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BIOL S401
Contemporary Biology Development
(Free Courseware)

香港公開大學
THE OPEN UNIVERSITY OF HONG KONG

Contents

Chapter 1 Stem cell research

1.1 About this module

Welcome to this free courseware module ‘Stem cell research’!

This module is taken from the OUHK course *BIOL S401 Contemporary Biology Development (http://www.ouhk.edu.hk/wcsprd/Satellite?pagename=OUHK/tcGenericPage2010&c=C_ETPU&cid=191154130000&lang=eng)*, a five-credit, higher level course that is part of the BSc programme in the Bachelor of Science in Applied Science (Biology and Chemistry) offered by the School of Science and Technology (http://www.ouhk.edu.hk/wcsprd/Satellite?pagename=OUHK/tcSubWeb&l=C_ST&lid=191133000200&lang=eng) of the OUHK. This course helps broaden your knowledge and develop critical thinking skills in different scientific research areas.

BIOL S401 is mainly presented in printed format and comprises five study units. Each unit contains study content, activities, self-tests, assigned readings, etc for students’ self-learning. This module (The materials for this module, taken from the print-based course BIOL S401, have been specially adapted to make them more suitable for studying online, and multimedia elements have been added where appropriate. In addition to this topic on ‘Stem cell research’, which is an extract from Unit 3 of the course, the original Unit 3 also includes the topics ‘ethical and social concerns of stem cell research’, and ‘Contemporary research into stem cells’.) retains most of these elements, so you can have a taste of what an OUHK course is like. Please note that no credits can be earned on completion of this module. If you would like to pursue it further, you are welcome to enrol in *BIOL S401 Contemporary Biology Development (http://www.ouhk.edu.hk/wcsprd/Satellite?pagename=OUHK/tcGenericPage2010&c=C_ETPU&cid=191154130000&lang=eng)*.

This module will take you about **six hours** to complete, including the time for completing the activities and self-tests (but not including the time for assigned readings). Owing to copyright issues, textbook and assigned readings are not included in the free courseware.

Good luck, and enjoy your study!

1.2 Introduction

We’ll begin with a brief introduction to the two main types of stem cells, embryonic and adult stem cells. We’ll then discuss stem cell potency.

The second section “Stem cells in research and diseases management” will focus on the opportunities and roles of stem cells in diseases and medical research. Stem cells have a special position in contemporary biological sciences due to their unspecialized characteristics and continuous proliferation. We will focus in particular on the areas of diabetes and neuron regeneration.

BIOL S401, like most OUHK courses, is presented in the distance learning mode using print-based materials. The materials for this free courseware have been specially adapted to make them more suitable for studying online.

Stem cell research has aroused ethical concerns in the cancer research field and in society in general, especially with regard to stem cells harvested from human beings. Different sources of stem cells — human embryonic and adult stem cells — have led to different controversies. This module will first discuss the types of stem cell sources, followed by opportunities for research. Finally, we will introduce the ethical concerns related to stem cell research, addressing the importance of the balance between research and ethics.

This module should take around **6 hours** to complete, including time spent on activities and self-tests.

1.3 Types of human stem cells

The human body is made up of billions of cells working together to maintain the normal function of life. These cells are formed or divided from a fertilized egg. The egg splits into two cells and further divides into four cells and so on. The process continues until all the cells in the body are generated. Specialized cells group together and form tissues to complete a unique task, such as nerves and muscles. Cells are divided in a controlled manner to maintain their normal function. When cells are damaged or cell death occurs, the surrounding cells help the replacement by further cell division. However, when the damage cannot be repaired, diseases or medical problems may arise. Disruption of the normal process of embryo development by radiation, chemicals or viruses may lead to birth defects. For example, fetal alcohol spectrum disorder (http://en.wikipedia.org/wiki/Fetal_alcohol_spectrum_disorder) is the brain cell death of an embryo that has been exposed to the toxic effects of alcohol during the developmental stages. This damage is irreversible even after the removal of the alcohol, resulting in growth deficiencies and retarded brain development.

To replace cells or to develop a human body, stem cells act as an internal repair system. They start working in the body during early development and growth. Stem cells are unspecialized cells, which can divide continuously and maintain an undifferentiated state. Moreover, the stem cell products — their daughter cells — can differentiate into different types of cells for replacement and transform into specialized functional cells for the body, such as a muscle cell or a brain cell. Recently, scientists have distinguished two primary kinds of stem cells based on their characteristics: embryonic stem cells, and non-embryonic or adult stem cells. In the next section, we will discuss the types of stem cells in further detail. For now, complete the following activity to further your understanding of stem cell differentiation (The process of an unspecialized embryonic cell acquiring the features of a specialized cell such as a heart, liver, or muscle cell, which is controlled by the interaction of physical and chemical conditions outside the cell, usually through signalling transduction involving proteins on the cell surface.).

Let's start with the basics.

Activity 1

During human embryo development, the cells are differentiated to produce special functions of the body. A blastocyst is formed at the beginning stage to make any type of body cell, and can give rise to the cells of a given germ layer. The cells become more restricted when further developed, to form an eye or organ.

Watch the video animation (http://www.hhmi.org/biointeractive/differentiation-and-fate-cells) to understand this more.

Then answer the following questions:

1. What is a blastocyst?
2. How many days does it take for a blastocyst to form?
3. At the beginning of embryo development, there are three germ layers. Please give the names of the germ layers.

Activity 1 feedback

1. A blastocyst is a pre-implantation embryo of about 150 cells produced by cell division following fertilization. The blastocyst is a sphere made up of an outer layer of cells, a fluid-filled cavity, and a cluster of cells on the interior (the inner cell mass). The outer cell mass will be developed into a placenta and the inner cell mass will form a disk and change the geographic position together with embryo growth. Finally, it will form a germ layer and will make the entire animal from these cells.
2. About 5 days, usually 4-6 days
3. Ectoderm, mesoderm and endoderm

1.3.1 Basic concepts of stem cell sciences

Stem cells are a class of undifferentiated cells which are able to produce undifferentiated or specialized cell types after cell division. There are two main sources:

1. cells from the inner cell mass (ICM) formed during the blastocyst phase of embryological development (embryonic stem cells); and
2. adult tissue (adult stem cells), also called somatic cells (non-germ cells, sperm or egg).

Embryonic and adult stem cells share some common characteristics. They both have the potential to develop into different cell types in the body for growth and development. They are the repair system after tissue damage and injuries. Three important characteristics of stem cells can be identified.

Three important characteristics of stem cells

1. Stem cells have the ability to divide and renew through cell division for long periods of time, or even after a long period of dormancy (inactivity). The other cells, muscle cells or nerve cells, cannot replicate or proliferate. Stem cells can proliferate by cell division. Moreover, the stem cells are capable of long term self renewal, which means the stem cells remain unspecialized (the same as their parent stem cells) after many times of cell division.
2. Stem cells are unspecialized (Figure 1.1). A stem cell does not have any tissue-specific structure to perform specialized functions, for example carrying oxygen molecules through the blood stream or transmitting nerve impulses. However, the stem cell can produce specialized cells such as nerve cells and blood cells.
3. Stem cells can give rise to specialized cells after division, which is called differentiation (Figure 1.1). This process takes place in several stages and the cells become more specialized at each stage. The intermediate cell types are called committed progenitors, which will be discussed in a later section. There are certain signals both inside and outside the cell that trigger each step of the differentiation process. Internal signals are controlled by genes in the nucleus, and external signals include chemicals secreted by other cells, physical contact with the neighboring cells and molecules in the microenvironment (cytoplasm or tissue fluid). Apart from those signals triggering the differentiation process, investigation has revealed the involvement of epigenetics of DNA expression in cell and stem cell division. This differentiation process of stem cells helps to replenish those cells that cannot undergo any cell division, like blood cells and nerve cells.

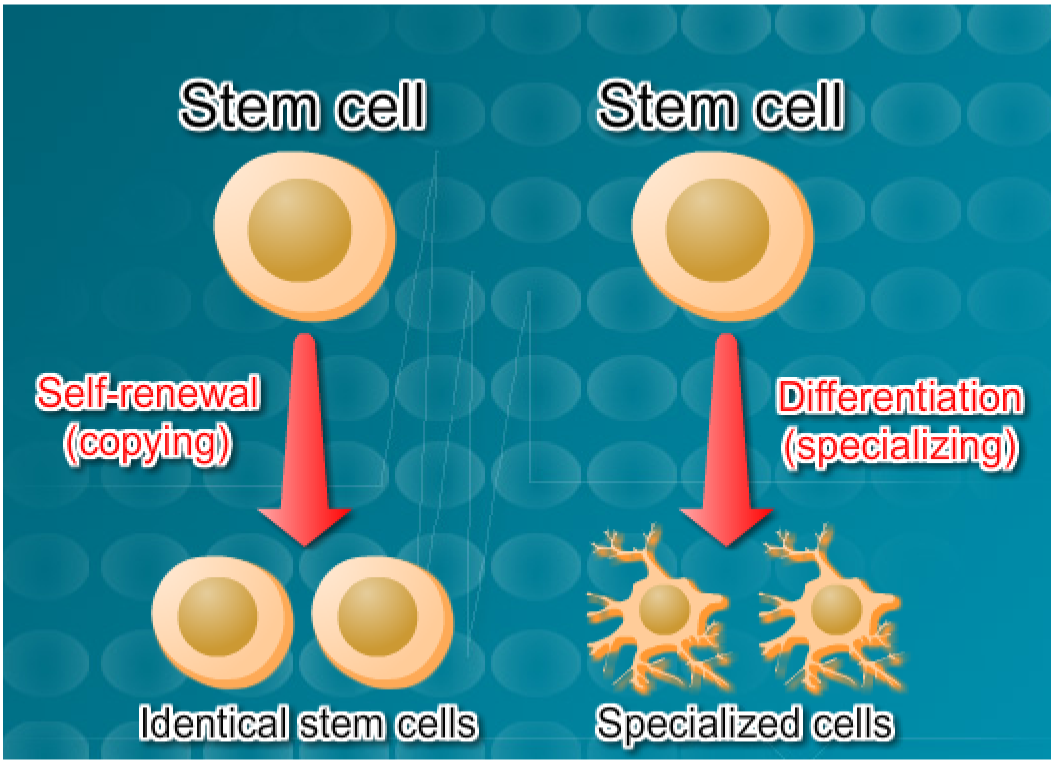

Figure 1.1 Characteristics of stem cells. Stem cells can give rise to both specialized and unspecialized cells.

Stem cells are unspecialized. They can self-renew by copying themselves to form identical unspecialized stem cells. Stem cells can also give rise to specialized cells after division. This process is called differentiation.

Now try the following self-test and check how much you have absorbed from what we have covered so far.

Self-test 1

1. Please give two characteristics of self renewing cells.
2. What are the factors in living organisms that normally regulate stem cell proliferation and self renewal?
3. What are stem cells? Please give two functions of stem cells.

Self-test 1 feedback

1. Characteristics of self-renewing cells: (a) the ability to divide and renew through cell division for long periods of time, and (b) to remain unspecialized after many times of cell division
2. Internal signals: genes in the nucleus and epigenetics, and External signals: chemicals secreted by other cells, physical contact with the neighboring cells and molecules in the microenvironment (cytoplasm or tissue fluid).
3. Stem cells are unspecialized cells, which can divide continuously and maintain the undifferentiated state. The functions of stem cells are: they differentiate into different types of cells to (a) develop, and (b) repair the damaged cells.

1.3.2 Potency

Potency is the ability or potential of stem cells to differentiate into other types of cells.

Table 1.1 below lists the full classification of stem cell potency:

Potency	Description	Example
Unipotent	Only produce cells of their own type, have self-renewal property with the help of stem cells	Muscle stem cells
Oligopotent	Differentiate into a few types	Lympholid or myeloid stem cells
Multipotent	Differentiate into a closely related family of cells	Hematopoietic (audlt) stem cells that become red and white blood cells or platelets
Pluripotent	Differentiate into almost all cell types	Embryonic stem cells: cells derived from the mesoderm, endoderm and ectoderm germ layers during blastocyst development
Totipotent	Differentiate into all possible cell types	Zygote formed at egg fertilization and first few cells resulting from zygote division

Table 1.1 Potency classification of stem cells

Embryonic stem cells are one of the most potent cell types, as they have the potential to become any type of cell in the body, except extra-embryonic membranes or the placenta. Therefore, embryonic stem cells are considered to be pluripotent (Source: Nabil, W (2005) 'Embryonic stem cells may help sterile women', Journal of Young Investigators, Vol. 13, http://www.jyi.org/news/nb.php?id=378.).

Stem cells give rise to specialized cells in different stages. The intermediate cell types are known as **committed progenitors** (Figure 1.2). They are not fully differentiated cells but have different properties from stem cells. These cells divide many times to produce fully differentiated and functional cells through different steps. Figure 1.2 shows the different steps.

This hierarchy can be applied to many types of tissue specific stem cells. One example of the process of differentiation is the hematopoietic stem cells (Stem cells that gives rise to all red and white blood cells and platelets) and mesenchymal stem cells (A term that is currently used to define non-blood adult stem cells from various tissues, e.g.

bone cells, cartilage cells, fat cells and other kinds of connective tissue cells, such as tendons. Currently there is no clear information whether mesenchymal stem cells from different tissues are the same.). These cells give rise to all the types of blood cells and bone cells.

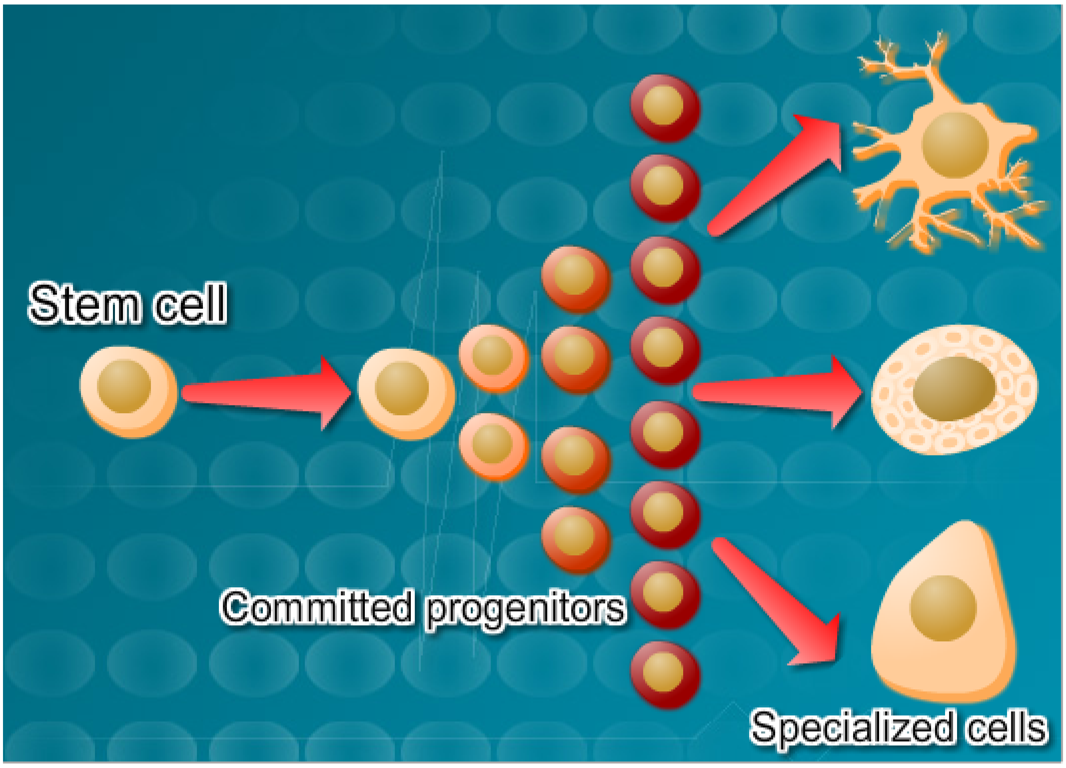

Figure 1.2 Process of differentiation. Stem cells can give rise to specialized cells through a series of procedures. The committed progenitors are the intermediate cell type for the transition of undifferentiated stem cells to specialized cells for maintaining the body functions.

A stem cell divides into two daughter cells: one is an undifferentiated stem cell and the other one is a committed progenitor. The progenitors are the intermediate cells between stem cells and specialized cells, which are multipotent and divide rapidly. These cells become more specialized by each cell division. Finally, the working cells, also called the specialized cells, are formed. There is no further cell division once the cells are formed.

1.3.3 Embryonic stem cells

An embryo is formed after sexual reproduction, when a male's sperm fertilizes a females's egg to form a single cell, a zygote. This cell undergoes a series of cell division, forming two, four, eight cells and so on (Figure 1.3). After four to six days, a mass of cells is produced, which is called a **blastocyst**. It consists of an inner cell mass (ICM, embryoblast) and an outer cell mass (trophoblast), forming the embryo and placenta respectively after implantation to the uterus. ICM is the source of embryonic stem cells, which are totipotent (i.e. they have total potential to develop into any cell type in the body). In normal pregnancy, the blastocyst stage continues until implantation in the uterus, when it is called a fetus. This usually occurs at the end of the 10th week after fertilization, at which stage most of the major organs of the fetus have been created.

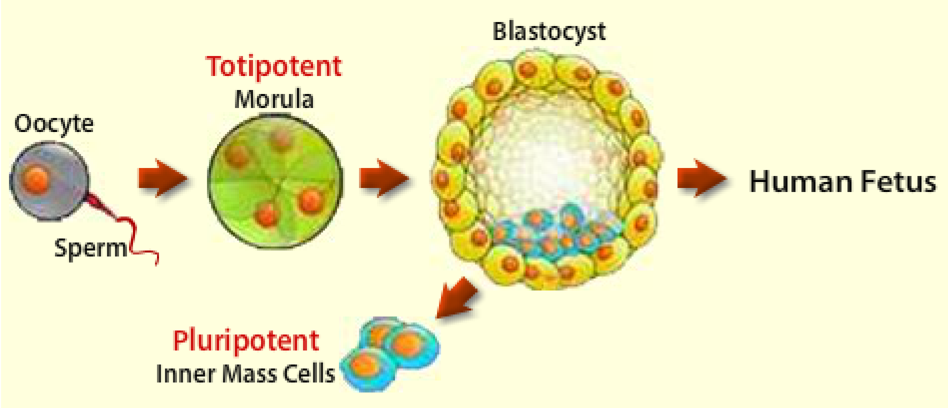

Figure 1.3 The beginning stages of blastocyst development. Cell division begins after fertilization of the egg, which forms a zygote and further develops into a blastocyst.

Source: Saxena, Singh and Gupta 2010 (Saxena, A K, Singh, D and Gupta, J (2010) 'Role of stem cell research in therapeutic purpose — a hope for new horizon in medical biotechnology', Journal of Experimental Therapeutics and Oncology, Issue 8, pp. 223–33.)

Embryonic stem cells can be harvested from a blastocyst of a four to five day old human embryo, which is usually created by *in vitro fertilization (IVF)* (*http://en.wikipedia.org/wiki/In_vitro_fertilisation*). These embryos are usually donated by the IVF clinics where several eggs are fertilized in a test tube, and are not implanted into a woman. Most of these cells are completely unspecialized.

The extracted stem cells are then transferred to a culture dish containing a nutrient-rich broth and anchor medium. Without the signal or stimulation to differentiate, the cells begin to divide and replicate, maintaining an unspecialized state in the body. These undifferentiated cells can then be stimulated to create specialized cells under suitable conditions. The manipulation of the conditions or factors in differentiation is one of the most important areas for further investigation, because this is the key step in creating specific replacement cells, tissues or organs for therapeutic uses.

Activity 2 (Page 8) introduces how the inner cell mass (ICM) cells of blastocyst-stage early human embryos removed and cultured to create a cell line. These cells can be grown in a controlled environment indefinitely. Various growth factors induce the differentiation of these cells to develop into cells with a specific function, such as muscle or nerve cells.

At this point, test your understanding of embryonic stem cells with Self-test 2 (Page 9).

Activity 2

Watch the following video animation (http://www.hhmi.org/biointeractive/creating-embryonic-stem-cell-lines).

Then answer the following questions:

1. What has been added to the culture environment to help the growth of stem cells?
2. What kinds of signals trigger the differentiation of stem cells? Name two of them.

Activity 2 feedback

1. Mouse embryonic fibroblast
2. Growth factors, sonic hedgehog and retinoic acid

Self-test 2

1. At what stages of human development can the embryonic stem cells be found?
2. Name one common source of embryonic stem cells for research.

Self-test 2 feedback

1. Embryonic stem cells can be found at the blastocyst stage, 4–6 days after fertilization.
2. A blastocyst of a human embryo is created by *in vitro* fertilization (IVF).

1.3.4 Adult stem cells

Adult or somatic stem cells exist in the body after embryonic development. These undifferentiated cells are found among differentiated tissues, such as brain, bone marrow, blood, blood vessels, skeletal muscles, testis, ovary, skin and the liver. The primary role of adult stem cells is to maintain and repair the tissue where they are found. They remain in a dormant or non-dividing state for many years until activated by disease or tissue injury. Adult stem cells can divide or self-renew indefinitely, to allow them to generate a wide range of cell types from the organ of origin, or regenerate the entire original organ. Adult stem cells reside in a specific area of each tissue (stem cell niche) and only a small number of cells are found in each tissue. However, their capacity to divide is limited once they are removed from the body. Therefore, cell culturing of the adult stem cell is rather difficult.

These adult stem cells are not completely unspecialized. Although it is well accepted that adult stem cell differentiation is limited to the organ of origin, other evidence suggests that adult stem cells can differentiate into other cell types. An example of an adult stem cell is the blood forming (haematopoietic) stem cells found in bone marrow. The red blood cells carry oxygen throughout the body, which only survive for about 120 days. The blood-forming stem cells continue to divide and produce cells for the function of red blood cells at the same time. These stem cells divide to maintain the cell reserve, as well as replacing the old or damaged red blood cells and differentiating to other blood cells. Bone marrow transplants have been used since 1968 to treat patients with leukemia and other blood-related diseases.

Adult stem cells or somatic stem cells are two common names used in scientific field. Somatic cells refer to the cells of body apart from germ cells, sperm or eggs). However, the definition of adult stem cells requires further investigation, as there are many sources and origins of stem cells in mature tissues.

1.3.5 Different characteristics of human embryonic and adult stem cells

Human embryonic and adult stem cells have different abilities in terms of the number of cell types they can differentiate into. Embryonic stem cells can give rise to most of the body cells, and are pluripotent, while adult stem cells have limited potency and differentiate into cell types of their tissue of origin.

Embryonic stem cells can be grown and harvested easily in culture with a well controlled environment, but adult stem cells are rare in mature tissues. Therefore, isolation is rather difficult. Methods for culturing of adult stem cells are not well developed. This may slow down the development of the usage of adult stem cells in cell replacement therapies, as large quantities of cells are required.

The tissues derived from embryonic and adult stem cells may differ with regard to immune rejection after transplantation. There is only limited information available for embryonic stem cell transplantation, as the first phase clinical trial testing the safety of cells derived from embryonic stem cells was only approved in the US in 2009. There is the possibility of rejection due to the difference of genetic makeup of the embryonic stem cells and the recipient. For adult stem cells, there is less likely to be a rejection after transplantation, as scientists are able to culture the patient's own cells and differentiate them into specific cell types. This can minimize the immune response for rejection of the transplanted tissue. This is an important consideration before any transplantation, as rejection can aggravate the situation and continuous administration of immunosuppressive drugs causes many side effects.

The animation in Activity 4 (Page 11) gives a comprehensive picture of stem cell biology on the embryonic and adult stem cells. It also discusses two examples of haematopoietic and intestinal stem cell. Finally, the animation introduces the techniques of culturing and controlling stem cell growth under *in vitro* conditions, and the potential therapeutic values of stem cell research.

Embryonic and adult stem cells are the two major types of stem cell. There are other stem cell types found to be useful, such as cord blood stem cells. Stem cell therapy is also being extensively studied in the medical field. These are the current and potential areas of research, which we will discuss in the next section.

To round off this section on the types of stem cells in humans, attempt Self-test 3 (Page 11).

Activity 3

1. Why can't adult stem cells substitute for the use of human embryonic stem cells in research?

Activity 3 feedback

Human embryonic stem cells have greater developmental potential than adult stem cells. They can give rise to almost all cell types of the human body, and are pluripotent. However, the adult stem cell is multipotent, and is restricted to a specific subpopulation of cell types.

Activity 4

Watch the following animation (http://www.youtube.com/watch?v=mUcE1Y_bOQE).

Then answer the following questions.

1. What are the functions of CDX2 and Oct-3/4 in a blastocyst?
2. What are three tissues or systems with poor regeneration power after injuries or degenerative diseases?

Activity 4 feedback

1. CDX2 is the gene that controls early embryogenesis, which is required to form the placenta. Oct-3/4 gene expression facilitates the formation of the inner cell mass, maintains pluripotency and differentiates into trophectoderms.
2. The nervous system, the heart and the pancreas.

Self-test 3

1. There are two main types of stem cells the body. Name these two kinds and explain their function.
2. Summarize the different characteristics of embryonic and adult stem cells in the following table.

	Embryonic stem cells	Adult stem cells
Potency		
Cell culture		
Transplantation, rejection		

3. What are the roles of stem cells in the body?
    1. We are not sure what roles stem cell play in the body.

2. They produce new specialized cells to replace dead or used cells.
3. They can produce insulin.
4. They fight against infections.

Self-test 3 feedback

1. Embryonic stem cells are harvested from the blastocyst of a four to five day old human embryo. An embryonic stem cell consists of an inner cell mass (ICM, embryoblast) and an outer cell mass (trophoblast), forming the embryo and placenta respectively after implantation to the uterus. Adult or somatic stem cells exist in the body after embryonic development, to maintain and repair the tissue where they are found.
2. Different characteristics of embryonic and adult stem cells

	Embryonic stem cells	Adult stem cells
Potency	Pluripotent	Multipotent
Cell culture	Embryonic stem cells can be grown and harvested easily in culture with a well controlled environment.	The culturing methods of adult stem cells are not well developed.
Transplantation, rejection	There is a possibily of rejection due to the difference in the genetic makeup of the embryo stem cells and the recipient.	Rejection is less likely: patient's own cell is cultured and differentiated into specific cell types. Rejection still occurs if the genetic makeup of donor cells is different from recipient cells.

3. B. We understand the roles of stem cells in this unit. Scientists have revealed the function of stem cells extensively (Not A). Cells in the pancreas produce insulin (Not C). White blood cells fight against infection (Not D).

1.4 Stem cells in research and disease management

Stem cells do not serve any specific function in the body, though they have the capacity to serve different functions after specialization. Each cell in the human body is derived from the first few cells formed at the beginning of embryological development, the stem cells. Therefore, these cells extracted from the embryos can be used to derive every cell type desired under suitable conditions in the laboratory. This property explains why scientists are interested in stem cell research, especially for regenerative medicine. This section is divided into two parts: (1) stem cell research, and (2) stem cells and disease management. The subsection on stem cell research discusses the potential areas of bench side research in general, and you will then move on to look at the research into particular diseases, for example diabetes and neural sciences.

1.4.1 Stem cell research

Identifying and isolating adult stem cells

Stem cell isolation and identification are critical procedures prior to cell culturing. However, there is no universal technique for isolating and identifying stem cells. In general, scientists use some laboratory tests to check for the following characteristics: undifferentiated marker and capability of self-renewal. Specific tests have been developed to identify embryonic and adult stem cells. The following are some general methods used:

- **To test for the presence of cell surface markers of undifferentiated cells**
    - Microscopic examination of chromosomes to assess any damage or change in chromosome. Undifferentiated cells should have no detection of genetic mutation in the cells.
- **To identify embryonic stem cells**
    - Clonogenic assay is an in vitro test to see whether a single cell can differentiate and self-renew.
    - Examination by microscope to assess the health and status of the cells.
    - Check for the presence of biomarker. Transcription factor, Nanog and Oct4, maintain the cell in an undifferentiated state and help to turn the genes on and off at the appropriate time. This is an important part of cell differentiation and embryonic development.
- **To check for pluripotency of the embryonic stem cell**
    - Allow the cells to differentiate spontaneously in cell culture and manipulate the medium to see whether a specific cell type is formed.
    - Inject the cells into an immunosuppressed mouse to check for the formation of tetratoma (a benign tumor with a mixture of differentiated cells).

Isolating and identifying human adult stem cells is difficult, as it is rare in adult tissue, especially in the brain, the liver or the skin. There are limited resources and techniques to identify adult stem cells:

- Testing for bone marrow or haematopoietic stem cells (HSC) is carried out by transplanting one single cell to an individual without HSCs. If new blood and immune cells are produced, it demonstrates the potency, and this can minimize the harmful effect of the foreign cell.
- To culture the stem cells to see whether they can give rise to genetically identical cells. These cells after isolation can then repopulate or reform the tissue after being transplanted into an animal.

Generating specialized cells from stem cells

Before transplantation, the embryonic stem cells have to be stimulated and become specialized cells, as the stem cells may grow out of control and give rise to tumors. Therefore, many scientists have worked out the appropriate conditions for specialization and different stages of the whole process. The most important thing is to ensure no single embryonic stem cell is transplanted to the patients.

Integrating cells into the body

Once the specialized stem cells are obtained and cultured, the next obstacle is to transplant them into a human or an animal. The integration of tissue or organs into a new place allows them to function properly in the recipient's body. Nerve cells need to connect to the brain to work properly.

Overcoming rejection by the immune system

Stem cell therapies face the problem of rejection by the recipient's immune system. The immune system protects the body against disease development by recognizing foreign molecules, like microorganisms, other human cells and tissue. This results in organ failure after transplantation. Strong immunosuppressive medicines are required to minimize or prevent the rejection. However, this may also expose the recipients to other infections. Scientists have developed a technique, cell nuclear transfer — somatic cell nuclear transfe r technique (SCNT) (http://en.wikipedia.org/wiki/Somatic-cell_nuclear_transfer) — to overcome this obstacle, by replacing the nucleus of donor stem cells to a recipient nucleus prior to any cell division. As the replaced embryo cell has been cloned, and is identical to the patient cells, they will not be rejected by the immune system after transplantation.

For more details on SCNT, watch the animation in Activity 5 (Page 14).

Now that you have a deeper understanding of how stem cells are identified and extracted for research, we will go on to see how stem cells are used for disease management.

Activity 5

Somatic cell nuclear transfer (SCNT) is one of the cloning methods. It is achieved by replacing the nucleus of a healthy egg with the nucleus of a donor egg. The resulting embryo can generate the embryonic stem cells with same genetic makeup of the donor.

Watch the following animation (http://www.hhmi.org/biointeractive/somatic-cell-nuclear-transfer-animation).

What cell has been used as the donor cell?

Activity 5 feedback

The skin cell has been used as the donor cell.

1.4.2 Stem cells and disease management

The capacity for long term self renewal in stem cells marks the importance of this area in treating patients. Stem cells can replace damaged cells in the body after injuries. These properties have led to the investigation of the potential uses of stem cells in supplying cells to treat diseases such as Parkinson's disease (Damaged cell type: brain cells) , heart disease (Damaged cell type: heart muscles), diabetes (Damaged cell type: pancreatic cells) and other degenerative diseases. With these diseases, cells have been irreversibly lost and cannot be self regenerated. There are only treatments, but no cures for these diseases. Therefore, directing the stem cells to become the appropriate specialized cells followed by transplantation is the hope of these patients with damaged tissues. The stem cells can be generated to various cell types.

The therapeutic usages of adult stem cells have been established, including bone marrow transplants and skin grafting. A bone marrow transplant requires the removal of bone marrow from the donor and transplantation to the patient with a blood disease (leukaemia or an anaemia), to generate new blood cells. This technique is called regenerative medicine or cell therapy, which is similar to organ transplantation but works with cells only. However, the use of embryonic stem cells has just been approved in the United States in 2009. Scientists believe that there is still a long way to go before stem cell therapy can replace or replenish damaged cells and tissues in actual human patients.

Neurological diseases

Neurological diseases are disorders of the central and peripheral nervous system, including the brain, spinal cord and the peripheral nerves, which share common characteristics of neural dysfunction, progressive deterioration and loss of neural cells. However, they have diverged pathological and genetic mechanisms.Therefore, stem cell replacement therapy should be disease specific to provide optimal treatment to the patients.

Both embryonic and adult stem cells are transplanting approaches for neurological diseases, for example haematopoietic and bone marrow derived stem cells, neural stem cells, and mesenchymal stem cells. The therapy for Alzheimer's disease is to repopulate the degenerated brain. Currently, stem cell treatment is undergoing preclinical studies using animal models, with some promising results in transplanting stem cells with molecules of neurological function together. There is an improvement in a mouse's cognitive functions and the disease's pathogenesis hallmarks. However, scientists have suggested an addition of other factors is needed to support the therapy. A recent work reported on the generation of neuronal cells in a mouse brain by using neural and mesenchymal stem cell transplantation together with a small compound, with the improvement of cognitive function of the animal model. With the current technology, there is still a long way to go to ensure the safety and efficacy of stem cell therapy in human beings.

Potential areas of stem cell research in disease management

The following are some areas that could benefit from more research into how stem cells could be used to manage disease.

- Production of specific cell types in the laboratory for drug testing or drug screening

Drug testing for newly developed drugs on cell lines is common in pharmaceutical research. Large amounts of cells with the same characteristics or properties can be used to test the medicines developed. Therefore, the amount of testing done on animals can be reduced considerably.

- Study of disease processes with the aid of stem cells

To obtain the damaged cells in a disease for studying the process is very difficult, especially the cells with poor regeneration after injuries or degenerative diseases, such as nerves and the pancreas. Scientists could engineer the damaged cells to carry the disease gene from stem cells. This model can help our understanding of disease processes.

This section has covered some current and potential areas of stem cell research in biological and medical sciences. Can you think of any other potential areas? You are encouraged to think about other possible applications and to look for more information about current developments in stem cell research.

Apart from the advancement of technology, ethical issues are also a major concern when conducting research on animals or, more importantly, on human beings. It is important for you to know that striking the balance between research and ethics is crucial in research design and methods. The next section will introduce some of the different angles on embryonic research taken by members of society and the scientific field.

Self-test 4

1. In what ways can stem cells help to treat patients?
2. How can stem cells be used?
3. Based on the two types of stem cells discussed so far, what are their advantages and disadvantages in treating diseases?
4. What are the focuses of stem cell research that scientists are investigating today?
    a. When and how embryonic stem cells make decisions to produce more specialized cells.

b. How stem cells work in adults.
c. How stem cells help to treat diseases.
d. All of the above.

Self-test 4 feedback

1. With degenerative diseases such as Parkinson's disease (brain cells), heart disease (heart muscles), and diabetes (pancreatic cells), cells have been irreversibly lost and cannot be self regenerated. The capability of long term self renewal in stem cells mark the importance of this area in treating patients.
2. **Adult stem cells:** bone marrow transplants and skin grafting. **Embryonic stem cells:** repopulating the degenerated cells and transplanting stem cells to the patients.
3. **Adult stem cells:** Advantages: long history, treating blood cell cancer through transplantation. Disadvantages: less proliferative, requires high compatibility between donor and recipients, invasive collection procedures. **Embryonic stem cells:** Advantages: plastic and versatile, pluripotent. Disadvantages: control of development has not been determined, ethical concerns about the use of embryos.
4. The research helps us understand the control and process in transition from stem cells to specialized cells (A), how stem cells work (B) and how stem cells can be used in medicine and disease management (C). Therefore, the answer is (D), all of the above.

1.5 References

Below are the resources referred to or cited by the developer(s) of the original unit:

Gonneau, C (2010) University of Edinburgh's MRC Centre for Regenerative Medicine.

Larsson, J (2007) University of Edinburgh's MRC Centre for Regenerative Medicine, www.eurostemcell.org (http://www.eurostemcell.org/).

Nabil, W (2005) 'Embryonic stem cells may help sterile women', *Journal of Young Investigators*, Vol. 13, http://legacy.jyi.org/news/nb.php?id=378.

Saxena, A K, Singh, D and Gupta, J (2010) 'Role of stem cell research in therapeutic purpose — a hope for new horizon in medical biotechnology', *Journal of Experimental Therapeutics and Oncology*, Issue 8, pp. 223–33.

1.6 Conclusion

This module has introduced the general biological properties of stem cells. You came across the current uses of stem cells and their research areas. You also learnt about different types of stem cells and how these characteristics relate to the therapeutic use of these cells. The unique properties of stem cells give potential for the therapy of degenerative diseases. The application of stem cell therapy in neurological disease has been used as an example.

If you would like to learn more on this subject, you are welcome to enrol in *BIOL S401 Contemporary Biology Development (http://www.ouhk.edu.hk/wcsprd/Satellite?pagename=OUHK/tcGenericPage2010&c=C_ETPU&cid=191154130000&lang=eng)* offered by the School of Science and Technology (http://www.ouhk.edu.hk/wcsprd/Satellite?pagename=OUHK/tcSubWeb&l=C_ST&lid=191133000200&lang=eng) of the OUHK.

1.7 Glossary

adult (somatic) stem cell — rare undifferentiated cell found in many organs or tissues with limited capacity for self renewal and differentiation. Different cells vary in their differentiation capacity and are limited to organ or tissue specific cell types.

bone marrow stromal stem cells (skeletal stem cells) — a multipotent subset of bone marrow stromal cells able to form bone, cartilage, stromal cells that support blood formation, fat and fibrous tissue.

cell-based therapies — cell-based therapies, including the use of blood formation, fat and fibrous tissue formation.

cell culture — *in vitro* cell division and cell growth in an artificial medium for experimental research.

clone — to generate identical copies of a DNA fragment or genetically identical copies of a cell, or organism. The identical molecule, cell, or organism that results from the cloning process.

1. In respect to DNA: To clone a gene, a region or fragment of DNA, and make copies of that region using laboratory techniques.
2. In respect to cells grown in a tissue culture dish: a clone is a cell line that is genetically identical to the originating cell, which is produced by cell division (mitosis) of the original cell.
3. In respect to organisms: an identical individual clone refers to an animal produced by somatic cell nuclear transfer (SCNT) or parthenogenesis.

differentiation — the process of an unspecialized embryonic cell acquires the features of a specialized cell such as a heart, liver, or muscle cell, which is controlled by the interaction of physical and chemical conditions outside the cell, usually through signalling transduction involving proteins on the cell surface.

embryonic stem cell line — embryonic stem cells, which have been cultured under *in vitro* conditions that allow proliferation without differentiation for a long period of time.

fetus — the developing human from approximately eight weeks after implantation of an embryo to the uterine wall until the time of its birth.

hematopoietic stem cell — a stem cell that gives rise to all red and white blood cells and platelets.

human embryonic stem cell (hESC) — pluripotent stem cell derived from early-stage human embryos, up to and including the blastocyst stage, which are capable of dividing without differentiating for a prolonged period in culture.

***in vitro* fertilization** — fertilization similar to natural embryonic stem cell.

inner cell mass (ICM) — the cluster of cells inside the blastocyst. These cells will develop to the embryo and ultimately the fetus, which may be used to generate embryonic stem cells.

long-term self-renewal — the ICM cells may be used to generate new cells for long period depending on the specific type of stem cell.

mesenchymal stem cells — a term that is currently used to define non-blood adult stem cells from various tissues. Currently there is no clear information whether mesenchymal stem cells from different tissues are the same.

mitosis (cell division) — a type of cell division that allows a population of cells to increase its numbers with same number of chromosomes remaining.

neural stem cell — a stem cell found in adult neural tissue that can give rise to neurons and glial (supporting) cells, including astrocytes and oligodendrocytes.

neurons — principal functional units of the nervous system, which consists of a cell body and dendrite.

preimplantation — preimplantation means that the embryo has not yet implanted in the wall of the uterus.

proliferation — continuous division of single cells into two identical daughter cells.

regenerative medicine — treatments in which stem cells are induced to differentiate into the specific cell type required to repair damaged or destroyed cell populations or tissues.

reproductive cloning — treatments in which stem cells are induced to differentiate into the specific cell type required to repair damaged or destroyed cell, of which the nucleus is replaced by the somatic cell nucleus. In mammals, this would require implanting the resulting embryo with a substituted nucleus in the uterus, where a living organism with identical genetic makeup of the somatic cell donor is developed. The first animal to be created by reproductive cloning was Dolly the sheep.

somatic cell nuclear transfer (SCNT) — can be used for therapeutic or reproductive purposes, but the initial stage that combines an enucleated egg and a somatic cell nucleus is the same as reproductive cloning.

teratoma — a multi-layered benign tumor that grows from pluripotent cells injected into mice with a dysfunctional immune system, which is used to test whether they have established a human embryonic stem cell (hESC) line by injecting stem cells into such mice, hence to verify the resulting teratomas contain cells derived from all three embryonic germ layers.

therapeutic cloning — production of cells that exactly match a patient by combining a patient's somatic cell nucleus and an enucleated egg. A scientist may harvest embryonic stem cells from the resulting embryo that can be used to generate tissues that match a patient's body and are less likely to be rejected by the patient's immune system.