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REVIEW ARTICLES

The essence of the cell therapy method in chronic ischemia of the lower limb

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Abstract

Background: The results of the of cell therapy use in experimental models of ischemia of the lower limbs, in the majority of cases performed on mice and rats, and also on bigger animals demonstrated the possibilities and effectiveness of cell therapy in restoring blood flow to ischemic regions of the member. The third important property of stem cells is that they can be differentiated into diverse specialized cell types, such as muscle cells, endothelial, nervous, etc. Stem cells are the basic unit of the body, from them are formed 240 types of specialized cells and tissues of the body. These cells are involved in the revascularization and increase the secretion of numerous pro-angiogenic factors (VEGF, bFGF, PlGF-1 and MCP-1). All preclinical studies demonstrate a local neovascularization, with a functional effect, particularly in the form of increased blood flow and the number of newly formed vessels. Aspects and perspectives of cell therapy in the treatment of chronic peripheral angiopathy, especially on lower limbs are considered in this work.

Conclusions: Angiogenic cell therapy today provides a therapeutic method and also an innovation that represents a breakthrough concept in treatment of ischemic diseases, especially of the legs and heart, the improvement of prognosis of these patients. This method comes to substitute the conventional methods of treatment of these diseases, which until now claim to be less effective or even ineffective, and simultaneously takes an important step in the progress of therapy, which further enriches the arsenal of methods of medical treatment. Cell therapy is one of the most perspective methods of treatment at the current stage, with the use of mature autologous mesenchymal cells, in order to increase the number of capillaries (angiogenesis), and larger caliber vessels (vasculogenesis).

Key words: ischemia, stem cells, angiogenesis, regeneration.

Introduction

The essence of cell therapy method consists in active substitution and stimulating effect on the functional deficient cells and tissues in some organ and separate systems, stimulating reparative and metabolic processes, immunocorrection, immunostimulation and stimulation of angiogenesis using stem cells [16]. At the base of developed technology of drugs manufacturing from stem cells for cryopreservation and treatment is the provision on necessity of preservation by biological objects of the viability, meaning their possibilities of functioning after defrosting and introduction into the body, which ensures high clinical outcomes [1]. The advantage of cell therapy is receiving by the patient a number of biologically active and balanced compounds of natural origin, which may influence the variety of whole body metabolism,and also stem cells are able to perform replacing functions [2].

Angiogenesis represents a multistage process involving changes at the level of the extracellular matrix, proliferation of endothelial cells, migration and differentiation of them into new capillaries. Studies on tumor biology have led to the discovery of complex interactions (autocrine and paracrine) between tumor cells, stromal cells and endothelial cells being under the influence of the extracellular matrix composition. In the last years it has become increasingly evident that the formation of new vessels is the result of the interaction of different proangiogenic and antiangiogenic molecules, represented by growth factors and some components of the extracellular matrix. The study of angiogenesis and its role in tumor biology led to a vast theoretical baggage as well as to some results in the treatment of cancer by clinical studies of some drugs with antiangiogenic effect [4, 1, 2]. Microvasculature is a dynamic system that plays an important role in various physiological and pathological processes evolving from a sleeping to an active status. New vessels can arise after the process of angiogenesis, vascular remodeling and recruiting precursor of endothelial cells from bone marrow and blood vessels [5, 3]. Angiogenesis is a process that also depends on the cooperation and the interaction between different cell types, growth factors and various extracellular matrix components.

Stem cells are defined by three main features. First of all, they are not specialized cells (unlike the cells, from that are formed muscles, brain, blood) Secondly, the stem cells are able to divide a long period of time, and, as a result of the division, it forms two identical cells [17]. The third important property of stem cells is that they can differentiate into diverse specialized cell types, such as muscle cells, endothelial, nervous, etc. Stem cells are the basic unit of the body, from them are formed 240 types of specialized cells and tissues of the body. A large number of stem cells are contained in the umbilical cord blood, in the human embryo, in the placental complex, in the bone marrow of an adult. The main characteristic of them is the ability to self-sustaining [6, 13]. Cell therapy or regenerative one

allowed to obtain clinical results of new quality in various areas of medicine: gerontology, oncology, gynecology, hematology, immunology, endocrinology, cardiology, obstetrics, psychiatry, neurology and neurosurgery, surgery, traumatology.

Sources of obtaining progenitor cells:

- Bone Marrow stromal cells
- Multipotent adult progenitor cells – MAPC
- Human umbilical cord stem cells
- Hematopoietic stem cells
- Neural stem cells
- Embryonic stem cells
- Nuclear transplantation of embryonic stem cells.

After the origin progenitor cells (stem) are divided into two groups:

1. Embryonic cells, fetal
2. Mature mesenchymal cells.

The most frequent source of embryonic stem cells is blastocyst. These cells can give birth to any cell lines of the body in respective conditions of the growth and defferentiation [18].

Disadvantages: may cause appearance of tumors by embryonic genesis (teratomas).

Advantages:

1. Present pronounced multipotention.
2. Source of them may serve placenta and umbilical cord which may be isolated from these cells then cryopreserved and kept for the duration of the individual's life
3. Possess a weak antigenic load.

Albeit umbilical cord blood contains a smaller number of cells in comparison with bone marrow, the quality of the graft is superior toward the bone marrow.

Mature mesenchymal progenitor cells:

- Can be isolated from bone marrow of the patient.
- They are a subpopulation of cells from bone marrow.
- Are distinguished in a long row of cells in vitro and in vivo.
- Do not form teratoma.

Disadvantages: Do not possess multipotention of embryonic cells. In some cases can exist contraindications for harvesting these cells such as chronic alcoholism, smoking, treatment with cytostatics and glucocorticosteroids, intolerance to proteins of animal origin and specific cytokines, patients with chronic kidney disease and diabetes. With age the reserves of these cells decrease [7, 14, 15].

The effects of progenitor cells

- Normalize and stimulate the metabolism;
- Increase immune and neuroendocrine activity;
- Possess expressed antitumor effect;
- Slow down premature aging, rejuvenating the organism;
- Have a marked therapeutic effect for a wide range of pathologies;
- Anti-inflammatory;
- Immunomodulation;
- Angiogenic effect, improve vascularization;
- Stimulate cell regeneration;
- Replace the affected tissue.

The role of endothelial progenitor cells (EPC) in the cell therapy

In 1997, T. Asahara [21] found in peripheral blood endothelial progenitor cells (EPC) which, after isolating and multiplying ex vivo are able to stimulate post-ischemic angiogenesis [3]. EPC Series originating from marrow and expressing the antigen CD34 + plays an important role during postnatal vasculogenesis in physiological and pathological conditions. HSC and EPC derived from bone marrow or peripheral blood, help the process of post-ischemic neovascularization in adults [4]. It is revealed that the affected tissue by ischemia triggers an increase in the concentration of systemic pro-angiogenic growth factors (VEGF-A, PlGF-1, SDF-1, EPO), thus induce progenitor cell mobilization from bone marrow into peripheral circulation. These stem cells, reaching the ischemic territory ("homing") adhere to the endothelium, where they are incorporated into new groups which then differentiate into endothelial cells. Moreover, progenitor cells produce factors capable of stimulating angiogenesis and vascular remodeling. However, the molecular mechanisms of these cells stage are largely unknown. Indeed, various phenomena, such as the mechanisms for targeting ("homing") to the site of neovascularization, the nature of these signals, the involvement of growth factors, the role of adhesion molecules are studied further. The discovery of medullar origin EPC in the peripheral blood of adults allowed the development of strategies of proangiogenic cell therapy in ischemic diseases. The administration of EPC or bone marrow cells, intravenously or directly to the ischemic territory, contributes to the stimulation of neovascularization in various animal models [5]. Similarly, injection of CD34 + cells significantly improves post-ischemic angiogenesis in a model of heart failure, and lower limb ischemia [5, 9]. Stem cell therapy may also be based on the administration of bone marrow mononuclear cells. Autologous transplantation of bone marrow-derived mononuclear cells stimulates neovascularization in the leg or in the infarcted heart in various species of animals [8, 19]. Finally, the administration of mesenchymal stem cells improves the process of post-ischemic neovascularization. These cells are involved in the revascularization and increase the secretion of proangiogenic numerous factors (VEGF, bFGF, PlGF-1 and MCP-1) [10]. All preclinical studies demonstrate a local neovascularization, with a functional effect, particularly in the form of increased blood flow and the number of newly formed vessels. The results of the use of cell therapy in experimental models by ischemia of the lower limbs, in most conducted in mice and rats, and also on bigger animals have demonstrated the effectiveness of cell therapy possibilities and restoration of blood flow in ischemic regions of the member [20]. It demonstrated increase of the number of circulating endothelial progenitor cells (EPCs)

in response to experimental ischemia [11], and subsequent experimental demonstration of ingress into capillaries and arterioles of these cells in the affected tissue.

The antiangiogenic system is a group of active molecules aimed at inhibiting the process of angiogenesis. In normal tissue there is a well-established balance between angiogenesis and anti-angiogenesis process that maintains constant the number of blood vessels depending on the functional needs of the tissue [12]. As antiangiogenic factors may serve some drugs: carboxyamidotriazole, itraconazole, chemotherapy preparations used to treat malignant tumors with the purpose to inhibit, or arrest tumor angiogenesis [16].

Conclusions

Angiogenic cell therapy today provides a therapeutic method and also an innovation that represents a breakthrough concept in treatment of ischemic diseases, especially of the legs and heart, the improvement of prognosis of these patients. This method comes to substitute the conventional methods of treatment of these diseases, which until now claim to be less effective or even ineffective, and simultaneously takes an important step in the progress of therapy, which further enriches the arsenal of methods of medical treatment.

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