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Regenerative medicine

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The concept of "regenerative medicine" is now on everyone's lips and the use of stem cells to treat the most complex diseases is the subject of frequent discussion in medical circles. Regeneration is the ability of a living organism to renew or restore the damaged tissues and organs. So it is a science of self repair.

In all tissues, there is a constant renewal of cells during life. This is because the life span of a cell is limited. On average, 99% of cells live about 30 days. An epidermal skin cell lives 10 days and a red blood cell lives 4 months. This is how the living organism is programmed: to kill cells after a certain lifetime. This gets rid of aged and malfunctioning cells. The dead cells must be replaced. It turns out that there is constant cellular renewal in the body. In 70 years, about 10 tons of cells die off and are produced in the body of an average person.

How does the mechanism of creating new cells to replace the lost cells work: 1. Proliferation of terminal differentiated cells. This is the process of dividing specialized (somatic) cells that already exist. 2. Self-renewal and differentiation of stem cells, i.e. obtaining new specialized cells from stem cells. 3. The reprogramming of differentiated cells.

Stem cells: they are cells with unique ability to develop into specialized cell types in the body. They are the main participants in the process of tissue renewal and repair after damage. Properties of stem cells: 1. *The ability to unlimited division*. Note that normal cells have a certain limit of division (Hayflick limit), this is 52 divisions under favorable conditions. After this, division stops. At the same time the stem cell division never stops. 2. *The ability to divide asymmetrically*, that is, part of the progeny of the stem cell will be stem cells and another part will be specialized differentiated cells. An undifferentiated stem cell can produce different types of specialized differentiated muscle, skin, fat, and cartilage cells.

Types of stem cells that are differentiated by potency:

1. *Totipotent cells* (zygote) - These cells can produce any cells of the body and extra germinal tissues. The development period of these cells is very short.
2. *Pluripotent cells* (embryonic stem cells, ESCs). One pluripotent cell can create an entire organism.
3. *Multipotent cells* are cells which are present in a living organism after its birth (postnatal period). They have limited potency: they can differentiate only within the germ sheets: ectoderm (skin, nervous system), mesoderm (muscles, skeleton, heart and kidneys) or endoderm (gastrointestinal tract, lungs, liver).
4. *Progenitor cells*. In an adult, it is precisely the progenitor cells that are present in the body. Humans have only 1% of stem cells in their bodies. For this reason, most human diseases are associated with tissue damage and loss of tissue and organ repair ability. The vast majority of tissues cannot regenerate on their own after severe damage. This leads to internal organ dysfunction, serious illness and death.

What is regenerative medicine: In the last 3 decades, a new field of medicine - regenerative medicine - has been actively developing. Regenerative medicine is a branch of medicine that uses tissue engineering and molecular biology as a way of replacing, engineering and regenerating human cells, tissues or organs.

Traditional methods mainly treat the symptoms, while regenerative medicine techniques are aimed at treating the cause of the patient's condition by replacing defective cells (organs) or correcting a defective gene. In regenerative medicine methods are used to treat diseases whose treatment with classical methods has a low chance of success. Regenerative medicine is a revolutionary field of medicine which offers solutions and gives hope to people suffering from serious life-threatening diseases-like autoimmune diseases,

oncological diseases, type 1 diabetes mellitus, heart failure, postinfarction myocardial fibrosis, massive burns and soft tissue trauma, liver cirrhosis, parkinsonism, Alzheimer's disease, orphan and hereditary diseases, malformations, cartilage, joint and bone injuries, spinal trauma and peripheral nerve injuries, infertility treatment. Today there are four interrelated areas of regenerative medicine:

1. Cell therapy - live cells are used as medicines. This is the most popular direction.
2. Gene therapy - control of genes in cells or use of genes as a healing agent. Involves introducing genetic constructs into living tissue cells or modeling the genome.
3. Regenerative pharmacology - regenerative medicine without cell culture. A new, promising field that will help create new tissue to replace dead tissue.
4. Tissue engineering - creation of artificial organs or tissues from cells. Involves the use of a framework on which living cells are planted to mimic the creation of organs.

History and research: The term "stem cell" was first used in his works by the German scientist Valentin Haacker at the end of the XIX century. Then the term was used by the Russian scientist Alexander Alexandrovich Maksimov in a study published in 1909 and forwarded the theoretical rationale that all blood cells develop from one progenitor. Today it is known that all blood cells originate from hematopoietic cells (hemocytoblasts) - stem cells of the bone marrow, which create blood cells in the process of differentiation. Based on the research, the first technology of regenerative medicine - bone marrow transplantation - was created. And the first bone marrow transplantation surgery was performed in 1968 by the American Edward Donald Thomas. Subsequently it was proved that besides hematopoietic cells the bone marrow contains bone marrow stromal cells - cells with multipotent differentiation properties. Today these cells are known as mesenchymal stromal cells yielding differentiated connective tissue cells. In 1981, scientists isolated embryonic stem cells from a mouse blastocyst that were pluripotent. Their characteristics were amazing: they could retain their properties outside the body for a long time and when they entered the body they gave birth to new tissues. In 1988 Eliane Gluckman isolated stem cells from umbilical cord blood. In 1998, human embryonic stem cells were isolated. These studies have been associated with attempts to use stem cells for regeneration of human tissues. In 2006 the Japanese scientist Shinya Yamanaka proved that by introducing several transcription factors it is possible to turn a mature cell into an induced pluripotent cell. Mature cells of the body become induced pluripotent cells, which after differentiation become blood cells, heart and vascular cells, cells of the nervous system and all other organs. Today there are already several protocols for the clinical use of cell therapy drugs for the treatment of severe diseases such as Parkinson's disease and diabetes based on induced pluripotent cells.

Cell Therapy: Cell therapy is used for the replacement of damaged cells and tissues; stimulation of the body's own progenitor cells and enhancement of reparative regeneration, increase of the natural ability of the body to self-regenerate; for targeted delivery of drugs, genetic constructions and biomolecules to diseased tissues or organs to restore their functions. There are 3 sources of cell therapy:1.Autologous cells - the patient's own cells. They are isolated from the patient, grown or modified and then injected into the same patient's body.2.Allogeneic cells are donor cells. A popular example of using such a source is bone marrow transplantation.3.Xenogenic cells are animal cells. One of the actively developing areas is the creation of chimeric animals with genetically altered cell structure in certain organs so that they are as close as possible to human cells. In the future, xenogenic cells could be very much in demand but now cell therapy operates in practice with human cells - autologous and allogeneic cells.

How cells are grown in the laboratory:
Skin cells are extracted in small quantities from a living organism and grown in a specialized laboratory of ultra cryo preservation along with biosafety measures. Millions of cells can be grown in a relatively short time. Growing cells is a labor-intensive task. Automated stations are used to grow a large number of cells.

Examples of cell preparations developed using stem cells: One of the most important developments in recent years is cell therapy for diabetes. Scientists have developed a capsule for subcutaneous administration. The capsule is designed in such a way that it receives nutrients and secreted substances come out of it. The

embryonic stem cells inside the capsule are protected from the cells of the human immune system. A certain amount of time after the capsule is placed under the skin of a diabetic patient, the embryonic stem cells differentiate into pancreatic progenitor cells that produce insulin, glucagon and somatostatin hormones produced by the pancreas. As a consequence, the patient's glucose levels are maintained at normal levels.The drug is now in clinical trials.

Mesenchymal stromal cells: characteristics, features, applications-stem cells are present in all adult organs, but the largest source of stem cells is the bone marrow, which contains 2 types of stem cells. 1. Hematopoietic stem cells, which are used in oncoimmunology, transplantology and other fields. 2. Mesenchymal stem cells (mesenchymal stromal cells, MSCs) - the most sought-after type of stem cells in cell therapy.

Peculiarity of MSCs: MSCs have an important feature: they work very closely with the resident tissue-specific stem cells, regulating their bioenvironmental function through the secretion of bioactive (paracrine) factors. Today scientists consider MSCs as key regulators of tissue renewal and repair after damage.

The secretion products of these cells can stimulate angiogenesis and neurogenesis (growth of blood vessels and nerve endings), two necessary conditions for full tissue repair. MSCs are the most commonly used cells in regenerative medicine. They can be isolated from bone marrow, adipose tissue, umbilical cord matrix, tendons, lungs and periosteum. To obtain a sufficient number of cells for therapeutic purposes, MSCs are multiplied in a designated laboratory setting.

Practical applications of cell preparations based on MSCs: 1. Bone regeneration in case of injuries, after surgical operations. In this situation, the multipotency of MSCs, their ability to turn into bone cells, is used. 2. Cartilage regeneration of joints, including osteoarthritis. 3. Restoration of soft tissues lost as a result of trauma, surgery or disease development. 3. Healing of skin wounds of different genesis. 3. Plastic surgery.

Drugs based on MSCs: Today in the U.S. there are about 20 registered cell-based drugs for the treatment of various diseases. In 2018, Alofisel was registered in Europe for the treatment of perianal fistulas in Crohn's disease. With cell preparations, some modifications can be made in the laboratory to give them new properties. This is how gene-cell therapy drugs are developed. They are based on the genetic modification of cells in order to fight malignant diseases. Examples of gene-cell therapy drugs: KYMRIAH (Tisagenlecleucel) for the treatment of leukemia, and Zynteglo (Betibeglogene autotemcel) for the treatment of beta-thalassemia.

Medical Practices of stem cell therapies:

A. Autologous therapy: Processed from patient's or recipient's own body or tissues-Platelet rich plasma(PRP) therapy 2. Stromal vascular fraction (SVF) therapy from adipose tissue 3. Bone marrow concentrate (BMC) therapy.

B. Allogenic cell therapy: HLA matching potent stem cell therapy from donor (bone marrow)or cell bank and from umbilical cord-cells are collected, processed and cryopreserved using ultralow temperature cryo banking facilities 1. Mesenchymal stem cells(MSC)therapy 2. Bone marrow concentrate (BMC)therapy. Rehabilitation therapy (non biological therapy): regenerative simulations and healing by advanced biomedical device and physiotherapt: 1. Hyperthermia therapy 2. Extracorporeal shockwave therapy (ESWT) 3. Hyperbaric oxygen therapy(HBOT) 4.Cupping therapy.

a. Platelet rich plasma therapy(PRP):an autologous product which is produced from patient's own peripheral blood and contains enriched platelet count(4-5 fold)at physiological pH.Categories:1.RG-PRP(regenerative grade PRP for aesthetic health solutions like hair loss and facial rejuvenation.

2. RGX-PRP:high potency enhanced PRP formulation for pain management and sexual dysfunction.

3. hPure-PRP(high pure PRP);for dry eye diseases and neuronal tissue repair.

b. Bone marrow concentrate (BMC) therapy: Stem cell collected from bone marrow is harvested: A single dose can reduce pain, promote joint function, reduce swelling, improve condition of joint cartilage.

c. Stromal vascular fraction (SVF) therapy: Is an autologous product that is prepared from patient's own adipose (fat) tissue collected by liposuction. Cell therapy is targeted to Aging process, lack of vitality, organ failure, metabolic condition and

nervous system. d. mesenchymal stem cell(MSC) therapy: Allogenic MSC has been revolutionizing therapeutic modalities for chronic, immunological and degenerative conditions.

Pitfalls of regenerative medicine: Without a doubt, regenerative medicine and in particular, cell therapy using MSCs is a real breakthrough in health care. Scientists agree that this field of medicine has great potential. The methods of regenerative medicine can, firstly, increase the life expectancy of patients and secondly, improve the quality of life of people suffering from chronic diseases. However, to date, regenerative medicine techniques have not been incorporated into mainstream medical practice in most fields of medicine. Because in many experimental studies regenerative medicine and cell therapy have had temporary / limited effects. They have harmful potential like tumor/ cancer formation. MSCs suppress the immune system and promote the formation of new blood vessels, these properties can also support tumor growth and metastasis. During the repair processes, there is a possibility of fibrotic reactions and fibrosis.

But this is not about rejecting regenerative medicine techniques as potentially dangerous. It is about the fact that stem cells need further study.

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