

Original Article: Advances in Stem Cell Therapy for Regenerative Medicine



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ABSTRACT

One of these new concepts that was created with the increasing development of medical science and biological knowledge was “Regenerative Medicine”, which is referred to as the medicine of the future. It has been less than 20 years since the concept of regenerative medicine entered the medical field and has become one of the areas of interest of universities, research centers, and biotechnology and pharmaceutical companies. Regenerative medicine seeks to find new methods of preventing, diagnosing, and treating diseases, so that it can move from traditional medicine that works around the diagnosis and treatment with chemical and, to some extent, biotechnological drugs, towards individual-centered medicine and even precision medicine, for which biological products and drugs will play an important role. Despite the extensive advances in medical science, a significant number of human diseases are still incurable and only the symptoms of the disease are controlled. Therefore, regenerative medicine tries to treat these diseases definitively by using the same tools that the body naturally uses to repair damaged tissues and organs. These tools include: body cells, the material that surrounds cells in their natural habitat, and molecules that affect cells. Stem cells are one type of cell used in this field and have received special attention due to their great ability to transform into other cells and repair damaged areas. Stem cells play a major role in the development of organisms from the embryonic period and these cells can be identified in body tissues both during the embryonic period and after birth and are responsible for maintaining cellular balance in the normal state as well as during the process of repairing a tissue after disease.

Introduction

If we consider the human body as a building, stem cells are the foundation of this building [1]. They are the only cells that have the ability to produce and create specialized cells and can make more than 200 specialized cells such as blood, bone and muscle cells [2]. These cells are produced

by the bone marrow. Initially, one type of stem cell builds the body [3].

Then another group of these cells acts as a repair and maintenance team to support these structures. Research currently being conducted in the field of stem cells is increasing human knowledge about how the stages and processes of development occur during the embryonic period, as well as how damaged

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cells in the body are replaced after illness and how the normal function of tissues and organs in the body is restored as a result of various injuries [4-6]. This knowledge will be very effective in discovering new therapies using cells, and the direct use of stem cells in the treatment of many diseases has also been considered, and in numerous studies

conducted in this field, the positive effect of this approach has been identified in a number of diseases [7]. There are different types of stem cells. Embryonic stem cells are the most versatile. Because they can become all the cells of a developing fetus [8] (Figure 1).

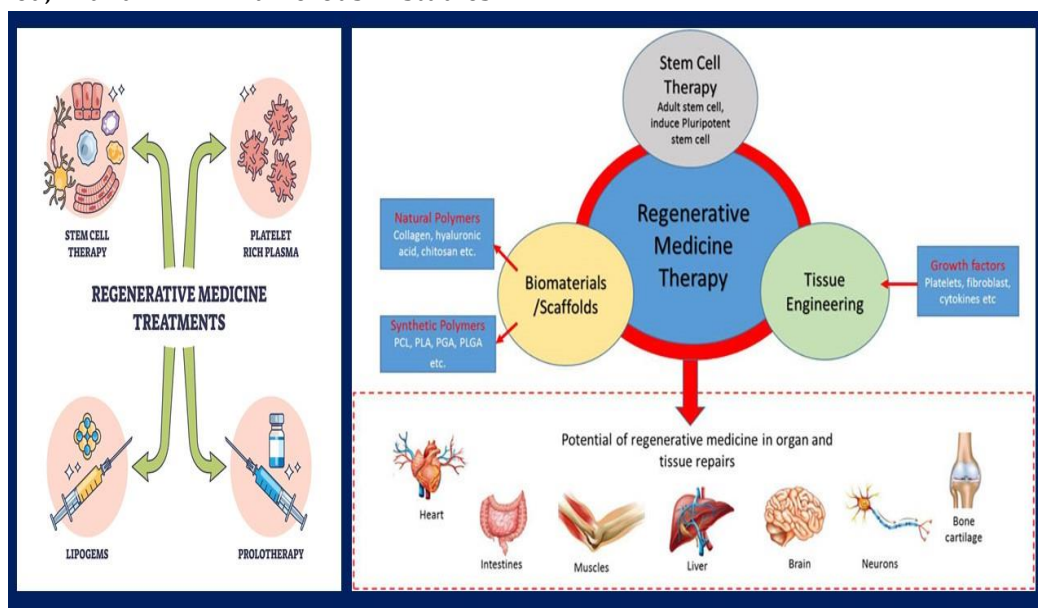


Figure 1. Advances in Stem Cell Therapy for Regenerative Medicine

Most stem cells in the body have a lower ability to create cells and may only help maintain and repair the tissues and organs in which they live. Stem cells can be classified based on where they are and what they do [9]. Stem cells can also be classified based on differentiation. In these conditions, they include pluripotent and unipotent stem cells. Pluripotent stem cells are actually the same embryonic stem cells that can become any type of cell and tissue. Medical researchers obtain embryonic stem cells from donated umbilical cord blood or embryos created during in vitro fertilization [10]. Unipotent or multipotent cells are also tissue-specific stem cells.

These cells can make new stem cells, but only for the tissue in which they live. If we were to classify stem cells based on their origin, we would again have two main categories:

embryonic stem cells and adult stem cells. Embryonic stem cells are the same cells that are obtained from fetal tissue and can become any cell. They can even become a complete, differentiated embryo [11]. To achieve this, Advanced Therapy Medicinal Products (ATMPs) are defined. ATMPs are therapeutic and medicinal products based on genes, tissues, and cells that are used in humans. ATMP products are divided into four different groups, which are:

1- Gene therapy drugs: These drugs contain genes that lead to therapeutic, preventive or diagnostic effects. These products are mainly used by introducing recombinant genes into the patient's body to treat a wide range of diseases, including genetic abnormalities, cancer or chronic diseases. A recombinant gene is actually a piece of synthetic DNA in the

laboratory that is made and provided as a combination of one or more gene fragments from different sources [12].

2- Cell therapy drugs: These drugs include cells and tissues that have been manipulated to change their biological characteristics or cells and tissues that have been used for purposes other than their intended use. These drugs can also be used to treat, diagnose, and prevent diseases [13].

3- Tissue engineering drugs: These drugs include cells and tissues that have been modified to regenerate, repair, and replace human tissues [14].

4- Combination drugs: These drugs consist of a biological drug along with other materials and compounds. A typical example of this type of drug is cells embedded in a biodegradable scaffold or substrate [15].

Despite significant annual growth in the regenerative medicine industry, one of the economic problems facing companies active in this industry is the high R&D intensity index in this field.

This indicator indicates the percentage of the company's annual profit that is spent on research and development of new products in the company. It has been shown that companies active in the field of regenerative medicine spend an average of 21% of their annual profit in the R&D unit on research and development of new products, which is considered a major challenge for economic investors in this field [16].

Therefore, the Royan Advanced Medical Products Development Center, considering the aforementioned challenge, has focused on designing and carrying out the research and development stages of products based on regenerative medicine before the desired product enters the market [17].

In this regard, the center's production unit works to find reliable cell sources and examine the safety and efficacy of cell products. The

quality control unit also pays serious attention to the effort to monitor the production of safe and efficient products in compliance with international standards [18].

Also, the quality assurance unit closely monitors the documentation of all production stages from beginning to end based on defined protocols in compliance with international standards [19]. Therapeutic products in the regenerative medicine industry are classified into 4 groups, including the following:

- ✓ Primary cell-based therapeutic products [20].
- ✓ Stem or progenitor cell-based therapeutic products.
- ✓ Cell-based immunotherapy therapeutic products [21].
- ✓ Gene therapy products.

In each of the above categories, a number of products have received commercialization approval from international regulatory organizations such as the US Food and Drug Administration (FDA), Health Canada, the European Medicines Agency (EMA), the Korean Food and Drug Administration (KFDA), Australia and New Zealand, and their number is increasing every year [22]. Among the products with commercialization approval that have entered the clinic:

- ✓ 38% in the field of skin diseases.
- ✓ 30% related to diseases of the musculoskeletal system.
- ✓ 8% related to inflammatory diseases and the immune system.
- ✓ 4% eye diseases [23].
- ✓ 4% types of cancer.
- ✓ 4% related to types of cardiovascular diseases [24].

Companies active in the regenerative medicine industry in the world are active in four specific areas, including the following:

1- Therapeutics and Devices: The majority of companies active in the regenerative medicine industry, i.e. 58% of them, are active in the field

of producing therapeutic products or devices. These companies are active in the field of developing and producing cell therapy products, small molecules, biological drugs, gene therapy products and tissue engineering biomaterials and implantable devices [25].

2- Tools: The second group of these companies is active in the field of devices and equipment related to regenerative medicine and constitutes 19% of all companies active in the regenerative medicine industry. These companies are active in the field of developing clinical and bioprocess equipment, support equipment, solutions and consumables, and storage equipment [26].

3- Cell banks: 13% of all companies active in the regenerative medicine industry are engaged in the storage and banking of cells from umbilical cord blood and adult stem cells.

4- Services: About 13% of all companies active in the regenerative medicine industry are

companies providing specialized support services such as conducting clinical trials, determining the characteristics (characterization) of products and their quality control [27].

Regenerative medicine is expected to have a significant impact on healthcare for costly, specific and chronic diseases such as cardiovascular diseases, stroke, diabetes, soft tissue regeneration, neurological diseases such as ALS, Parkinson's and Alzheimer's, which currently account for the majority of healthcare costs. From an economic perspective, the market in this area was predicted to reach \$ 8.8 billion by 2016. Because stem cells have the ability to transform into many different types of cells, scientists believe that these cells could be useful in treating and understanding various diseases (Table 1).

Table 1. Uses of Stem Cells

Stem cell applications	Description
Growing new cells in the laboratory to replace damaged organs or tissues	Stem cells can help grow new cells or tissues, which can be used to treat damage and failure of organs such as the liver or heart.
Repairing parts of organs that are not working properly	Stem cells are able to enter and improve the function of failing organs, such as the heart or kidneys.
Investigating the causes of genetic defects in cells	Stem cell research can help identify the causes and factors of genetic defects and provide ways to treat or prevent these problems.
Researching how various diseases, especially cancers, develop	Stem cells are used to gain a better understanding of the cellular and molecular processes that lead to various diseases, especially cancer.
Treating cancers, various malignancies, treating various anemias, and various metabolic diseases	Stem cells are used in bone marrow transplants and other cell-based therapies to fight cancer and blood and metabolic disorders.
Testing new drugs for their safety and effectiveness	Stem cells are used in drug trials to test the efficacy and safety of new drugs before they are marketed and used clinically.

But this figure exceeded the projected amounts and reached \$18.9 billion. In 2018, growth of

\$13.8 billion (73% from 2017) was observed, so that the regenerative medicine market is

expected to increase by 23.3% annually to \$53.7 billion by 2021, to \$170 billion by 2030 and to \$530 billion by 2050. From an economic perspective, the annual growth rate (CAGR) of this industry has been announced to be 24% from 2010 to 2015, which makes this area very attractive for investment by large pharmaceutical companies [28].

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History of Stem Cell Products

The regulation of cell therapy has changed rapidly in recent decades. In 2014, the first stem cell therapy was recommended for approval in the European Union by the European Medicines Agency (EMA). The global market for stem cell therapy is estimated to reach \$928.6 million by 2031. Looking ahead to the next decade, the global market for stem cell therapy is estimated to reach \$928.6 million by 2031. Autologous transplantation is expected to hold the largest market share between 2022 and 2031 [33].

Stem Cell Therapy for Difficult Diseases

1- Use of Cord Blood Stem Cells: One of the difficult-to-treat diseases worldwide is HIV, with nearly 38 million people living with HIV-1.4, but antiretroviral therapy interventions to manage the disease are available to only half of this population. In the results of the study published in March 2023, umbilical cord blood stem cells were shown to target the first female HIV patient of mixed race. According to the researchers, using umbilical cord blood stem cells instead of matched adult donors, as has been done previously, increases the potential for treating HIV through stem cell transplantation in people of any race [34].

2- Heart failure: Given that mesenchymal progenitor cells (MPCs) are allogeneic, immune-selected cells with anti-inflammatory properties, they can improve outcomes in heart failure with reduced ejection fraction (HFrEF). In February 2023, the largest cell therapy trial to date for chronic heart failure due to low ejection fraction (EF) demonstrated the potential of mesenchymal progenitor cells (MPCs) in addressing inflammation. For the first time, we have discovered that stem cells can successfully treat the inflammation that causes heart failure. "For the first time, we have discovered that stem cells can successfully

treat the inflammation that causes heart failure,” explained Dr. Emerson C. Perrin, medical director at the Texas Heart Institute. “The results of the trial are significant because this disease is currently not treated with drugs that treat the symptoms,” Dr. Perrin said. Dr. Perrin noted that the data showed that this treatment reduced the risk of heart attack or stroke in patients by up to 58 percent, and the benefit increased to 75 percent in patients with high inflammation. Stem cell therapy provided these results because reducing inflammation caused by activated MPCs may reduce plaque instability that leads to heart attacks and strokes. Dr. Perrin highlighted these results as an important milestone in the field of cardiac cell therapy [35].

3- Multiple Sclerosis (MS): Results from an Italian study published in *Neurology* in December 2022 showed that autologous hematopoietic stem cell transplantation has the potential to delay disability in active secondary progressive multiple sclerosis (MS). “Hematopoietic stem cell transplantation was associated with a slower progression of disability and a higher likelihood of disability improvement compared to other treatments,”

said study author Dr. Mathilde Ingles, from the University of Genoa, Italy, explaining the findings. In a 10-year retrospective study, 79 people were evaluated for the disease. After five years, 19 percent of those who received stem cell transplantation experienced less disability than at the start of the study. This was compared to four percent of patients who took medication [36].

4- Parkinson’s disease: In February 2023, a milestone was reached in the treatment of Parkinson’s disease (PD). At Lund University in Sweden, a new stem cell transplant therapy has been given to humans for the first time. Parkinson’s occurs when an area of the brain loses nerve cells that produce dopamine. This chemical helps regulate body movement. Because the loss of these nerve cells leads to a decrease in dopamine levels in the brain. As part of the STEM-PD clinical trial, eight patients have been enrolled to receive stem cell transplants into the brain (Figure 2). The stem cell treatment, designed to replace lost dopamine cells, provides healthy dopamine cells [37].

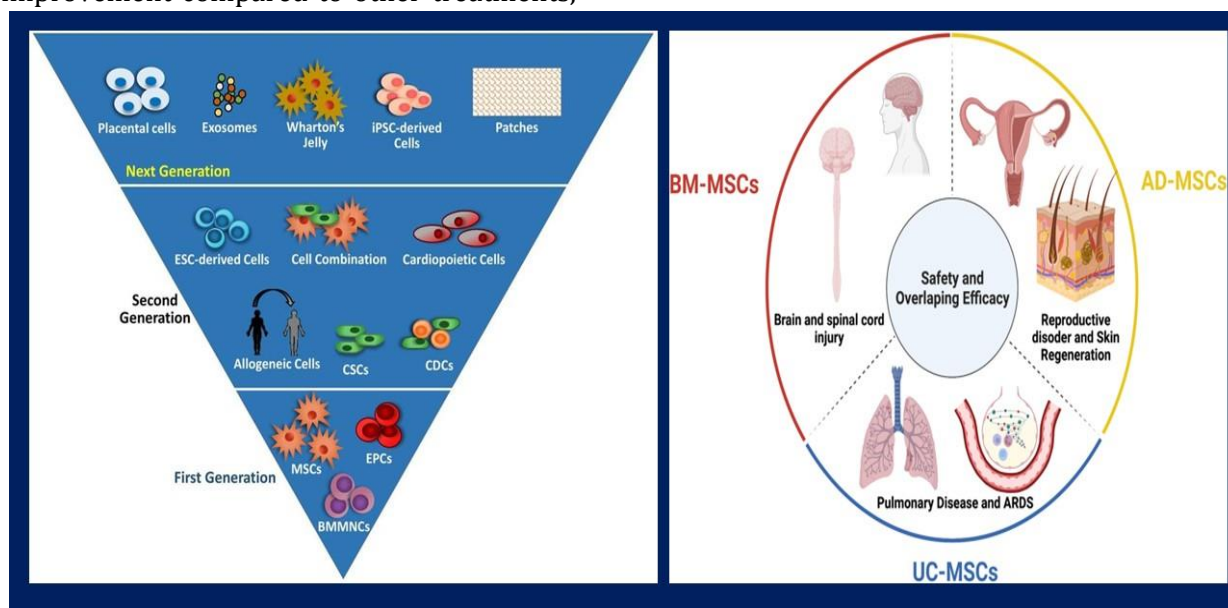


Figure 2. Stem Cell Therapy for Difficult Diseases

Stem cell production in a new way

The Medicines and Healthcare Products Regulatory Agency (MHRA) announced in March 2023 that the UK Stem Cell Bank is trialling automated robotic technology to grow stem cells. The UK Health and Social Care Secretary Steve Barclay explained that the UK is only the second country to have this technology trialled. Over the course of 12 months, the robot will be tested for its effectiveness in producing stem cells. According to Mark Bailey, chief scientific officer at the MHRA [38], the availability of cell-based therapies has previously been limited because they are often very difficult to produce. For example, human mesenchymal stem cells (hMPC) are the most promising multipotent stem cells for medicine, despite the limitations of mass production, high manufacturing costs and contamination. Bailey added: "The creation of an innovative stem cell robot, which is being tested by the UK Stem Cell Bank, could change this and make the manufacturing process easier due to its potential to reduce human error and produce a more consistent end product. Ultimately, this could lead to safer and more effective treatments for Parkinson's and other diseases [39]."

Angiogenesis in RM for the treatment of cardiovascular diseases

Cardiovascular diseases are the leading cause of death worldwide, claiming an estimated 17.9 million lives annually. Several approaches to regenerate infarcted heart muscle have been tested with minimal success due to limited healing of necrotic heart tissue after reperfusion of the infarcted areas. This is attributed to the limited ability of the heart muscle to repair itself and the rapid formation of non-contractile fibrotic scars. One such approach is RM via myocardial cell transplantation, which can only improve cardiac function for a short time due to poor

cell preservation. As an alternative approach, there is now a focus on administering exosomes to enhance the angiogenesis process. Exosomes are rich in miRNA and mRNA. Their unique structure and function favor their therapeutic application for myocardial regeneration following MI [40].

Angiogenesis and Cancer Treatment

Angiogenesis is essential for tumor progression, proliferation, and metastasis. Inhibition of tumor vasculature has been successfully used in experimental studies to treat oral, prostate, and renal cancers. Among the proposed approaches in RM cancer is the inhibition of hypoxia-inducible factor-1 α (HIF-1 α), which is responsible for the direct initiation of liver-derived growth factor (HDGF) and vascular endothelial growth factor (VEGF) expression. This in turn leads to the inhibition of endothelial cell proliferation.

1- For damaged nerve regeneration:

Regeneration of damaged sciatic nerve can be achieved using the natural material chitin combined with nanoparticles and conductive hydrogels. The nerve regenerative changes also included successful angiogenesis and Schwann cell adhesion [41].

2- Gene therapy for damaged nerve regeneration:

The lack of ability to regenerate severed axons makes nerve injury a serious event and usually results in permanent disability. However, regeneration of neural tissues in RM can be achieved by removing suppressor cytokine 3 signaling in neural cells to enhance the recovery and regeneration of damaged nerve axons [42]. Clinical trials have confirmed motor recovery and full resumption of mobility in all limbs in paralyzed mice subjected to complete spinal cord crush. This can be achieved by cytokine-stimulating JAK/STAT3 signaling and axon regeneration following transduction of cortical motor

neurons of paralyzed mice using an adeno-associated virus expressing hyper-IL-6 (hIL-6).

3- Stem cell (SC) transplantation: Stem cells are undifferentiated cells that retain the ability to self-renew and differentiate into specialized cells. Their therapeutic application aims to overcome the limited regenerative capacity of damaged tissues and organs and to restore impaired metabolic and functional disorders. The therapeutic use of stem cells to regenerate damaged organs began in the late 1990s for the treatment of cancer. Experimental trials have used both autologous and allogeneic transplants [43].

Stem cell classification and their therapeutic value in RM

There are two types of stem cell classification. According to the stage of development, the first approach is to divide them into embryonic stem cells (ESCs) and adult stem cells (ASCs). Another approach is to divide them into totipotent stem cells (TSCs), pluripotent stem cells (PSCs), multipotent stem cells (MSCs) and unipotent stem cells (USCs) based on their growth potential [44].

Application of organoid technology in RM

Organoids are complex three-dimensional cellular structures arranged in clusters of miniature organ-like structures. They are grown in vitro in suspension cultures, to avoid direct physical contact with the bottom of the dish. Organoids are self-organized structures derived from stem cells and contain fully differentiated functional cell types that resemble the structure and function of native organs [45].

Organoids can be generated directly from various organs through reprogramming of differentiated cells, or from pluripotent embryonic stem cells. Intestinal organoids, liver organoids, pancreas organoids, kidney organoids, heart organoids, lung and airway

organoids, brain and infectious disease organoids, and female reproductive tract organoids are examples of engineered organoids [46].

Although regenerative medicine is relatively old, recent technological advances have revolutionized this branch of medicine. Recent research on how some reptiles can regenerate lost or damaged limbs has provided important information and enriched the current knowledge. In short, RM could save millions of lives by treating serious, incurable health problems such as diabetes, stroke, paralysis, and MI. It could also enable the replacement of missing limbs or the correction of congenital anomalies. Approaches such as gene editing, 3D bio printing, living robotics, soft nanorobotics, and combinations of these approaches based on artificial intelligence are expected to replace several classic lines of therapy in the next few years [47].

What therapeutic approaches are used to treat diseases?

Currently, in the field of medicine, specialized treatments are reviewed and proposed for each patient according to his or her specific molecular and cellular genetic conditions. Reconstruction in the field of medicine includes the discussion of tissue engineering and cell therapy, and protocols will be designed and used according to the patient's condition. Even in all these areas, various books have been written and translated to familiarize people with these methods, and there are also basic knowledge companies, so that they can provide more information and services to the community [48].

The success rate of cell therapy

In the field of individual-centered medicine, people with the same diseases will not have the same treatment. It should be evaluated according to the molecular and cellular genetic

conditions of each person and the treatments they have previously had for the disease, and a specific treatment protocol for that person should be designed and used. In general, due to the exclusive and meticulous examination of patients and the receipt of individual-centered treatments, the improvement of patients in cell therapy is at a better level than traditional methods [49].

Types of cells in cell therapy

The selection of cell types will vary according to the type of patient, the patient's needs, and the type of tissue. Hematopoietic stem cells, mesenchymal stem cells, keratinocytes, fibroblasts and melanocytes are examples of these cells that are very effective in regenerating damaged tissue. According to the need, the cells are received from reputable centers such as stem cell companies. This method is used only in reputable centers that have a medical license and approval from the Food and Drug Administration and the Deputy Ministry of Health [50].

Treatment with Mesenchymal Stem Cells

Treatment with mesenchymal stem cells is one of the methods of treating MS, but this treatment method is still in the clinical trial stage. Mesenchymal stem cells play a role in repairing myelin and can have positive effects on the immune system of patients with MS. The treatment method is that mesenchymal stem cells are obtained from the patient's bone marrow or other tissues. These cells are multiplied in the laboratory and then injected into the patient's body [51].

Can stem cell injections help cure MS?

Analysis of the results of clinical trials conducted so far for the treatment of MS shows that cell therapy for MS has promising results. The studies conducted state the following results:

- ✓ Stem cells can regulate the immune system of patients with MS.
- ✓ These cells release nutritional factors, which include molecules for the growth of brain neurons.
- ✓ Stem cells have the ability to regenerate cells damaged in MS and differentiate into specialized cells with normal function [52].

Is cell therapy for MS approved?

Currently, no stem cell therapy for the treatment of MS has been approved by the United States Food and Drug Administration (FDA), and all treatment steps and study results obtained are from clinical trials conducted in this field. Cell therapy is currently being approved by the FDA for the treatment of leukemia [53].

Although this treatment has been approved for general use in clinical trials for the treatment of multiple sclerosis, experts want more studies to be done to see if it can be used to treat multiple sclerosis. Doctors may use adult stem cells to replace damaged or abnormal stem cells in the bone marrow. For example, stem cell transplants may use donated adult stem cells to replace stem cells in the bone marrow [54].

Doctors use them to treat: Blood cancers such as leukemia, multiple myeloma, and non-Hodgkin lymphoma. People with these diseases often need a stem cell transplant after receiving intense chemotherapy or radiation therapy to kill cancer stem cells in their bone marrow. Stem cell therapy, as a new medical method, relies on the body's ability to regenerate and repair damaged tissues. In this method, stem cells are collected from various sources in the body, such as bone marrow or fat tissue. Due to their special ability to transform into different types of cells, these cells can be used to regenerate damaged tissues in many organs

and systems of the body [55]. The treatment process usually consists of several steps:

1- Extraction of stem cells: The doctor first collects stem cells from the patient's body. These cells are usually taken from bone marrow or fat tissue.

2- Processing of cells: The extracted cells may be processed and prepared in special laboratory environments to enhance their regenerative properties [56].

3- Injection or transplantation: The prepared cells are injected into the damaged area or into the diseased organ. This injection can be given directly to damaged tissue such as joints, heart, or even brain.

The advantage of this method is that because the stem cells are taken from the patient's own body, the risk of rejection or immune reaction is very low. Also, due to the ability of stem cells to repair and regenerate naturally, they can help improve conditions such as joint, heart, nerve and even some blood diseases. This method is known as a leading approach in regenerative medicine and research in this field is progressing rapidly [57].

Examining the use of stem cells and regenerative medicine in the treatment of infertility

A new approach to the treatment of infertility has been created using mesenchymal stem cells. 4 types of mesenchymal stem cells, including bone marrow stem cells, fat-derived stem cells, menstrual blood mesenchymal stem cells and umbilical cord mesenchymal stem cells, have each been used to treat infertility diseases and have opened new doors to health [58].

Accordingly, menstrual blood mesenchymal stem cells can be isolated from menstrual blood. These cells have the ability to proliferate, self-renew and multi-differentiate. These cells also have numerous advantages over stem cells derived from other sources,

including ease of collection, safe proliferation and non-invasiveness without worrying about ethical requirements or rejection by the recipient. Infertility is a problem that affects approximately 15% of couples today [59].

Although assisted reproductive techniques are widely used today, only 40-50% of couples who request it can have a child with their genetic makeup. Especially in people with premature ovarian failure, the fertilization rate with current treatments does not exceed 5-10%. For this reason, many studies are being conducted to obtain eggs from stem cells with their proliferation and differentiation properties. In addition, regenerative cell therapies that can replace assisted reproductive techniques and correct impaired infertility have also been investigated in animal and human studies [60].

Premature ovarian failure

In recent years, research has been conducted on extracellular vesicles derived from stem cells, which eliminate the safety problems. In terms of safety and efficacy, clinical studies involving large populations are needed.

1- Premature ovarian failure (POF): According to the definition of the European Society of Human Reproduction and Embryology (ESHRE), this disease is defined as a disease under 40 years of age, defined as oligo/amenorrhea lasting at least 4 months and a follicle-stimulating hormone (FSH) level of more than 25 IU/l measured at least 4 weeks apart. Its incidence has been reported to be 1% on average. The cause of the disease is not fully understood, and genetic, environmental, enzymatic, infectious and iatrogenic factors are considered to be to blame. Current treatments are not sufficient and different treatment approaches are needed [61].

2- Polycystic ovary syndrome (PCOS): Polycystic ovary syndrome is another cause of infertility that causes increased ovarian function and anovulation. It is characterized by

high androgen levels, irregular menstruation, and the presence of multiple small cysts in the ovaries. Its incidence is between 5 and 10% of women of reproductive age and is the most common endocrine disorder among women of reproductive age. Current treatments are inadequate in many patients. Regenerative medicine applications are being investigated in the treatment of inflammatory and immune processes [62].

3- Endometriosis: This is a chronic inflammatory disease in which the basal layer of the endometrium is located outside the uterine cavity. Its prevalence is between 6 and 10% and it is a multifactorial disease. Genetic, environmental, and immune mechanisms are involved in its pathogenesis. Today, infertility and pain treatments cannot provide sufficient success for these patients [63].

4- Asherman's syndrome: This disease is characterized by intrauterine adhesions, hypomenorrhea, or amenorrhea. Scar tissue formed in the uterus may interfere with embryo implantation and cause infertility or recurrent miscarriage. A history of pregnancy-related curettage is present in 90% of patients. Although hysteroscopy and hormonal treatments are used today, advances in reconstructive techniques may increase the success of disease management. Stem cells are undifferentiated cells found in fetal or adult tissues. These cells are cells that can renew themselves, or differentiate if necessary [44].

5- Stem cells in fertility: Induced pluripotent stem cells were obtained from mouse fibroblast culture in 2006 and have been shown to be able to form all three germ layers and maintain a karyotype similar to embryonic stem cells. Since these cells are generated from adult cells, ethical issues arising from embryos are avoided. On the other hand, researchers transplanted skin cells from azoospermia and fertile men along with bone morphogenetic protein 4 (BMP4), bone morphogenetic protein

8 (BMP8), retinoic acid (RA), and LIF into mouse testes and studied them. Another study showed that human fibroblast-derived stem cells transformed into spermatogenic cells both in normal culture and by exogenous transplantation [35].

Oogonia were obtained by culture with ovarian-derived gonadal cells. Although induced pluripotent stem cells are promising, they have teratogenic potential, and the use of nucleic acid integration methods, epigenetic modifications, and genomic instability limit their use in therapy. The researchers also found that bone marrow-derived stem cells, injected intravenously or directly into the uterus of mice with which they had formed intrauterine adhesions, increased endometrial estrogen-progesterone receptors and reduced the area of fibroids.

6- Stem cells in female fertility: Endometrial stromal stem cells are composed of epithelial and endothelial cells. Stromal cells contain CD44, CD73, and CD90, but are CD34 and CD45 negative, epithelial cells are stage-specific embryonic antigen (SSEA-1), N-cadherin, and NTDPase2 positive, and endothelial cells are CD 31 and CD 34 phenotypes. In the absence of endometrial injury, these cells remain quiescent. In the presence of endometrial injury, these cells are homing to the injured area by chemokines and the C-X-C chemokine receptor type 4 (CXCR4). Cord blood stem cells are CD29, CD44, CD73, CD90, and CD105 positive, and CD31, CD45, and HLADR-85 negative [66]. Easy to obtain, low risk, and low immune response are very advantageous. In animal models of POI, ovarian function has been shown to promote ovarian repair by anti-apoptotic activity in granulosa cells, reducing FSH levels and increasing estrogen and progesterone. Furthermore, a mouse model of PCOS induced by dehydroepiandrosterone has been shown to reduce inflammatory cytokines and improve infertility [7].

Furthermore, it has been observed that activating matrix metalloproteinase 9 has the same effect. In patients with premature ovarian failure, the transcription factor phosphorylates the protein O3a (FOXO3a) and the protein O1 Forkhead Box (FOXO1), causing early follicle activation and thus increasing the number of follicles.

7- Amniotic fluid-derived stem cells:

Amniotic fluid-derived stem cells are often used in regenerative medicine due to their immunomodulatory properties and ability to differentiate. VEGF, transforming growth factor alpha and beta improve ovarian function by activating the EGF and bone morphogenetic protein (BMP) signaling pathways. In mouse models of POF, these cells are follicular, especially if they have the CD4C/CD105+ antigen. It has been shown to prevent atresia and restore ovarian function [28]. Extracellular vesicles derived from mesenchymal stem cells are currently being used to reduce the immunological reactions of stem cells. However, although all of these methods are promising, much more study is needed before they can be put into routine practice.

Discussion

What will be the big advances in stem cells and regenerative medicine in 2018?

- 1- Advances in cell therapy and gene therapy: This year, cell therapy and gene therapy will be in the news again. Especially in the field of CAR-T cells.
- 2- At least 20 products related to stem cells and regenerative medicine will receive approval from the US Food and Drug Administration in 2018 [9].
- 3- Further development of the use of induced stem cells in Japan: In 2018, the development of the use of induced stem cells for activities related to regenerative medicine will accelerate. The clinical trial of Masayo Takahashi's team is one of these measures.

4- Further development of the use of induced stem cells in the United States.

5- Intrauterine tests will make further progress.

6- Studies on embryonic stem cells in the United States will face fewer restrictions and will receive research funding [10].

7- Using CRISPR to edit genes in human embryos: Among the measures in this case is the use of this technique to silence some genes by the research team of the Fredrik Lanner laboratory.

8- Progress in the treatment of Parkinson's disease using stem cells.

9- Increased advertising of stem cell clinics, even in television commercials.

10- There are differences of opinion about the use of CRISPR in human embryos.

11- The California Institute for Regenerative Medicine has announced its plans for further research and increased funding for stem cell and regenerative medicine studies.

12- At least one state in the United States will pass laws to deal with unauthorized clinics and the necessary actions will be taken.

13- The FDA will also deal legally with unauthorized clinics [62].

14- Some government officials will also address the issue of dealing with the illegal activities of some clinics related to stem cells and regenerative medicine.

15- More patients will sue unlicensed clinics providing stem cell and regenerative medicine services.

16- Some unlicensed clinics will also counter-sued lawmakers and patients.

17- Unlicensed clinics in Florida will cause a lot of noise. This is while the number of regenerative medicine clinics is higher in California.

18- Some information related to unlicensed clinics will leak.

19- Stem cell biotechnology will continue to advance.

20- Efforts related to preventing the aging process with the help of stem cell anti-aging factors will expand [63].

Conclusion

The interest in stem cells is due to their regenerative abilities. Researchers hope that through these cells they will be able to gain a better understanding of how diseases occur and, based on this, develop appropriate treatments for diseases. In addition, stem cells are used as a type of regenerative medicine and have the potential to grow into new tissues and be used in organ transplants. Stem cells can also be programmed into tissue-specific cells to test new drugs. For example, researchers can create nerve cells to test a new drug for neurological diseases. Below is a list of some diseases that are treated with stem cells:

- ❖ Anemias.
- ❖ Blood disorders or inherited abnormalities of red blood cells.
- ❖ Bone marrow cancers.
- ❖ Leukemia.
- ❖ Lymphoma.
- ❖ Inherited disorders of the immune system.
- ❖ Inherited disorders of the immune system and other systems.
- ❖ Inherited metabolic disorders.
- ❖ Inherited platelet abnormalities.
- ❖ Phagocyte disorders.
- ❖ Solid tumors.

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