that naturally reside within the heart, myoblasts (muscle stem cells), adult bone marrow-derived cells including mesenchymal cells (bone marrow-derived cells that give rise to tissues such as muscle, bone, tendons, ligaments, and adipose tissue), endothelial progenitor cells (cells that give rise to the endothelium, the interior lining of blood vessels), and umbilical cord blood cells, have been investigated as possible sources for regenerating damaged heart tissue. All have been explored in mouse or rat models, and some have been tested in larger animal models, such as pigs.

A few small studies have also been carried out in humans, usually in patients who are undergoing open-heart surgery. Several of these have demonstrated that stem cells that are injected into the circulation or directly into the injured heart tissue appear to improve cardiac function and/or induce the formation of new capillaries. The mechanism for this repair remains controversial, and the stem cells likely regenerate heart tissue through several pathways. However, the stem Cell population that have been tested in these experiments vary widely, as do the conditions of their purification and application. Although much more research is needed to assess the safety and improve the efficacy of this approach, these preliminary clinical experiments show how stem cells may one day be used to repair damaged heart tissue, thereby reducing the burden of cardiovascular disease.

Stem Cell Therapies Today

There are several stem cell therapies which are routinely used to treat disease today.

These include:

- Adult Stem Cell Transplant: Bone Marrow Stem Cells
- Adult Stem Cell Transplant: Peripheral Blood Stem Cells
- Umbilical Cord Blood Stem Cell Transplant

Adult Stem Cell Transplant: Bone Marrow Stem Cells

Perhaps the best-known stem cell therapy till date is the bone marrow transplant, which is used to treat leukemia and other types of cancer, as well as various blood disorders.

Why is this stem cell therapy?

Leukemia is a cancer of white blood cells, or leukocytes. Like other blood cells, leukocytes are made in the bone marrow through a process that begins with multipotent adult stem cells. Mature leukocytes are released into the bloodstream, where they work to fight off infections in our bodies. Leukemia results when leukocytes begin to grow and function abnormally, becoming cancerous. These abnormal cells cannot fight off infection, and they interfere with the functions of other organs. Successful treatment for leukemia depends on getting rid of all the abnormal leukocytes in the patient, allowing healthy ones to grow in their place. One way to do this is through chemotherapy, which uses potent drugs to target and kill the abnormal cells. When chemotherapy alone can't eliminate them all, physicians sometimes turn to bone marrow transplants. In a bone marrow transplant, the patient's bone marrow stem cells are

replaced with those from a healthy, matching donor. To do this, all of the patient's existing bone marrow and abnormal leukocytes are first killed using a combination of chemotherapy and radiation. Next, a sample of donor bone marrow containing healthy stem cells is introduced into the patient's bloodstream. If the transplant is successful, the stem cells will migrate into the patient's bone marrow and begin producing new, healthy leukocytes to replace the abnormal cells.

Adult Stem Cell Transplant: Peripheral Blood Stem Cell Transplant

While most blood stem cells reside in the bone marrow, a small number are present in the bloodstream. These multipotent Peripheral Blood Stem Cells, (PBSC's), can be used just like bone marrow stem cells to treat leukemia, other cancers and various blood disorders. Since they can be obtained from drawn blood, PBSCs are easier to collect than bone marrow stem cells, which must be extracted from within bones. This makes PBSCs a less invasive treatment option than bone marrow stem cells. PBSCs are sparse in the bloodstream; however, so collecting enough to perform a transplant can pose a challenge.

Umbilical Cord Blood Stem Cell Transplant

Newborn infants no longer need their umbilical cords, so they have traditionally been discarded as a by-product of the birth process. In recent years, however, the multipotent-stem-cell-rich blood found in the umbilical cord has proven useful in treating the same types of health problems as those treated using bone marrow stem cells and PBSCs. Umbilical cord blood stem cell transplants are less prone to rejection than either bone marrow or peripheral blood stem cells. This is probably because the cells have not yet developed the features that can be recognized and attacked by the recipient's immune system. Also, because umbilical cord blood lacks well-developed immune cells, there is less chance that the transplanted cells will attack the recipient's body, a problem called graft versus host disease.Both the versatility and availability of umbilical cord blood stem cells makes them a potent resource for transplant therapies.

Scientists are still years away from growing whole human organs in lab dishes - but not for lack of trying. Research groups around the world have convinced various types of stem cells to grow, divide and even differentiate in lab dishes. Most of this research is performed in stem cells obtained from other organisms, such as mice, rats and frogs.

The final step, creating a functional organ out of differentiating stem cells, is more challenging. Obstacles to success include the problem of delivering oxygen and nutrients to cells on the inside of the organ, as well as creating physical scaffolds upon which to grow and differentiate cells. Scientists are working closely with engineers to build and test

different scaffolds. Early in 2002, University of Utah bioengineers earned applause from around the world for their imaginative nerve cell scaffold.

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