Journal of Experimental and Basic Medical Sciences 2024;5(1):1-6

Review

Stem Cells: General Features and Characteristics

Yeliz Göçer[1], Oytun Erbaş[1]

Stem cells are known for their potential fate, also referred to as "developmental power". Stem cells are undifferentiated cells found in both embryonic and adult cells.[1]

There are some characteristics that indicate whether a cell is a stem cell. One of these is the ability to self-renew. This ability is the ability of the parent cell to produce an exact copy of itself. Another is the differentiation property. Differentiation is a process that occurs during development, in which cells assume the specific functions of a completely different cell, such as the oxygen-carrying ability of a red blood cell or the ability of a nerve cell to send an electrical signal. With this ability, these unspecialized stem cells can be converted into the desired specialized cells with the help of various signals, either naturally or in laboratory settings. Additionally, classifying stem cells according to their location and potential helps facilitate their production and treatment processes. As the developmental process progresses, the potential for differentiation becomes limited. There are different types of stem cells with varying differentiation potentials depending on where they are found.[2,3]

ABSTRACT

The discovery of stem cells and various experimental studies on stem cell biology, types, and their use in therapies are promising and shed light on scientific research in many fields. Due to the renewal, differentiation ability, and potential of stem cells, they can be transformed into various cells in organs and tissues. Their potential characteristics guide scientists in the most effective way to eliminate or prevent diseases and diseases. They are seen as an alternative treatment for some tissue and organ damage and have been proven effective. Embryonic stem cells have the potential to create a new individual and have cell properties that can create all body tissues, but stem ethical problems arise due to their ability to create an individual. Adult stem cells (ASCs) have become the favorite of regenerative medicine due to their limited but specific effects on important multipotent potentials in certain tissues. Parameters such as ease of harvest, rapid growth, and derivation power are also included in research to facilitate them. The use of mesenchymal stem cells in treatments is particularly common. Stem cells are widely used in many areas of regenerative medicine, such as orthopedics, plastic surgery, skin, and venereal diseases, due to the ease of harvest and the abundance of the obtained quantity. The wide range of ASCs is due to their specific multipotent potential for different tissues. With developing technology, stem cell use has been approved for the treatment of many diseases. However, the development of research and treatments is limited due to ethical problems and debates. Despite this, easy and effective treatments are increasing day by day. This chapter covers stem cell definition, types, and characteristics, and where they originate from.

Keywords: Adult stem cells, embryonic stem cells, hematopoietic stem cells, induced pluripotent stem cells, mesenchymal stem cells, neural stem cells.

[1]ERBAS Institute of Experimental Medicine, Illinois, USA & Gebze, Türkiye

Correspondence: Yeliz Göçer. Institute of Experimental Medicine, 41470 Gebze-Kocaeli, Türkiye

E-mail: yelizgocerr@gmail.com

Cite this article as: Göçer Y, Erbaş O. Stem Cells: General Features and Characteristics. JEB Med Sci 2024;5(1):1-6.

doi: 10.5606/jebms.2024.1066

Received : September 10, 2023
Accepted : September 17, 2023
Published online : February 26, 2024

Human embryonic stem cells (ESCs) are early-stage cells with the ability to differentiate into any cell type in the body. These cells are also known as human pluripotent stem cells (iPSC) since they can differentiate into any type of cell found in the body. They are clusters of cells in the blastocyst, five to seven days after zygote formation.[4]

Cord blood stem cells are obtained from the umbilical cord at birth and can differentiate into several cell types in the body. They have limited differentiation capabilities similar to adult stem cells (ASCs), but unlike ASCs, they can grow indefinitely in culture. They are an unlimited source for tissue and disease models.[5]

Adult stem cells are not found in all tissues in the body but can produce a limited number of cell types in the tissue they are located in. For example, stem cells taken from the liver can only produce liver cells, which is an example of the cell's ability to self-renew by copying itself.[6]

Induced pluripotent stem cells are obtained by artificially reprogramming ASCs to a more embryonic-like state. We can describe this process as the "reverse direction of time." Induced stem cells have many of the properties of ESCs but are not the same. This groundbreaking technology is useful for creating disease models, but it is not a technology that will reduce the need for ESCs.[7]

Human ESCs derived from somatic cell nuclear transfer (SCNT) are the gold standard for stem cell research. In this technique, the nucleus of an egg cell is removed and replaced with the nucleus of an adult cell (such as a skin or blood cell) and then stimulated chemically or electrically to grow.[8]

Researchers have different perspectives on the potential of stem cells based on their location and the understanding of the process of stem cell formation, and their potential uses in disease modeling and therapy have been shaped accordingly.

STEM CELL BIOLOGY

The zygote formed by the union of sperm and egg divides successfully to form an embryo in the blastomere stage (2-12 cells) or the morula stage (day 4). These are totipotent and have the ability to form an entire organism. Later, the blastocysts consist of two different cell types: the inner cell mass (ICM), which becomes the epiblasts (7-9 days) that induce the development of a fetus, and the trophectoderm (TE). These cells multiply successfully to intermediate formations and eventually all form tissues to make up the body. The dividing cells inside the blastocyst, which are 5-6 days old, are derived from the ICM mass and are called ESCs. This type of stem cell has the ability to form all cells of the embryo and all tissues and organs derived from them. Here, cells multiply in order to form both temporary formations and all permanent tissues. The dividing cells within the ICM mass of the blastocyst, which is 5-6 days old, are derived as ESCs. These stem cells have the ability to form all cells belonging to the embryo and all tissues and organs originating from them. Embryonic stem cells are pluripotent, meaning that they can differentiate into the germ layers named endoderm, mesoderm, and ectoderm that are formed during embryogenesis. These layers provide a basis for the differentiation of cells and tissues to form a fetus and an adult organism. Cells from the ectoderm can differentiate into tissues such as the liver, lung, and intestine, while those from the mesoderm can differentiate into nerve and skin cells, and those from the endoderm can differentiate into tissues such as the heart, muscle, and kidney. Signals affecting the specialization process can be realized through external pathways such as physical contact between cells, internal pathways controlled by genes within deoxyribonucleic acid (DNA), and chemical secretion surrounding the tissue, as well as through various experimental methods in laboratory settings, leading to differentiation and the ability to transform into cells with similar properties in tissues. The blastocyst then develops into the gastrula stage. It is not possible to obtain ESCs from a developing organism (fetus, prenatal, childhood). This is when ASCs are introduced, also known as somatic stem cells, which are undifferentiated and exist among all differentiated cells throughout the body after development. Their task is to provide for the renewal, healing, and growth of daily lost cells. Adult stem cells can have multipotent and unipotent potentials. There are many types of somatic stem cells with limited differentiation potentials. Mesenchymal stem cells (MSCs) can be found in multiple tissues. These cells can differentiate into bone, fat, and cartilage cells in the bone marrow. They are considered exceptional since they possess pluripotent properties and have the ability to specialize into cells from any germ layer.[1,2]

Skin stem cells create keratinocytes, which are responsible for the protective layer in the epidermis.[9,10]

Neural cells produce nerve cells, as well as their supporting cells such as oligodendrocytes and astrocytes, in the nervous system.[11]

Dental pulp stem cells (DPSCs) are located in the dental pulp. They have osteogenic and chondrogenic potential.[12]

Hematopoietic stem cells (HSCs) create all types of blood cells, including red, white, and platelet cells.[13]

The proliferation time of somatic stem cells is longer than that of ESCs. It is possible to induce somatic stem cells to regain pluripotent properties. This technique was used in the famous cloning of Dolly the sheep, in which ASCs were transformed into stem cells with similar pluripotent properties.[2,3]

TYPES OF STEM CELLS

When examined in detail, types of stem cells can be classified under three main headings. The first and fundamental type of stem cell is ESCs derived from embryos. These cells have totipotent potential and have the capacity to form a new individual. However, due to ethical debates, their research and therapeutic use are limited. The second type is ASCs, which have the widest range. These stem cells are the most commonly used cells in regenerative medicine. The third type is iPSC. These cells have been the subject of research for the treatment of various neurodegenerative disorders as they acquire similar properties to ESCs.[1,2]

EMBRYONIC STEM CELLS

Embryonic cells are cells that have totipotent potential, meaning they have the ability to form all the tissues and stem organs in the body. These cells are formed after the fusion of sperm and egg. With advances in technology, it is now possible to derive, differentiate, and multiply these cells under good conditions. They are derived from the ICM of the embryonic blastocyst and are also known as iPSC that can differentiate into all three germ layers both *in vitro* and *in vivo*. They can be maintained for a long time (approximately 1-2 years with cell division every 36-48 hours) with their potential unchanged in an undifferentiated phenotype. Physical microdissection or complement-mediated immune dissection can be used to isolate them. To prevent unwanted early and natural differentiation, rapid freezing (shock) or vitrification techniques are used. The culturing period of ESCs, which requires special care, should be long-term for therapeutic and research applications. In contrast, somatic stem cells and MSCs have limited renewal properties and can no longer undergo division. The lifespan of cells depends on the type of cell, donor type, donor age, and telomerase activity. Telomeres are structures that protect chromosome length. Telomerase is an enzyme that adds special short sequences to the ends of chromosomes and supports cell division. Telomerase activity is quite high in ESCs.[1,2,14]

Embryonic stem cell research is illegal or highly restricted in many countries. However, Singapore and South Korea are among the least restrictive countries.[3,14]

ADULT (SOMATIC) STEM CELLS

Adult (somatic) stem cells are another type of stem cell that has high potential and can differentiate into various types of cells depending on the tissues they are in. Like other stem cells, they have two important properties: they can self-renew for a long time and can differentiate into a specific cell with a specific function. These cells are progenitors and are semi-differentiated in fetal and adult tissues. In short, ASCs are cells that can renew themselves and can differentiate into a specific cell of the organ from which they originated, while remaining undifferentiated in a differentiated tissue. They are responsible for tissue repairs in cases of injury, disease, or cell renewal. They have been a focus of interest in many fields, such as the treatment of degenerative diseases and the rejuvenation of aging tissues. Their continuous renewal and cell formation bring to mind irregularly proliferating cell forms that trigger cancer. However, current information suggests that it can be taken to a dimension that can treat cancer.[1,2,6]

Although limited studies have been conducted, there are some treatments that have been approved as a result of clinical research. One of these is bone marrow transplantation using HSCs to renew blood cells. Hematopoietic stem cells are continuously produced by the bone marrow and are also responsible for renewing blood cells, which is their most important function.[13]

It is used to treat various types of cancer and associated conditions. Cell migration, plasticity, and cell activation should be coordinated for tissue repair. To be effective in healing wounds on the skin, different epidermal stem cells taken from various skin regions must work in harmony with fibroblasts and immune cells. The only stem cell-based products approved by the Food and Drug Administration for various skin disorders and skin burns are progenitor hematopoietic cells obtained from cord blood. The other approved treatment is Holoclar, which is based on ocular stem cells and was approved for corneal damage in Europe in 2015.[6,15]

There is a wide range of somatic stem cells, including bone marrow, dental root, blood, brain, spinal cord, blood vessels, striated muscle, digestive system, cornea, retina, epidermal tissue of the skin, pancreas, and liver, among others.

Mesenchymal stem cells, which have an important role in the development of regenerative medicine derived from stem cells, have been proven in some cell therapies, leading to more research and discussion about stem cells. MSCs have become an alternative treatment without the ethical debates surrounding embryonic and fetal stem cells. They were first isolated by Friedenstein in 1974 and can be obtained from various tissues such as bone marrow, umbilical cord, menstrual blood, endometrial polyps, and adipose tissue. The ease of harvesting and quantity of MSCs in clinical and experimental applications provide convenience in research. According to the information obtained, 2-5 of the MSCs are obtained from 1 million mononuclear cells in the bone marrow.[16,17]

Mesenchymal stem cells have been proven to have treatments for bone tissue repair,[18] hematopoietic recovery,[19] osteogenesis imperfecta,[20] and more. MSCs can be isolated with certain surface markers (CD44, Stro-1, CD29, CD105, etc.). They are responsible for structures such as adipose tissue (Wnt signal), bone (LRP-5/Wnt signal, telomerase, Cbfa-1), tendon (mechanical transmission signal), muscle (bHLH), and cartilage (cell adhesion, Sox, etc.). Their characteristic features provide convenience for use in treatment. Using stem cells, it is possible to replace damaged cells with healthy cells without replacing the entire organ. In addition, tissue-specific stem cells do not form cancerous structures, unlike ASCs. They can be easily and quickly obtained from the body and cause fewer ethical problems.[2,3,20,21]

Adipose stem cells (ASCs), which also have an important role in regenerative medicine among ASCs, have been used in therapies thanks to their versatile therapeutic abilities. ASCs are somatic stem cells resident in adipose tissue with differentiation potential among mesenchymal lineages. It is known that they exhibit strong immune responses to promote cell renewal during wound repair. They can be easily cultured and expanded *in vitro*. Their use in cellular therapy is facilitated by reduced immune privilege. Stem cells isolated from fat and bone tissue have provided extensive treatment opportunities in orthopedics. A study conducted by tissue engineers showed that bone marrow-derived mesenchymal stromal cells (BM-MSCs) wrapped in a thrombocyte-rich plasma hydrogel combined with calcium phosphate micro-particles improved the ectopic bone formation potential of MSCs in their spherical structures. In a study on mice, compared to adipose stem cells, there was a significant increase in the expression of osteogenic markers such as alkaline phosphatase and collagen type 1. However, further research into additional effects was recommended.[21]

Stem cells are not only used in bone diseases but also in the treatment of neurodegenerative disorders. Recently, the neuroprotective effects of neural stem cells in reducing brain tissue damage have been the subject of discussion.

As a result of research on the use of MSCs in the treatment of cardiovascular diseases, a decrease in infarct size by 7% was observed in acute myocardial infarction and chronic ischemic mouse models after MSC transplantation. In addition, an improvement in heart function by 11% was reported. With further research and current information, it is possible to achieve significant success in the treatment of cardiovascular diseases.[22]

INDUCED PLURIPOTENT STEM CELLS

In 2006, Yamanaka and Takahashi[23] made an important discovery in stem cell therapy by showing that it is possible to convert ASCs, which are multipotent, into iPSC. In this study, the life of the fetus was not endangered. The four transcription factors (Oct-4, Sox2, KLF4, and Myc) expressed in ESCs were also found to be present in iPSC. Actually, in Yamanaka's original paper, 24 factors were initially used, but effective four factors were found through trial and error. These four genes code for transcription factors that act like switches that turn on and off the activity of other genes. Initially, scientists used viruses to introduce these four genes, but in some animal experiments, it caused cancer. When this result was reached, safer methods were preferred. In other experiments, they showed that two of the four genes could be found in other genes. In their research, the retroviral transduction of mouse fibroblasts could induce fibroblasts to acquire pluripotency. This new stem cell is called an iPSC. Yamanaka was influenced by the research of two scientists that took place in 1962 and 1987 before this discovery.[24,25]

First, it impressed Yamanaka when scientist John Gurdon successfully cloned frogs by transferring a nucleus from a frog's somatic cells to an oocyte cell. This caused a complete reversal of cell development, and at that time cell differentiation was thought to be unidirectional. The course and outcome of the experiment revealed that it is even possible for a somatic cell to acquire pluripotency.[24,26]

The second was a study by Davis[27] that focused on fibroblast DNA extraction. Three genes were found that first appeared in the myeloblast form. Mandatory

expression of one of the genes called myogenic differentiation 1 (Myod1), caused fibroblasts to transform into myeloblasts. These results revealed that cells can be reprogrammed and used to transform cells from one lineage to another.

Induced pluripotent stem cells were initially derived from fibroblasts. Biopsies were taken and subjected to many tests to obtain these cells. The use of easily accessible cells is also a research topic. In this process, researchers used peripheral blood cells, epithelial cells found in the kidney, keratinocytes, and fibroblasts were preferred as the best source. One of the biggest reasons for this is its better controllability. Their rapid growth abilities were the subject of the teratoma test. Teratomas are benign tumors. In addition to their rapid growth, they have high pluripotency with the ability to transform into tissues of all three germ layers.[1,28]

Induced pluripotent stem cells can differentiate into many different cell types, but they differ from ESCs in important aspects such as the location of their epigenetic effects. However, it is known that producing living animals like iPSC mice is more challenging than ESCs. Induced pluripotent stem cell research will contribute significantly to the advancement of regenerative medicine in the future. Treatments will be carried out under better and easier conditions.[4,28]

Stem cells with appropriate properties should be preferred for therapeutic use. However, iPSCs can be the treatment door for almost any disease. For neural repair, brain-derived stem cells are multipotent and are responsible for the generation of all neural cell types during development. In addition, neurons derived from iPSCs have the ability to form structurally and functionally active synaptic networks. As a new technology, iPSCs are limited in terms of animal models. In the study, an ischemic rodent model was used, and it was observed that the neurological function of neural stem cells derived from human iPSCs was improved. In another study, it was observed that memory impairment was reversed. Induced pluripotent stem cell technology enables the production of autologous iPSC, eliminating both the problems of immune rejection and ethical limitations of non-patient-specific sources. They noticed that in a model of Parkinson's disease, autologous iPSC-generated dopaminergic neuronal transplantation remained active for a long time and improved motor function survived for two years.[29-31]

In conclusion, stem cell research holds immense promise in various therapeutic avenues. While ethical concerns persist, adult stem cells offer specific advantages in regenerative medicine. Their ease of harvesting and multipotent potential make them valuable assets across medical disciplines. Despite ongoing debates, advancements in stem cell research continue to pave the way for more accessible and effective treatments.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

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