Stem Cell Brief Introduction

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Abstract: Stem cells are derived from embryonic and non-embryonic tissues. Most stem cell studies are for animal stem cells and plants have also stem cell. Stem cells were discovered in 1981 from early mouse embryos. Stem cells have the potential to develop into all different cell types in the living body. Stem cell is a body repair system. When a stem cell divides it can be still a stem cell or become adult cell, such as a brain cell. Stem cells are unspecialized cells and can renew themselves by cell division, and stem cells can also differentiate to adult cells with special functions. Stem cells replace the old cells and repair the damaged tissues. Embryonic stem cells can become all cell types of the body because they are pluripotent. Adult stem cells are thought to be limited to differentiating into different cell types of their tissue of origin. This article introduces recent research reports as references in the stem cells related studies.
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1. Introduction

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Embryonic stem cells can become all cell types of the body because they are pluripotent. Adult stem cells are thought to be limited to differentiating into different cell types of their tissue of origin.

In the 3-5 days old embryo (blastocyst), the inner cells develop to the entire body of the organism. In some adult tissues (such as bone marrow, muscle and brain, etc) the adult stem cells replace the lost or damaged cells under the injury or disease conditions, etc.

Stem cells offer new potentials for treating diseases, which is referred to as regenerative or reparative medicine. All stem cells have three general properties: (1) capable of dividing and renewing themselves for long time; (2) unspecialized; (3) can give rise to specialized cells.

Both embryonic and non-embryonic stem cells can be efficiently cultured in the laboratory. The specific factors and conditions that allow stem cells to remain unspecialized are important.

Stem cells do not have any tissue-specific structures and cannot perform specialized functions. However, unspecialized stem cells can differentiate to specialized cells. When unspecialized stem cells give rise to specialized cells, the process is called differentiation. Factors cause stem cells to differentiate can be internal or external signals. The internal signals are controlled by the cell's genes, and the external signals for cell differentiation include chemicals, physical contacting and other factors the environment. The interaction of signals during differentiation causes the cell's gene expression. It is not clear if there are specific sets of signals to promote differentiation. Different stem cells may need different factors to differentiate.

Normally adult stem cells generate the cell types as cells in the tissue they are in. For example, the blood stem cell in the bone marrow normally differentiates to a type of blood cells. However, one type of adult stem cells can differentiate to other different type of the specialized under certain condition, which is important for the life existing and the medical applications. To get the technique to control the stem cell to differentiate to any type of the specialized cells will let us get the cells we need for the treatment.

Originally embryonic stem cells are derived from embryos after the female fertilized in vivo. In the animal studies it will be possible to get the embryonic stem cell from the animals' fertilized eggs, but it is important to get human embryonic stem cells from women body. So that, the human embryonic stem cells are derived from embryos developing from eggs that have been fertilized in vitro then donated for research purposes with informed consent of the donors. The human embryonic stem cells are not obtained from

eggs fertilized in a woman's body.

For the human embryonic stem cell culture, the stem cells are selected from a preimplantation-stage embryo and transferred into a plastic laboratory culture dish that contains a nutrient culture medium. The cells attach the culture dish surface. In the original work the inner surface of the culture dish was coated with mouse embryonic skin cells specially treated so that the stem cells will not divide, where the coating layer of cells is called a feeder layer. Also, the mouse cells in the bottom of the culture dish let give the cultured stem cells a sticky surface to attach and the feeder cells release nutrients into the culture medium for the cultured stem cells to use. Now the advanced culture technique grows embryonic stem cells without mouse feeder cells, which avoid the risk that viruses or other macromolecules in the mouse cells may be transmitted to the human cells.

Now, many embryonic stem cell lines have been generated and kept for a long time. The batches of cell lines can be frozen and shipped from one place to other place, and also commercial available.

As a cell line, the cultured stem cells should grow at least several months and can be subcultured for many passages. The cell condition can be checked with a microscope to see that the cells look healthy and remain undifferentiated.

To check the presence of transcription factors that are typically produced by undifferentiated cells is important to confirm the cells are stem cells. Two of the most important stem cell transcription factors are Nanog and Oct4. Transcription factors is important for genes to turn on and turn off at the right time, which is important in the processes of cell differentiation and embryonic development. Nanog and Oct4 are associated with maintaining the stem cells in an undifferentiated state and keep the capability of self-renewal.

To determine the presence of particular cell surface markers that are typically produced by undifferentiated cells is also an important way to identify stem cells.

Sometimes to examine the chromosomes under a microscope is useful to check the cell living condition.

Injecting the cells into a mouse with a suppressed immune system can get the benign tumor that is called a teratoma. Since the mouse's immune system is suppressed, the injected human stem cells are not rejected by the mouse immune system and we can observe the growth and differentiation of the human stem cells. Teratomas typically contain a mixture of many differentiated or partly differentiated cell types.

Stem cell can keep undifferentiated (unspecialized) under appropriate conditions. When the cells begin to clump together to form embryoid bodies, they begin to differentiate spontaneously. They can form all the needed cell types, such as skin cells, blood cells, muscle cells and nerve cells, etc. It is important to control the differentiation of embryonic stem cells. We can change the chemical composition of the culture medium, alter the surface of the culture dish, or modify the cells by inserting specific genes to control the cell's differentiation.

There are a lot of possible applications for us to direct the differentiation of embryonic stem cells into specific cell types and it may be able to use the resulting and differentiated cells to treat certain diseases in the future.

Adult stem cells are undifferentiated cells in the differentiated cells in tissues. The adult stem cell can renew itself and can differentiate to specialized cell types of the tissue, which repair the tissue when it needs. Another word "somatic stem cell" is the same meaning of "adult stem cell". Adult means mature but not un-mature (or embryotic). Somatic means that cells are the living body cell, but not the germ cells, or egg cells. However, in stem cell affaire the adult stem cell and somatic stem cell are the same thing.

The adult stem cells exist in most tissues, and they can be used for transplants. The adult hematopoietic, or blood-forming, stem cells from bone marrow have been used in transplants for more than 40 years. If the differentiation of adult stem cells can be controlled by the scientific techniques, these cells can be an efficient transplantation-based therapy technique.

The adult stem cell research began 60 years ago. In the 1950s, it was found that the bone marrow contains at least two kinds of stem cells. One population, called hematopoietic stem cells, forms all the types of blood cells in the body. A second population (named bone marrow stromal stem cells or mesenchymal stem cells or skeletal stem cells) is 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, and fat cells that support the formation of blood and fibrous connective tissue.

Before 1990s people thought that the brain cannot generate new nerve cells. After then we see that the adult brain 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.

Adult stem cells exist in most of the tissues, including bone marrow, peripheral blood, blood vessels, brain, heart, liver, skeletal muscle, skin, teeth, gut, ovarian epithelium and testis, etc. Adult stem cells are in a specific area of each tissue stem cell niche. Stem cells can remain in a non-dividing condition

(quiescent) for long time until they are activated by the factors to generate more cells to maintain tissues or to treat disease. Naturally there are only a very small number of stem cells in each tissue. The adult stem cells can be identified by labeling the cells in a living tissue with molecular markers and then determine the specialized cell types they generate. In normal living body stem cells divide when the body needs them.

Hematopoietic stem cells generate all the types of blood cells, such as red blood cells, B lymphocytes, T lymphocytes, natural killer cells, neutrophils, basophils, eosinophils, monocytes, platelet and macrophages, etc. Mesenchymal stem cells are from bone marrow (bone marrow stromal stem cells, skeletal stem cells) and they give rise to a variety of cell types, such as bone cells (osteoblasts and osteocytes), cartilage cells (chondrocytes), fat cells (adipocytes) and stromal cells.

Neural stem cells in the brain generate three major cell types: nerve cells (neurons), astrocytes and oligodendrocytes.

Epithelial stem cells in the lining of the digestive tract in deep crypts and generate several cell types: absorptive cells, goblet cells, Paneth cells, and enteroendocrine cells.

Skin stem cells exist in the basal layer of the epidermis and at the base of hair follicles. The epidermal stem cells give rise to keratinocytes, which migrate to the surface of the skin and form a protective layer. The follicular stem cells can generate the hair follicle and the epidermis.

Stem cell can make transdifferentiation in which certain adult stem cell types differentiate into cell types that is not the same cell type. Instead of transdifferentiation, the observed instances may involve fusion of a donor cell with a recipient cell. Another possibility is that transplanted stem cells are secreting factors that encourage the recipient's own stem cells to begin the repair process. Even when transdifferentiation has been detected, only a very small percentage of cells undergo the process. The adult cells can be reprogrammed into other cell types in vivo under a well-controlled process of genetic modification. This is maybe used in medical treatment.

Adult stem cells also can be reprogramed to become embryonic stem cells, which is called induced pluripotent stem (iPS). To get iPS it need to introduce several embryonic genes.

Comparatively, it is easier to culture embryonic stem cells but difficult to culture adult stem cells. Also adult stem cells in tissue are small amount, it is not easy to get good amount. In the transplantation treatment, immunology rejection is an important thing. Induced pluripotent stem cells (iPSCs) are reprogrammed adult cells becoming embryonic stem cells–like state. The introduced factors and expressed genes normally only exist in embryo.

The iPSCs are under researched if they can be used in the transplantation medicine, and drug development applications have been started. For the direct application in transplantation, the virus it used in this technique is a risk.

There are many methods to deliver the transcription factors into target cells to generate iPSCs. The first method is retrovirus or lentivirus transduction. The problem of this technique is the genome integration of virus DNA which could possibly alter differentiation potential or other malignant transformation. The second method is adenoviral vectors to induce iPSC. The advantage of adenovirus vector based expression is that the transgenes will not integrate into the house genome, thus reduces the risk of tumorogenesis. The third one is a plasmid based transfection that can avoid the genome integration also. Recently, the Cre-recombinase excisable systems are used in iPSC induction and subsequent transgene removal making the iPSC technology closer to clinic applications.

It is important to know how undifferentiated stem cells become the differentiated cells that form the tissues and organs. Turning genes on and off is the key factor for this process. Many serious problems for animal health, such as cancer, are due to abnormal cell division and differentiation.

Human stem cells are used to test new drugs and new medication methods are tested for safety on differentiated cells generated from human pluripotent cell lines.

The most important potential application of human stem cells is the generation of cells, tissues, organs and even part of the body that could be used for the medical treatments. Stem cells, directed to differentiate into specific cell types, offer the possibility of a renewable source of replacement cells, tissues and organs to treat diseases.

It is possible to generate healthy cells in the laboratory and then transplant these cells into patients with diseases.

It is possible for stem cell to treat many diseases, such as macular degeneration, spinal cord injury, stroke, burns, heart disease, diabetes, osteoarthritis, and rheumatoid arthritis, etc. It is possible to direct the differentiation of human embryonic stem cells in cell culture to form insulin-producing cells that eventually could be used in transplantation therapy for persons with diabetes.

In the embryonic development procedure, the stem cells differentiate to the specialized cells through a series of cellular changes regulated by the specific gene expressions. The embryonic stem cells can differentiate all adult cell types.

In 2006, Kazutoshi Takahashi and Shinya Yamanaka established for the first time murine ES-like cell lines from mouse embryonic fibroblasts (MEFs) and skin fibroblasts by simply expressing four transcription factor genes encoding Oct4, Sox2, Klf4, and c-Myc. They called these somatic cell-derived cell lines induced pluripotent stem (iPS) cells. These iPS cell lines show the similar morphology and growth properties as ES cells and express ES cell-specific genes. Transplantation of iPS cells into immunodeficient mice resulted in the formation of germ-cell-tumor (teratoma)-containing tissues from all three germ layers, confirming the pluripotent potential of iPS cells. iPS resolve the moral problem for the embryonic stem cell application. Also, iPS avoid the immune rejection for the stem cell transplantation and iPS can be obtained from the same person to use the cells.

The iPS cell lines could be generated from different cell types, such as fibroblasts, neuronal progenitor cells, keratinocytes, hepatocytes and B cells, etc. The four transcription factors play key role to reprogram the somatic cells stem cells.

The human keratinocytes from skin biopsies can be reprogrammed to pluripotency at much higher frequency and faster speed than fibroblasts as the endogenous c-Myc and Klf4 expression in keratinocytes is much higher than that is in fibroblasts.

The mesenchymal-to-epithelial transition (MET) is a crucial early phase during the reprogramming of fibroblasts into iPS cells. In contrast to keratinocytes fibroblasts need to undergo an initial MET during the reprogramming process. This additional transition step may result in reduced efficiency and a prolonged duration to reprogram fibroblasts to reach pluripotency. Also, hepatocytes and gastric epithelial cells in mice show to be more easily reprogrammed than fibroblasts.

Development of iPS cell technology has already revolutionized the fields of developmental biology and regenerative medicine. This technology has successfully treated sickle-cell anemia in a humanized mouse model.

For practical application of this technology in clinics, it needs to resolve issues involving the use of viral vectors for iPS cell establishment, the safe strategy to genetically modify iPS cells, differentiation of iPS cells into relevant cell types in vitro for transplantation, and removal of contaminating stem or progenitor cells before transplantation.

The above contents are the collected information from Internet and public resources to offer to the people for the convenient reading and information disseminating and sharing.

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