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Regenerative medicine in orthopedics

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Abstract
Regenerative medicine is an interdisciplinary field of science that has been experiencing its renaissance in recent years. It involves many hopes regarding the possibility of breeding the organ needed for transplantation for a given patient in laboratory conditions. The most important "component" in regenerative medicine are stem cells and other elements that create an ideal environment for their proper development and organization of tissue architecture.

Keywords: orthopedics; Regenerative medicine; stem cells

What does regenerative medicine do?
Some of the cells in the human body have regenerative capacities, including, for example, blood and epithelia that retain this ability throughout their lives. However, it should be known that most tissue is reproduced with great difficulty, e.g. liver or brain cells - with extensive organ damage it often becomes impossible to regain functional structures. In regards to these problems, the need for transplant organs is constantly increasing, but the number of donors, especially those showing tissue compatibility with the recipient, is significantly reduced.
If you have a transplant, you should take long-term immunosuppressive medications, the use of which has serious side effects, for example an increased risk of infection, and in extreme cases even carcinogenesis. This problem could be solved by transplanting tissues and cells taken directly from the patient himself, and this aspect is the main field of interest for regenerative medicine.
This modern interdisciplinary field aims at developing strategies that allow natural programming of tissue and organ regeneration by artificially promoting the proliferation and differentiation of stem cells. The beginnings of regenerative medicine should be seen already in the mid-twentieth century, when in 1956 for the first time a bone marrow transplant was performed for a patient suffering from leukemia. However, the development of tissue engineering has brought regenerative medicine the possibility of full development.

The main trends of interest in this field of medicine are cell therapy and tissue engineering. The first of the areas of interest for regenerative medicine is based on giving the patient stem cells in the form of an injection or infusion. The disadvantage of this method is that only a small portion of the cells survive and settle in the target site. This significantly influences the reduction of the therapeutic efficiency of transplantation. These problems can be avoided by creating an environment for these cells to survive and function properly. This role is fulfilled

by special scaffolds prepared from biomaterials. They become not only a mechanical support, but also a system of distribution of growth factors and nutrients. Their structure affects the formation of functional blood vessels after transplantation, ensuring the necessary gas exchange for survival.
When writing about regenerative medicine, one can not overlook biomedical engineering. At a time when some scientists are working on the possibilities of cell tissue regeneration, others are developing devices to replace the diseased organ. Some authors also count on gene therapy to restore normal function to cells damaged by various types of mutations.

What are stem cells?
When considering this type of cells in terms of their ability to regenerate, they should be classified in the following three groups: constantly dividing, dormant and non-dividing. Cells that are continuously dividing, otherwise known as labile ones, show the ability to continuously proliferate to replenish defects caused by cell death (epithelia, e.g., intestinal skin and villi, and blood). They contain wile stem cells that have the ability to differentiate into every cell in the body. Dormant tissues, also known as stable tissues, are part of the cells that under normal conditions do not divide, however, under the influence of a stimulating factor, such as injury, they can enter the cell cycle and divide (liver cells, kidneys and pancreas, fibroblasts, smooth muscle fibers and lymphocytes). Non-divisible cells have been excluded from the cell cycle and can not return to it. It includes the heart and skeletal muscles.
Stem cells that are used in regenerative medicine belong to the first type of cells, ie they are characterized by unlimited abilities to divide, self-renew and create various tissues of the body. These types of cells include their two subtypes, i.e. embryonic **pluripotent** cells, derived from the embryo cell pool and **multipotent** cells, present in a completely educated organism and reproducing the given structures throughout life.

The source of the cells collected for transplant should also be determined in relation to the relationship with the recipient. In a situation where the cells taken to produce the implant come from the donor itself, the type of transplant is referred to as **autologous**. If, in turn, they were taken from another donor, which shows tissue compatibility with the patient, it is an **allogeneic transplant**.

How are stem cells obtained?
Thanks to the great progress that has been made in medicine last years, the collection of stem cells in the present time is possible not only from the egg, embryo or umbilical cord blood of the newborn, but also from the adult tissues of each organism. These cells can be isolated mainly from bone marrow and peripheral blood. In studies conducted for the development of orthopedics, they are also obtained from the adipose tissue and synovial membrane of peripheral joints.
During the preparation for transplantation, a minimum amount of bone marrow is taken from the patient via a small pelvic puncture. A large number of stem cells are contained in the marrow. This procedure is completely safe for the patient. The resulting preparation, which contains the stem cells, is subjected to an appropriate treatment to purify and concentrate it, and then the solution is injected by the doctor into the treated area. The cells multiply and take over the functions of diseased tissues.
After the procedure of giving stem cells, the most important task that lies with the patient is to remember about regular medical checks and rehabilitation. This procedure must be individualized for each patient and depends on the type of disease being treated and the age and general health of the patient. Rehabilitation after administration of stem cells must be carried out systematically for a minimum period of 6 weeks.

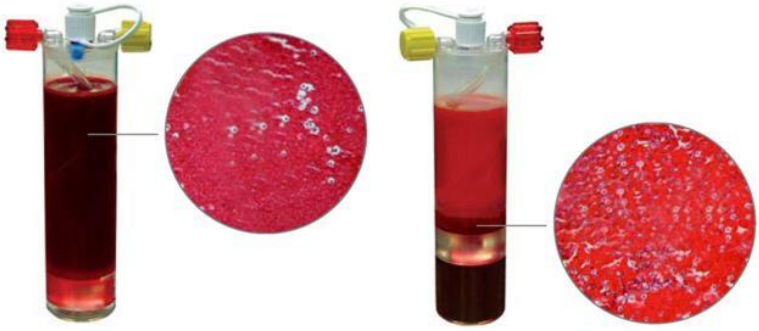

Fig.1. Whole human blood and after centrifugation

Application of biomaterials and growth factors
The ability to regenerate tissues largely depends on the environment in which the stem cells were present - the factors that stimulate their growth and proliferation, as well as the appropriately shaped network of blood vessels that provide nutrients and oxygen, as well as waste products.
Materials used for scaffolding can have very different character. For this purpose, biomaterials of organic origin (collagen, alginate, polylactide) as well as inorganic (polyglycol acid, polyesters) are used. Scaffoldings can also be made of ceramics, metals and various types of composites. They become not only a place to attach cells, but also give them access to the factors necessary for transformations. They facilitate the differentiation of cells, their organization into complex structures, and allow the development of an appropriate vascular network. They can not give rise to an immune reaction. Some of them are biodegradable - that is, after a certain time they undergo resorption in the body, others remain permanently.
Hormones, morphogens and growth factors are of great importance in creating such a complicated place of development of stem cells, which are designed to signal the growth of cells and protein components of the extracellular matrix (ECM). Growth factors are most often polypeptides that bind to target cell receptors and thus affect their migration, proliferation, differentiation, survival and secretion.

One of the most important factors involved in tissue regeneration is the **transforming growth factor TGF-β**. It performs three main functions, that is luring fibroblasts to the site of injury, forcing them to secrete collagen and stopping the activity of metalloproteinases, destroying elements of the extracellular matrix. Another not less important molecule is the **shallow-derived PDGF growth factor**. This molecule is involved in almost all aspects relating to tissue regeneration. Recruits neutrophils, macrophages and fibroblasts, and then activates them. It also affects angiogenesis. **FGF fibroblast growth factor** involves almost all major cells in the regeneration process: macrophages, fibroblasts and endothelial cells, stimulates angiogenesis. The **vascular endothelial growth factor VEGF** strongly influences the endothelial cells, accelerating the formation of new vessels.
Do not forget about other cells involved in the transmission of information, include molecules produced by cells of the immune system, which are primarily characterized by immunomodulatory activity, or **cytokines**. At the stage of wound regeneration, it is important that TNF and interleukin-1 tumor necrosis factor is present.

The greatest challenge for tissue engineering researchers is to combine all of these elements so that signaling molecules are delivered at the right time and concentration, and to be protected from damage. However, there are still many problems, in particular stopping the destructive progress of the disease, obtaining appropriate vascularisation, synchronized in time and space to supply the right signaling molecules. Despite the very optimistic results, it should be realized that regenerative medicine is not a substitute for reconstructive surgery and traditional transplantation, but it certainly will give hope to many people.

How are the stem cells prepared for transplantation?
Currently used systems for acquiring a cell preparation allow for easy and effective concentration of stem cells obtained from the comb of the iliac plate and transferring them to the destination, with or without graft material. The discovery of a function that allows the recovery and concentration of a mononuclear cell population has significantly reduced the problem of dilution of peripheral blood during bone marrow aspiration. The systems are based on proven technology for concentrating powerful stem cells that are obtained using an aspiration needle. Thanks to modern technologies, stem cells can be concentrated at the patient's therapy site. Numerous clinical evidence suggests that the concentration of cells positively affects the outcome of clinical procedures, e.g. bone transplantation.

In orthopedics it is possible to use the concentration system in the following cases:

- delayed union and non-union
- avascular necrosis
- spinal fusion
- cartilage regeneration
- osteonecrosis
- bone regeneration
- bone cysts.

What diseases can be cured with stem cells?

Currently, research is being carried out on the use of stem cells in the treatment of cancer, diabetes, Parkinson's disease and heart failure. However, the greatest future of these miraculous cells is seen in the treatment of musculoskeletal diseases.

After many years of conducting experiments, it turned out that stem cells can be used to treat professional porters, people practicing sports, young people and the elderly. This therapy may help to restore the fitness of people suffering from degenerative diseases of large joints, and sometimes it may even eliminate or delay the need for knee arthroplasty.

The following disease entities can be treated with stem cells:

- degenerative changes and pain in the knee joint, hip pain, shoulder joint pain and other joint pain
- injuries and reconstruction of articular cartilage, reconstruction of the anterior cruciate ligament and meniscal regeneration (meniscus)
- muscle damage, damage to overloaded tendons and damage to the ligaments
- detached tendon trailers (eg hamstrings, biceps arm and others)
- support for healing of bone union disorders (delayed bone union, no bone union, false pseudocyst)
- injury to the anterior knee ligament (ACL) .

Bone tissue diseases treatable with stem cell transplantation:

- Marrow stem cells can significantly improve bone formation in cases of non-union
- Marrow stem cells can significantly reduce joint pain and increase joint function in cases of osteonecrosis
- Allograft enriched with myeloid stem cells is as effective as autograft for bone grafts and spinal fusion procedures .

Only stem cells?

What is the future of stem cells in orthopedics?

Currently, stem cells are most often used in the case of regeneration of cartilage defects, joint pain and bone union disorders. In the United States of America, there is currently research into the use of these cells in non-surgical treatment of rupture of the anterior cruciate ligament (ACL) and other motor organ damage. The use of stem cells combined with surgical therapy is increasingly an alternative to joint arthroplasty procedures. Therapy using patient's cells combined with properly conducted rehabilitation can contribute to the patient's return to the efficient performance of everyday activities, and in the case of professional athletes to develop the highest form possible. The use of patient's own cells for the treatment of diseases in the body is one of the most innovative therapeutic methods in orthopedics, with broad horizons of further development.

Summary

For many people, regenerative medicine can be the last resort. Especially for those who have been waiting for a transplant for years without a success, have lost large amounts of tissue as a result of an accident or are suffering from chronic diseases that significantly prevent normal functioning. To create "custom organs" we are approached by dynamically conducted, multi-track studies aimed at better understanding and understanding the potential of stem cells, improving the quality and properties of biomaterials used in tissue engineering and developing techniques to reconstruct tissue *in vivo* as well as *in vitro*.

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