PriMera Scientific
Medicine and Public Health
Volume 1 Issue 3 November 2022
DOI: 10.56831/PSMPH-01-015
ISSN: 2833-5627

Stem Cells are the Future of Contemporary Medicine

Type: Review Article
Received: September 12, 2022
Published: October 08, 2022

Citation:
Zozylia IS., et al. "Stem Cells are the Future of Contemporary Medicine". PriMera Scientific Medicine and Public Health 1.3 (2022): 04-11.

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Abstract

This article is devoted to important issues of regenerative medicine and fetal stem cells administration as its valuable instrument. Herewith we will describe various types of stem cells, mechanisms of stem cells action and the spheres of their broad clinical application.

Keywords: regenerative medicine; stem cells; classification; differentiation; proliferation

Introduction

An invention of stem cells (SCs) was one of the most significant innovations in the XX century medicine. That event had become the 3rd issue in biology by its significance after establishing DNA spiral and decoding of human genome. Nowadays, regenerative medicine has been developing much faster. Stem cell is an efficient instrument for the organism regeneration. Property of any stem cells to generate different cellular types makes them enough comfortable system for investigating molecular-genetic events, which stipulate stem cells differentiation and, therefore, SCs might be used for lots of serious diseases. In particular, an essential study of SCs is one of the most actual and perspective fields of medicine.

Aim of the study

Investigation of SCs fundamentals: specific difference of the stem cells, their classifications, ways and sources of cells harvesting, stem cells clinical application in medicine.

Regenerative medicine is the most quickly developing field in general medicine for today. In much longer prospective, for sure, it would become a panacea against multiple diseases.

Nowadays, everywhere and everyone is speaking about stem cells. Many people can have an impression that stem cells are anything like the magic pills for all diseases. Similar to any substance, the medicines might be manufactured by the pharmaceutical company using any of its active components [1].

Certainly, SCs are regarded as an instrument for restorative benefits, therefore, cells will be regarded as a unique therapeutic agent. However, firstly SCs are proper intrauterine building material for human which we are getting from mother and a thing allowing us to be healthy in elderly period of

our life [2].

Hypothesis about SCs appearance was suggested by Alexander Maximov - a histologist of the previous century. Fist time, A. Maximov introduced the term of stem cells at the Congress of Hematologists in Berlin (1908) [3]. Specifically, that year is remarkable for history as the beginning of research devoted to essentials of stem cell technology. For many years, innovations made by Maximov were considered the most prominent break-through in biology of the XX century. In 1999 a respected magazine "Science" named Mr. Maximov's advancement as the 3rd by value scientific event within the field of biology just next to invention of double DNA spiral and decoded genome of the human.

During 1968-1969yrs. Aleksandar Friedenstein was the first scientist who proved that living stromal cells exist in the elderly aged human; and even much more fundamentally - the method of culture growth for multipotent mesenchymal stem cells (MMSCs) had been established that imposed great hope in a direction of biology science. In 1970 A. Friedenstein described and successfully cultivated fibroblast-like stem cells which were called mesenchymal stromal cells later on. In 1981 Martin Evans, Matthew Kaufman and Gail R. Martin were the first scientists who completed a successful trial for a purpose of separation and harvesting embryonal stem cells from the embryoblast on the mice. In 2012 Japanese scientist - Senya Yamanaka and British researcher John Gurdon received a noble prize for invention of adult stem cells reprograming into pluripotent iPSs - in the sense for transferring them into the state similar to embryonic stem cells (ESCs). Atomic bombing of Hiroshima and Nagasaki at the end of the Second World War (1945) had become a trigger to development of stem cell transplantology, which made the scientists to search for much efficient methods to protect humanity from the radioactive impacts. The first transplantations with hematopoietic stem cells derived from the bone marrow were performed on the mice, dogs and monkeys, which demonstrated the stem cell reparative potential after exposure to radiation [4].

The term "stemcell" is defined as a separate cell or the group of progenitor cells which possess capacity to self-renewal and differentiation into specialized tissues [5].

All stemcells have the next essential properties:

1. Ability to self-renewal helps to maintain a pool of non-differentiated SCs during the whole life. Self-renewal-is a division of cells when one or both daughter cells remain non-differentiated and preserve ability to producing the other SCs with the same properties to proliferation like in the parent cells.
2. Ability to proliferate - suggests an essential feature required for precise regulation of SCs numbers. Proliferation as a quite different from the process of self-renewal does not require that the daughter cells should possess all the features of SCs, including their ability to form cells offspring able to differentiate.
3. Ability to regenerate all functional elements of the tissue.

Division of stem cells [6]

Different types of SCs have not only various proliferative potential, but also may proliferate in a different way (see Fig.1):

a. Cells have capacity to divide symmetrically and in this case all daughter cells preserve all characteristics of the parent cells;
b. Cells can divide asymmetrically and then one cell preserves all features of the parent stem cell, whereas the other becomes more committed colony-forming.

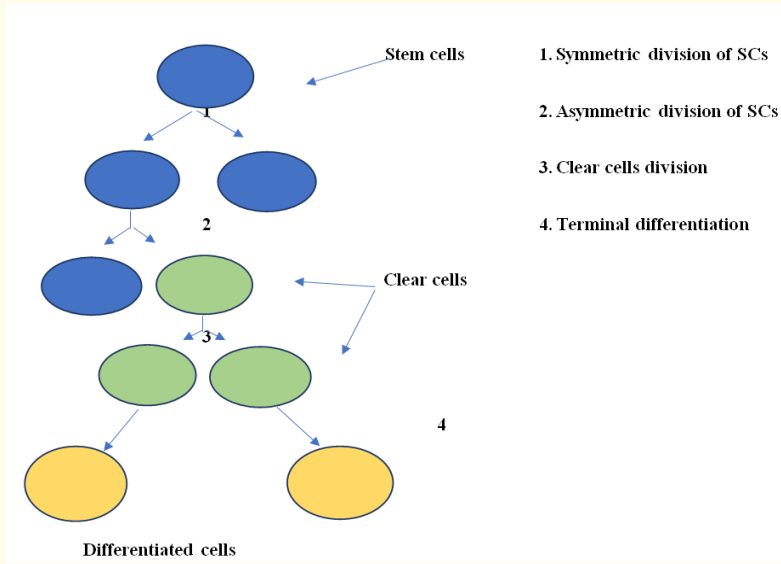

Figure 1: Division of stem cells and differentiation.

A logarithmic phase for the growth of daughter cells, remaining identical to each other and preserving all characteristics of the parent cell, takes place during a symmetric division. When asymmetrically divided, one cell remains as stem, whereas the other becomes more or less committed colony-forming. Linear accumulation of the number of cells progresses. Cell offspring of the stem tissue becomes more and more differentiated (liable to differentiation) in the tissues of the adult organism, partially preserving its capacity to proliferation and being the main source of tissues regeneration.

2 classifications of stem cells are commonly used in the scientific literature

1. By cells capacity to differentiate;
2. By the source of originor isolation of stem cells (see Fig.2);

Classification of stemcells by capacity to differentiation

Totipotent (ability to form the cells of any type).
Pluripotent (ability to form the cells of lots, but not all cell types).
Multipotent (ability to form the cells of several types).
Unipotent (ability to differentiate just into one type of cells).

Totipotent SCs (from Latin: “to tus” - full, unified). This unique cell produces all organs of embryo and the structures required for its developing: placenta and umbilical cord. Only fertilized oocyte and stage 2-8 blastomeres belong to the cells of this type.

Theterm “Pluripotent” is used to describe the cell, which can be a source of cells derived from any of 3 germinal layers (ectodermal, endodermal, mesodermal). ESCs, the primary germ cells and the cells of teratocarcinoma belong to such cell types.

Multipotent SCs possess ability to develop specialized cells of several types (for example, the cells of blood, liver or brain).

Unipotent SCs - are the cells which at usual conditions differentiate only into specialized cells of certain types.

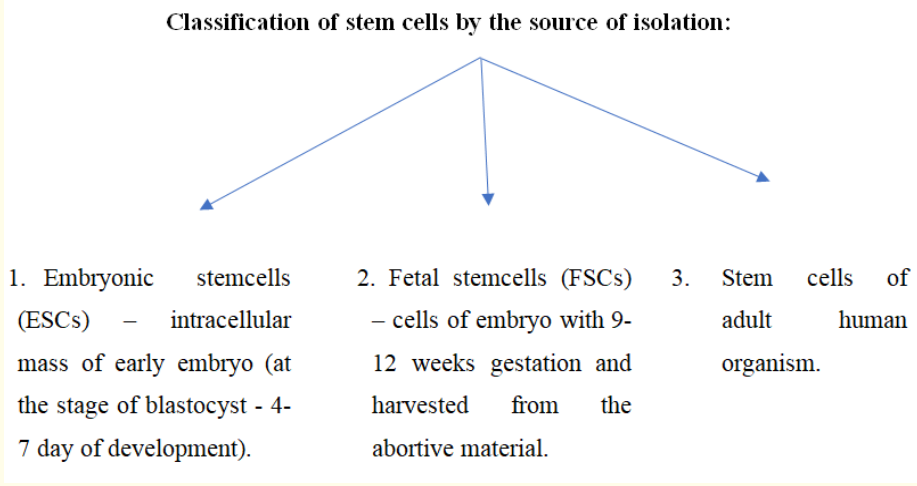

Figure 2: Classification of stem cells by the source of isolation.

SCs of adult body can be classified into 3 main groups: hematopoietic (blood forming), multipotent mesenchymal (stromal) and tissue-specific progenitor cells. Hematopoietic stemcells (HSCs) and cells progenitors are the most precisely characterized cells of the adult organism. They are localized in the bone marrow taking part in uninterrupted renewal of the cells of blood and immune system. An essential property of HSCs is restoration of all lineages of blood cells. These types of cells are widely used during bone marrow transplantation for treatment of leukoses, aplastic anemias, primary and associated immunodeficiency states [7]. Mesenchymal stem-cells (MSCs), which are first of all found in the bone marrow stroma, later have been also detected in the other human organs, including placenta, umbilical cord, liver and adipocellular tissue.

Tissue-specific progenitor cells (cell progenitors) - low-differentiated cells allocated in the various tissues and organs are responsible for renewal of cell population; specifically, they substitute the dead cells. For instance, myosatellitocytes (progenitors of muscle fibers), cells progenitors of lympho- and myelopoiesis. Such cells account for oligo- and unipotent characteristics with their main difference from the other stemcells that is a property of progenitor cells to divide during only a definite number of cycles, whereas the other stem cells possess ability to unlimited self-renewal. Therefore, such cells relation to the true stem cells is rather disputable [8].

Mechanism of stemcells functioning suggests performing a double task - direct replacement of the needed cell type, that had been damaged in the body; as well as contributing to so-called regenerative management. Thus, are paration of tissues happens by participation of the stemcell and under its “main guidance” using an isolation for the signal molecules that affect the other cells in the tissues which require reparation. Stemcell produces special chemical factors which are the “keys” to the “locks” for the receptors on the surface of the other cells and, in this way, they trigger or stop certain processes in them. At the same time, on the surface of stem cell there are proper cell receptors, which perceive information from microenvironment, react to it by activation or inhibiting different responses [9].

Throughout the gradient of definite signals, a migration of stem cells to the sites of damage occurs. Such a phenomenon is called “homing”.

The scientists also emphasize so-called “paracrine effect” which is characteristic for the stem cells. Different studies, precisely shown [10; 11] that application of SCs condition medium by its efficiency practically does not yield when using the proper stem cells, which confirms indispensable role of paracrine factors in inhibiting the pathological process. Paracrine factors look like different groups of cytokines, which exert marked pro-inflammatory, anti-apoptotic and pro-generative properties. Furthermore, more and more scientif-

ic results appear about ability of the stemcells for responding the exogenic effects and, depending on that, to modulate a synthesis of certain cytokines [12]. Growth factors released by the stemcells are significant aspects of protective cell influence. By producing environment with plenty of paracrine agents, SCs create some favorable conditions for restoration of cells proliferation and regeneration of the damaged tissues. In addition, some growth factors, for example, vascular endothelial growth factor (VEGF), are able to activate powerful inhibiting factors of cell death such as protein-kinase B, owing to which, anti-apoptotic effect of stem cells is maintained [13]. Future detailed research his demanded for precise understanding of the mechanisms of stem cells functioning.

Treatment with stemcells - is a discovery of epoch in medicine that can change our insight into therapy for many diseases and give humanity the essential benefits: health, youth, strength and longevity.

The principal directions for stem cell treatment of the patients include:

- Cardiovascular diseases (ischemic heart disease, arterial hypertension, sequelae of acute CVA);
- Sequelae of cranial and spinal injuries;
- Neurodegenerative diseases;
- Diseases of the peripheral nervous system;
- Demyelinating diseases;
- Parkinson's disease and syndrome of parkinsonism;
- Autoimmune diseases: systemic lupus erythematosus, rheumatoid arthritis, scleroderma, multiple sclerosis, psoriasis, non-specific ulcerative colitis, Crohn's disease;
- Autism spectrum disorders, cerebral palsy;
- Diabetes mellitus type 1, 2;
- Liver disease;
- Eye diseases;
- Infertility;
- Erectile dysfunction in men;
- Cosmetology

Stem cells are used in neurology for prophylactic effects or for exerting restorative action. Pre-clinical studies on animals allowed predicting three main mechanisms for recovery from neurology damages [14-16]: 1) structural maintenance for the damaged and adjacent tissue; 2) remyelination of the affected axons; 3) expression of neurons (intensifying the action).

The aim of stem cell treatment in neurology diseases is replacement of the lost neurons or recovery of their functions. Each subtype of SCs has its own potential for body restoration. In case of different neurology diseases, autologous macrophages, activated T-lymphocytes, glial cells, endothelial cells of brain, neuronal progenitors, Schwann's cells, SCs derived from olfactory neural epithelium; as well as fetal, neuronal and bone marrow derived SCs that can be administered to the patients [17]. Though, despite of numerous studies in vitro, not all of the above types of cells passed through the preclinical trials.

Irrespective of achievements in modern pharmacology, including surgery methods for treatment of ischemic heart disease, there is a definite group of patients where all above enumerated methods of treatment are non-effective.

These are the patients with:

- Refractory angina;
- Distal type of atherosclerotic damage in the coronary vessels;
- Extensive myocardial infarctions with history of complications resulting in severe heart failure (in 60% of cases after previous acute myocardial infarction, the processes of remodeling are mostly not reversible).

Most of such patients had already been performed different options for myocardium revascularization (percutaneous balloon angioplasty, stent placement, coronary artery bypass graft); however, often repeated reconstructions of the coronary arteries are not possible because of recurrent occlusions in the regenerated segments and presence of distal atherosclerotic lesions in the coronary arteries. Therefore, such patients possess only conservative therapy, which tends to be low-effective until that moment, and, in cases of severe heart failure, heart transplantation remains the only possible treatment method in the patients. However, the problems of donor organs deficiency and not enough effectiveness of devices mechanical replacement are still exceedingly critical and remain unresolved until presently. Therefore, such patients can benefit choosing the methods of regenerative medicine.

In cardiology diseases, stem cells stimulate the processes of neo-angiogenesis and differentiation of proper "tissue-specific depots", as well as externally administered stem cells which transform into robust cardiomyocytes. Likely procedures help to improve myocardial perfusion and the grade of local and gross contractility, to prevent remodeling of the myocardium and the processes of cell apoptosis [20]. Dohmann H. et al. analyzed anatomic-pathological, morphometric and immunocytochemical parameters on the material received at body autopsy of the patient suffering from refractory ischemic heart disease and chronic heart failure of ischemic genesis, who died over 11 months after trans-endocardial administration of autologous mononuclear cells from the bone marrow. Analys iswas made upon 3 sites of the myocardium: anterior lateral wall of the left ventricle (region of performing stem cell therapy), area of the interventricular septum (myocardium with preserved normal perfusion) and posterior basal wall of the left ventricle (zone of extensive scar tissue - the sites where stem cell treatment was not performed). In the region of stemcells injection, there was no evidence of myocardium damage. Tightness of capillaries per 1cm3 of tissue was higher in the anterior-lateral region in comparison with the posterior wall of the left ventricle. In addition, in the zone of stemcells injecting, hyperplasia of intramural cells and adventitia had been also noticeable. Therefore, active process of angiogenesis was demonstrable at the regions after administered stemcell therapy [21].

Regenerative properties of stemcells could be explained by any of 4 mechanisms that have been discussed at the moment:

1. Direct cellular trans-differentiation from the stemcells into cardiomyocytes [22];
2. Cytokines-induced mechanism [23] (plus increasing the residual and viable myocytes, specifically at the border area with infractions);
3. Stimulation of internal myocardial stem cells (endogenic stem cells) [24];
4. Induction of the cell fusion between transplanted stem cells and patient's proper myocytes [25].

Conclusion

Use of SCs is one of the most perspective directions in development of modern medicine. Nowadays, plenty of scientific facts provide proofs in favor of effectiveness of SCs administration in a range of severe diseases of cardiovascular, nervous, endocrine and musculoskeletal systems. SCs administrations in the clinic account for thousands of cases and such data had been published within the scientific journals worldwide. Nevertheless, there are lots of issues which still demand the future clinical studies in this direction.

In Ukraine, there are clinics which offer therapy for different diseases with the help of stem cells. In one of such clinics, Dr. Nataliia Sergeyevna Sych conducts her clinical practice, who successfully defended her PhD thesis in 2010 on the theme: "Cognitive impairments in the patients with acute period of brain infarction".

Nataliia Sergeyevna Sych – PhD., neurologist, pediatric neurologist, Deputy Head Doctor at Cell Therapy Center EmCell, Ukraine, has got over 15-year research experience in cell technologies. Doctor is the author and co-author of 45 patents and over 80 scientific articles published in the international journals. She is a developer for the internal therapy protocols in fetal stem cell treatment of various neurological diseases. On repeated occasions, Dr. Sych participated in the International conferences with oral reports and poster presentations: Morocco, Marrakesh, 2011 –report titled: "Fetal Stem Cells in Post-Stroke Cognitive Deficits, Embryonic Tissues Center EmCell", Hungary, Budapest (2011); report on the theme: "Clinical effect of fetal stem cells in multiple sclerosis", Great Britain, London (2012), "The state of neuroaminoacids in patients after a traumatic brain injury with convulsive syndrome", Romania, Bucharest, (April 2013), report on the theme:"Efficacy of fetal stem cell transplantation in autism spectrum disorders: a pilot study", the USA, San Diego

(May 2013); poster presentation titled: "Cognitive and neuroimmune disorders in patients in the acute period of ischemic stroke", the USA, San Diego (2018); and poster presentation on the theme:"Efficacy of fetal stem cell treatment for Parkinson's Diseases".

Doctor conducted webinars on the next topics

1. «Stem cells are essential for the future of medicine».
2. "New trends in treatment of children with autism". In the newspaper "News of Medicine and Pharmacy", №10 (728), 2020 p. V.I. Bobrova, a Professor at the Chair of Accidents and Emergency of P.L. Shupyk National Medical Academy of Post-Graduate Education wrote an article about the stem cells use where she mentioned about achievements of Dr. Nataliya Sych in developing this essential scientific theme.

Nataliya Sergeyevna is a member of the following professional Associations: 1. Alzheimer's association (starting from 2017). 2. American Association of Multiple Sclerosis (since 2017). 3. American Society of Gene + Cell Therapy (since 2020). In addition, she conducted a review for the scientific articles in the Journal Neuropsychiatric Disease and Treatment (2017 and 2019).

Doctor recommended herself as a hard-working, decisive, person with active social position; Dr. Nataliya is responsible, honest and constantly improving her professionalism, skills and demonstrates regular advancements in her health care activity.

From 2007 till 2010 Dr. Nataliya Sergeyevna Sych was awarded the President's grant while studying on the day-time Post-Graduate medical training program at P.L. Shupyk National Medical Academy of Post-Graduate Education. She had been also awarded: "Certificate of acknowledgement from the Head Doctor of City Clinical Hospital № 8 in Zaporozhe (2004); honorary mention from the Catholic Church of California State (San Diego) (2019); commendation from the President of NGO "Public initiatives for Health Care – Healthy Humanity" (2021); Reward from Darnytsa District State administration in Kyiv City (2021).

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