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Stem Cells and Regenerative Medicine

Kök Hücre ve Rejeneratif Tıp

Ceyda HAYRETDAĞ[1], Ender M. COŞKUNPINAR[2]

Abstract

Stem cells are self-renewing, non-differentiated cells that can be transforming into many different cell types and can form all the tissues and organs in our body when proper conditions are provided. Stem cells can be divided into three groups: adult stem cells, stem cells derived from cord blood, and embryonic stem cells. These cells, which have not yet differentiated, have the capacity of self-renewal, unlimited division and can transform into organs and tissues. Adult stem cells are found in many tissues and organs in the body and when damage occurs they multiply at that position to repair the damaged area. Discovery of stem cell differentiation also opened the doors for stem cell therapy in different fields such as; cancer, paralysis, Alzheimer's, parkinsonism, spinal cord injuries, heart diseases and many genetic diseases.

Keywords: Stem cell, regenerative medicine, personalized medicine

Öz

Kök hücreler, çok farklı hücre tiplerine dönüşebilen ve uygun koşullar sağlandığında vücudumuzdaki tüm doku ve organları oluşturabilen, kendini yenileyebilen, farklılaşmamış hücrelerdir. Kök hücreler üç gruba ayrılabilir: yetişkin kök hücreler, kord kanından elde edilen kök hücreler ve embriyonik kök hücreler. Henüz farklılaşmamış bu hücreler, kendini yenileme, sınırsız bölünme kapasitesine sahiptir ve organlara ve dokulara dönüşebilirler. Yetişkin kök hücreler, vücuttaki birçok doku ve organda bulunur ve hasar meydana geldiğinde hasarlı alanı onarmak için bu pozisyonda çoğalırlar. Kök hücre farklılaşmasının keşfi, kanser, felç, Alzheimer, parkinsonizm, omurilik yaralanmaları, kalp hastalıkları ve birçok genetik hastalık gibi farklı alanlarda kök hücre tedavisi için kapılar açmıştır.

Anahtar Kelimeler: Kök hücre, rejeneratif tıp, kişiselleştirilmiş tıp

Stem cell

Stem cells are cells that have the potential to replace the cells lost in the life of the organism in the embryonic and adulthood with the effect of environmental signals and transform into different cell types.[1,2]

Hematopoiesis could be described as the production, differentiation and development of blood cells.[3] The hematopoietic system includes bone marrow, liver, spleen, lymph nodes and thymus. The mechanism of cell differentiation and development is determined by the combined effects of specific growth and transcription factors or altered expression of growth factor receptors, or both.[4] It is possible to group stem cells according to their differentiation capacities. Totipotent stem cells can create all the cells in the body and the only example of this is the zygote.[4] In the early embryonic period, all blastomer from 4 cells to 8 cells are considered totipotent. Cells derived from this blastocyst inner cell mass can transform into many different cell types to form endoderm, ectoderm and mesoderm, and these cells are considered as pluripotent stem cells.[5] Adult stem cells, which are cells capable of differentiation only in a limited area or can only differentiate with a specific stimulus, are seen in the later stages of development.[5] The best example of this is hematopoietic stem cells. These cells are considered multipotent cells.[5]

[1]University of Health Sciences, Faculty of Medicine, Department of Anatomy, Uskudar, Istanbul, Turkey
[2]University of Health Sciences, Faculty of Medicine, Department of Medical Biology, Uskudar, Istanbul, Turkey

Correspondence:
Ender M. COŞKUNPINAR
Associated Professor, Department of Medical Biology, Faculty of Medicine, University of Health Sciences, İstanbul, Turkey
E-mail: ecoskunpinar@gmail.com

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1) Adult stem cells

They exist in many tissues and organs, and they can repair cell damage. These cells could be only transforming into their own cell group. Hence, their capacity to multiply is limited.[5-7]

2) Cord blood stem cells

Cord blood stem cells obtained from the cord fluid.[6] This fluid contained many stem cells from the baby, and these cells can be stored in cord blood banks for future use. Cord blood stem cells obtained during birth from the umbilical cord that connects the baby to the mother. Although these cells have been acquired in the early developmental stage, they classified in the adult stem cell class; hence, they can specialize into limited tissue and cell types.[6] Cord blood stem cells are important sources for blood and immune system disease treatment.[8] Furthermore, the FDA has approved five hematopoietic stem cell products derived from umbilical cord blood, for the treatment of blood and immunological diseases.[9]

3) Embryonic stem cells

They formed by fertilized zygote proliferation. Embryonic stem cells are formed during the blastocyst stage, and they have the capacity to form the entire organism.[10] Embryonic stem cells are obtained from embryos that reached the blastocyst stage before implantation.[10] Researchers study to find different culture methods to grow embryonic stem cells in the laboratory environment, however stem cells need supporting cells to grow. In addition, agents such as LIF (Leukemia Inhibitory Factor) and B-FGF needed for the protection of non-differentiated structures.[10] Another important feature of embryonic stem cells be their ability to divide continuously likes cancer cells, and unlike cancer cells, their karyotype is normal. Stem cell division is "asymmetric", and it is not just unlimited dividing cell like cancer cell.[10] If supportive cells and agents are, absent embryonic stem cells can be differentiated into all kinds of cells and tissues that form the living body. It should be noted that, although the mechanism of differentiation for some agents be known, the knowledge limited. Current studies are mostly focused on heart muscle, nerve, insulin-producing cells and blood cells.[11,12]

The first stem cell transplantation trial was made in 1957 by E. Donnall Thomas.[13] The first successful practice, however, were made towards the end of the 80's.[13] Some of the diseases that can be treated with stem cell transplantation are lymphomas (lymphoid cancer), leukemia, breast cancer, brain tumors, anemia, immune deficiencies.[13] Some illnesses that may be of benefit to future treatments are loss of vision, heart valve disorders, growing new teeth, organ production.[13]

Today, researchers investigate stem cell therapy, which may replace organ transplantation and will be a hope for patients.[14] Therefore, stem cell therapies are still research-based. However, promising studies on many topics such as heart muscle renewal, diabetes, rheumatoid diseases, nervous system diseases (Parkinson's, Alzheimer's), spinal cord injuries, liver injuries are continuing to rapidly grow.[14]

Stem cell therapies

Cells differentiated into organs such as brain, heart and liver cannot be renewed naturally if they experience severe damage.[15] Replacement of diseased cells with healthy cells are called cell therapy.[15] This treatment shows similarity to organ transplantation, but instead of the organs cells are used. Another difference from organ transplantation is that healthy cells may be taken from the same person, without a problem of tissue compatibility.[16] On the other hand, cord blood cells can be used for the same purposes.[16] However, cord blood cells also have limited use.[16] If the experiments succeed, stem cell therapies will not require extensive surgery or drug administration.[16]

Use of magnets in stem cell treatment

Stem cells used in the treatment will be taken from the patient's own bone marrow. Miniature magnet pieces will be added to these stem cells in labs.[17] The nanomagnets to be used in this method are currently used to obtain healthy results from MR scans.[17] The course of action is moving stem cells into target tissues and activating them at that place.[18] Hence, the procedure will be completed without the need for surgery or alternative treatment. Recent studies have shown that a very small percentage of cells (0.1–1%) present in a variety of solid tumors possess characteristics similar to stem cells, and such stem-like tumor cells have been designated cancer stem cells (CSCs).[18]

Embryonic stem cells treatment and therapy

In studies conducted with especially mouse embryonic stem cells, it has been scientifically proven that these cells can differentiate into different cell types.[19] Studies

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are still conducted to understand damage following transplantation and structures formed after transplantation and transformation mechanisms.[19] Correspondingly, human embryonic stem cells thanks to their continuous self-renewal and their potential to differentiate to all cell types will offer treatments to such as Alzheimer's, diabetes, Parkinson's, and infarction.[19] This property of stem cells also led to the emergence of a new field: regenerative medicine recently.[19] Furthermore, studies conducted with laboratory animals have proven that these cells can also form germ cells. For this reason, the use of stem cells in infertility treatment may come to debate soon.[20-24]

Limitations for embryonic stem cell therapy

One of the most crucial factors affecting success in tissue or organ transplantation is tissue compatibility between the patient and donor.[25] Similar problems may arise in embryonic stem cell therapies in the future, hence scientists develop different solutions.[25] These are they create stem cell banks with defined tissue characteristics, create a universal donor stem cell by modifying genes that are responsible of tissue compatibility, producing personalized stem cells by therapeutic cloning techniques.[25]

Although more than 80 embryonic stem cell strains have been reported worldwide, only a few of them have been tested for embryonic stem cell criteria and only a few stem cell strains have been used in studies. In the case of therapeutic uses, at least a few hundred thousand different stem cell strains are thought to be needed to avoid the problem of tissue compatibility. This leads to the requirement of biobanking for embryonic stem cells.[26] Perhaps the first condition for stem cell treatment in the future will be the acquisition of stem cell strains of the desired tissue type.[26] Another approach dealt now is the prevention of rejection of the transplanted cells in these cells genes responsible for tissue compatibility are replaced by gene engineering technique by the recipient body.[27] In fact, the provision of this situation is much more important than biobank formation.[26] Because the genetically altered cells obtained in this way can be used in many different individuals, if this becomes a reality there will be no need for stem cell biobanking.[26] Another alternative is the method of obtaining a stem cell specific to a patient by a therapeutic cloning technique.[28-30]

Especially, cloning, a method applied to livestock and laboratory animals in recent years can be used for therapeutic purposes, and since the clone-embryo and embryonic stem cells obtained after the procedure carry the same tissue matching genes as the person whose cells are used, the problem of rejection in the transplantation process can be abolished.[28,29]

Scientists have shown that cloned embryos have a largely different genetic program than those obtained by normal fertilization.[30] Therefore, it is currently unknown whether stem cells obtained by the same technique will have such problems in the future.[30] Because of these unknown factors, human cloning studies has been banned in many countries including the United States of America, and legal sanctions and penalties have been imposed on those who conduct these studies.[30] Recently, however, South Korean scientists have used cloning techniques for therapeutic purposes to obtain the first human embryonic stem cell strain.[31] This result has led to further exacerbation of ethical debates in all over the world.[31] The efficiency of the technique is extremely low, since only 1 stem cell strain is obtained after processing approximately 240 human oocytes.[31] In addition, since much of the work has been carried out with laboratory animals, it is not yet an acceptable technique for the use of human treatment.[31]

According to news in Nature the use of tissues from human embryonic stem cells in disease treatment has been restarted by the Geron Company in September 2010 after a 10-year pause.[32] Because of these clinical investigations, tissues from human embryonic stem cells will be used to treat damage to some organs in the human body.[32] However, Geron, the first company to test embryonic stem cells in humans, stopped work on this area.[32] The Geron Company was founded in 1990 and started experiments on stem cells in 1998.[33] In May 2008, the American Food and Drug Administration rejected Geron's 21.000-page application, which halted embryonic stem cell research.[33] However, a few days after Barack Obama was president, the obstacle was removed and researches restarted.[34] The Geron Company underwent "specialized stem cell injections" in four of the eight patients that had been paralyzed by spinal cord injury in the Phase 1 study.[35] Geron's CEO, John Scarlet, reported that although there were no serious side effects in these four patients, no evidence of treatment was available, so no new patients would be taken.[35] After Geron's decision to withdraw, the only approved work was continued by ACT Company. Robert Lanza, director of

the ACT Company, said patients and investors have great expectations that "embryonic stem cells" have significant potential in therapy and trade.[35] Lanza emphasized that there was a big pressure in this area originating from the expectation that there will be a big success in the early stages.[35]

Stem cell plasticity

The demonstration that hematopoietic stem can not only differentiate to blood cells but also other cell types, arose the term stem cell plasticity.[36] Recent studies have shown that hematopoietic stem cells can form bone, cartilage, neural cells, pneumocytes, skin, muscle, epithelial cells, endothelial cells, kidney and liver cells.[37] Furthermore, animal experiments showed that these tissues are not morphologically identical but also functional.[37] Bone marrow also contains non-stem cells of the hematopoietic stem cell class.[37] The most frequently used of these are so called "mesenchymal stem cells" are found in the bone marrow stroma and are capable of forming bone, cartilage, fat cells and nerve cells.[36,37] Today, it is a preferred group of stem cells in clinical based human applications.[36,37] Endothelial precursor stem cells (hemangioblast) are another group of cells that have been intensively studied in recent years for the reasons of importance of vascular pathologies.[36,37] Different mechanisms have been identified in the concept of stem cell plasticity.[36,37] The ability of a stem cell to create cells of a different tissue under proper conditions is termed "transdifferiation".[38] If the root cell is first transformed into a precursor cell and then a cell of a different tissue is called as "dedifferentiation". Stem cells used for regenerative purposes can form teratomas containing cells and tissues originating from endoderm (small intestine) and mesoderm (tooth, bone, cartilage). Another problem of these cells is their allogeneic property, namely they can be rejected. In the world where there are many controversies in terms of ethics and law, embryonic stem cell researches are carried out only with controlled permission.[38] In this regard, the Ministry of Health in our country has banned working with embryonic stem cells until the necessary legal infrastructure has been provided.[38] Nowadays it is possible to do research if necessary regulations have been prepared and if appropriate ethical conditions are met.

Horwitz et al.'s research that involved mesenchymal stem cell application resulted in osteogenesis imperfection first raised a hope in neurological applications.[38] It has not been possible to elucidate the basic biological mechanisms of partial clinical outcomes, which have been achieved with many laboratory studies.[39] However, there is expectation of neurological success from embryonic stem cells.[39] While it seems likely that almost all tissues can be formed in the laboratory, there is a need for further studies for functionally applicable cellular therapies.[39]Studies continue for unanswered questions. In the long run, regenerative medicine will be one of the important areas in the future.[39] The most important problems faced in this area are probably ethical problems.[39] All researchers must carry out well planned researches without leaving ethical principles.[39]

Stem cell differentiation

There are various internal and external factors that trigger the differentiation of stem cells.[40] There are genes in stem cell DNA that can create various tissues. One of the factors that affect division is telomer length.[40] External factors that contribute stem cell differentiation are: chemical secreted by neighboring cells, physical connections with neighboring cells and molecules in the microcirculation.[40]

Regenerative therapeutic approaches in neurological diseases

In neurological diseases, stem cell and regenerative approaches can be evaluated in several categories. We can collect the neurological diseases that have undergone stem cell therapy in 4 groups.

First group, stem cell applications are used in acute phase diseases. This group includes stroke, traumatic brain or spinal cord injuries, neonatal hypoxic and ischemic encephalopathies or perinatal asphyxia.[41]

The second group is chronic neurodegenerative diseases. Among the diseases in this group, ALS (Amyotrophic Lateral Sclerosis), Alzheimer's, Parkinson's, Huntington's disease and has suitable conditions for stem cell applications.[41]

In the third group, chronic inflammation and immunological diseases are present. Among them, the most suitable disease for stem cell applications is *Multiple Sclerosis*.[41]

In the fourth group, there are genetic diseases especially seen in children.[41] Within these illnesses, neuronal ceroid lipofuscinosis, mucopolysaccharidoses and leukodystrophies are suitable for stem cell applications.[41]

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As could be seen from these stem cell applications in neurological sciences offer new possibilities for treatment in wide range of settings.[41]

Stem cell applications in spinal cord injuries

Traumatic spinal cord injuries are one of the major problems all over the world.[42] With this kind of injury of the central nervous system, there are cell losses in the tissue, serious loss of myelin, and therefore it becomes almost impossible to establish a new neural connection.[42] For this reason, it is not possible to obtain an adequate result with only decompression and FTR methods.[42] On the other hand, hematopoietic stem cells obtained from transplanted bone marrow demonstrate that cells in damaged tissues have renewed and repaired their myelin sheath.[42]

Stem cell use in cancer

Todays, it has been shown that a very small percentage of cells (~0.1-1%) present in a variety of solid tumors possess characteristics similar to stem cells, such stem-like tumor cells have been designated cancer stem cells.[43] Bone marrow and cord blood derived stem cells are used for the compensation of damaged cells after chemotherapy and radiotherapy. Bone marrow transplantation is made in two forms as autologous and allogeneic.[43] At the University of Texas, Dr. Michael Andreff and his team genetically manipulated stem cells derived from bone marrow injected a protein called interferon alpha. These cells slowed the progression of leukemia, and are effective in breast cancer, ovarian cancer and brain tumor formation.[43]

Use of stem cells in tooth renewal treatment

Recently, a number of adult stem cell types have been isolated from dental tissues, including dental pulp stem cells.[44] Experts say that tooth production in a mouse has started using stem cells. During the first phase of the study, scientists produced extracts containing the cells necessary for dental development from the stem cells in 5 days and then injected it into the jaw bone of the mouse.[45] At the end of the 5th week, gingiva was split apart, and the tip of the tooth was visible.[45] After 2 weeks, they announced that a tooth was formed with normal tooth hardness and sensitivity and it easily food grinding.[45]

Recent studies on tissue and organ formation

In a study conducted in 2009, it was stated that 2 mm diameter eye close to the eye size of a newborn mice was formed from embryonic stem cells.[46,47] It was thought that this work will contribute to the continuing work against blindness and other eye diseases.[46,47] Another study reported that stem cells found in hair follicles are used to form skin tissue and this tissue is used for burn injury treatment.[46,47]

Recent studies on stem cells

We believe that the basic scientific studies done in animals will enlighten human therapy applications. Recently, scientists had been discovered of CRISPR/Cas9 endonucleases in bacteria and their modification for use in genetic research, these methods have the potential to therapy planning for a lot of diseases.[48] Use of CRISPR/Cas9 has created a whirlwind within the scientific community in the last few years, as the race to move beyond just disease analysis and toward the goal of gene and cell therapy moves further.[48] Recently, clinical studies have been ongoing with embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSC) particularly in Asia and the United States.[48] However, it is reported that there are some deficiencies in the treatment of diabetes which is performed by adult stem cells.[48] Regenerative medicine and expanded stem cell research shows the potential for the development of *in vitro* applications to resolve problems encountered in the treatment of many diseases such as Parkinson's disease, Alzheimer's disease, spinal cord injuries, diabetes, cancer with expanded stem cell research with technological advances in nanotechnology and materials science.[49]

As it can be understood from this stem cell therapy based treatments of genetic based diseases are possible in laboratory conditions or in animal experiments, but the use of stem cell therapy is yet to be verified in humans. However, successful treatments that can be applied to people are being approached step by step fashion. Finally, recent results and current controversies in the field are reviewed and permanent challenges to further development are explored.

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