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INSULIN-PRODUCING CELLS IN THE TREATMENT OF TYPE 1 DIABETES: A LITERATURE REVIEW

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ABSTRACT

This review discusses the prospects for the treatment of insulin-dependent diabetes mellitus. The use of insulin-producing cells of various origins is relevant and may in the future replace radical transplantation of the whole pancreas and transplantation of individual islets of Langerhans. The authors have paid attention to the peculiarities of obtaining stem cells by directed differentiation and proliferation of various fractions of stem cells, as well as to the prospects for their use in clinical practice. The regenerative features and possible complications of each pool of cells used are considered. Attention is paid to the phenomenon of plasticity which helps in transplantation and subsequent functioning. At the same time, general methods for isolating stem cells from niches containing the largest number of available progenitor cells, as well as the results of the introduction of insulin-producing cells, are considered.

Keywords: *insulin-dependent diabetes mellitus, insulin-producing cells, methods of treating type 1 diabetes mellitus, stem cells.*

INTRODUCTION

Due to severity of the course and the high risk of complications, insulin-dependent diabetes mellitus (DM) occupies a special place, since it is associated with the direct destruction of beta-cells that secrete insulin into the bloodstream. A decrease in the insulin results in blood hyperglycemia, which leads to serious health disorders, including cardiovascular pathologies, renal failure, ketoacidosis, neuro- and encephalopathy, as well as impaired visual clarity, which in some cases leads to absolute blindness. Therefore, the replenishment of beta cells in the patient's body is the main direction in the treatment of this pathology. Currently, several methods have been developed to achieve this goal. The first is transplantation of a donor pancreas, a radical method, which, due to numerous complications and the necessary lifelong therapy with immunostatics, is not so often used in clinical practice. The second is a direct transplantation of whole islets of Langerhans, which is common in European countries, but limited in use due to the lack of donor material and the difficulty in its direct introduction into the gland tissue. The third is the use of progenitor cells which, as a result of genetic reprogramming, acquire the ability to secrete insulin [1]. Progress and development in the field of genetic engineering, the most favorable and effective replenishment of insufficiency of gland function by insulin-like cells, and, finally, good survival

and a lower risk of complications increase the relevance and the number of applications of this method in the field of diabetes treatment.

METHODS AND PRINCIPLES OF STEM CELL ISOLATION

Currently, stem cells are one of the main directions in the development of therapy for various chronic and non-chronic diseases, so their isolation and subsequent transplantation are an integral part of this therapy. The main niches for the formation of stem cells are body tissues containing generations of unipotent cells, peripheral blood and bone marrow including a pool of multipotent cells, placenta and umbilical cord which are a source of multipotent stem cells [2].

Among the tissues containing various generations of unipotent cells, the main ones in terms of their concentration and relative ease of obtaining are adipose tissue, skin and mucous membranes, in particular the nasopharynx and oropharynx. After direct sampling of donor material (scraping, liposuction), it is necessary to divide the cells into fractions in order to isolate the necessary unipotent cells. This goal is achieved by cell sorting with flow cytometry, immunomagnetic and enzymatic separation. Peripheral tissues are superior in concentration of stem cells to any other niches of their formation, however, the presence of type-specific differentiation and the acquisition by cells of the initial features of the donor tissue limits their use for the treatment of various pathologies [3].

The bone marrow contains a heterogeneous population of progenitor cells, among which hematopoietic and mesenchymal stem cells play a leading role [4]. The direct isolation of these cells from the bone marrow is a direct aspiration of the ilium contents followed by passages through needles of decreasing diameter in order to create a suspension of cells and separate two germ fractions according to their ability to quickly adhere acquiring a fibroblast-like structure corresponding to mesenchymal stem cells. However, this operation is accompanied by severe pain and high risks of complications for the donor's body, and therefore direct aspiration is rarely used. In order to minimize the development of a negative effect, collection and mobilization of peripheral blood stem cells are currently used, which concentration in 1 ml of blood is 3-5 CD34+ cells and therefore requires exposure to cytokines and growth factors to increase their concentration [5].

Stem cells located in the placenta and umbilical cord blood are the most favorable for the use in regenerative medicine, since these cells have the lowest risk to cause complications associated with transplant rejection and with HLA conflicts between the donor and recipient, due to the lack of antigenic markers in these stem cells that affect the development of the above complications [6]. In addition to the immunological advantage, they are simply isolated and possible to store for a long term without wasting the ability to differentiate and proliferate with the help of various cryotechnologies and the use of anticoagulant systems [7]. The placenta is a source of amniocytes and mesenchymal stem cells, which, along with the properties of all stem cells, have anti-inflammatory, immunomodulatory and anti-fibrotic functions with the induction of angiogenesis and expression of pluripotential markers OCT-4, SOX-2, Nanog on the membrane surface. Cord blood contains hematopoietic (UC-HS) and mesenchymal stem cells, which, like placental cells, are pluripotent and are also capable of synthesizing cytokines that help avoid transplantation rejection [8]. A special place in regenerative medicine belongs to embryonic stem cells, which, depending on their origin, are divided into ES (embryonic stem) and EG (embryonic germ) cells. ES cells are obtained from in vitro cultured embryos at the early blastocyst stage, and EG cells are isolated from the germinal crest of an embryo after an involuntary termination of pregnancy (4-5 weeks). The advantages of these cells are the ability for long-term proliferation, stability of the diploid karyotype, stable expression of early embryonic SSEAs markersf, and pluripotency, which make it possible to use these cells for the regeneration of almost all tissues [9].

THE PHENOMENON OF PLASTICITY IN THE USE OF STEM CELLS

One of the urgent tasks of modern science is to determine the limits of plasticity of various types of cells. As a result of the analysis of gene expression of various cells, it was revealed that there are cells that are phenotypically similar to human ectoderm cells, which suggests that such cells can be used to replace insulin-producing cells of the pancreas [10]. Donor insulin-producing cells, which are transplanted both as part of the whole pancreas and as isolated islets of Langerhans, can also be used to treat insulin-dependent DM. Thus, an effective method is highlighted for the treatment of type 1 diabetes by transplantation of insulin-producing cells or cells that can replace them.

Embryonic stem cells offer large prospects for the development of regenerative medicine. Such features of stem cells as high proliferation, low specialization and the ability to differentiate into any functional cell type, allow us to get an unlimited source of beta cells without the direct involvement of a donor. As a result of experimental induced differentiation of embryonic stem cells into pancreatic progenitor cells and

their subsequent transplantation into mice, the ability of cells to continue maturation process to a state of normal functioning was revealed, and a new hormone betatrophin was discovered, which has a positive effect on growth and improves glucose tolerance [11].

Pluripotent stem cells are the most suitable object for therapy in case of damage to the pancreatic insular apparatus. Pluripotent stem cells are similar in their properties to embryonic ones, but they have the ability to generate autologous specific cells. Endocrine islets have been successfully created in the laboratory by separating differentiating stem cells, transforming them into clusters that accelerate their development. Clustering of endocrine cells stimulates their metabolic maturation, and, as a result, the cells respond to sugar levels in the same way as mature insulin-producing cells. When modifying the state of the cytoskeleton, the efficiency of insulin-producing cells increases, normalizing glucose levels faster in severe diabetes [12].

OBTAINING AND USING XENO- AND ALLOGENEIC BETA-CELLS

The most promising and necessary way to cure DM is to create a new source of beta cells. Currently, a large number of replacement options for these cells are being studied, which are initially divided into replacement by donor beta-cells and replacement by cells that do not have the same source of development as the cells of the islets of Langerhans.

Substitution with beta-cells, namely xenogeneic cells obtained from other species, has a significant advantage. Preferably, cell replacement by porcine pancreatic islets is studied. The use of these cells is due to a number of reasons: porcine pancreas is a by-product of pork production and has been used as an exogenous source for insulin production for many years; porcine pancreatic islets regulate glucose levels in the same physiological range as in humans; pigs can be genetically modified to make their islets more suitable for human transplantation. However, the use of these cells is limited because porcine beta-cells can cause a rejection reaction with a high risk due to the presence in humans of antibodies to the Gal saccharide located on the surface of cells of lower mammals, as well as the possibility of xenogeneic cells to cause the development of PERV zoonosis [13].

Currently, the most accessible way to cure DM is the replacement of beta-cells with allogeneic cells of adults, namely transplantation of the whole pancreas or its individual islets. However, these transplantations are accompanied by a number of problems, among which the main ones are the need for a complex invasive intervention in the patient's body and the lifelong use of immunosuppressive therapy, as well as problems associated with the extraction of donor material. At the moment, the method of autotransplantation of cells of the islets of Langerhans is being actively developed. Pancreatic beta-cells are an inactive population of cells which expansion occurs during the neonatal period and gradually fade in early childhood, but their proliferative capacity may increase under certain physiological and pathological conditions [14].

Thus, special drugs can be used to increase the number of beta-cells ex vivo for the purpose of transplanting them from donors, and it’s also possible to stimulate endogenous cell proliferation in vivo in order to increase the pool of one's own beta cells [15].

RESULTS OF THE INTRODUCTION OF INSULIN-PRODUCING CELLS IN THE TREATMENT OF DM1

The development of genetic engineering and the use of various methods of reprogramming the genetic code, along with technological progress and the emergence of new equipment to control and maintain the necessary glycemia, are a promising direction in the development of methods for the treatment of various chronic diseases. Insulin-dependent diabetes mellitus is one of the main representatives of the group of these diseases. The introduction of the possibility of formation and transplantation of insulin-producing cells contributes to the development of therapy for this pathology in modern clinical practice. Various methods for obtaining beta-cells that are directly damaged in DM1 contribute to the choice of the most appropriate option, taking into account all the risks of complications, the individual characteristics of the body and the proliferative potential of the cells used. However, although this method is the most modern and promising, it is accompanied by a number of difficulties limiting its use. The main one is the creation of a complex technology for obtaining beta-cells, taking into account the accuracy and efficiency of multistage differentiation and obtaining a pool of cells ready for transplantation and replacement of damaged patient cells [16]. However, the development of science and this field of medicine at the present time, contribute to an increasing study of the potential of progenitor and donor beta-cells, which in the future will be used to modify and expand the application of this method.

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