УДК 616.379 008.64:576.344.

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PERSPECTIVES OF USING STEM CELL TECHNOLOGIES FOR THE TREATMENT OF DIABETES MELLITUS

A very promising solution to the problem of diabetes mellitus can be the use of medical biotechnology, namely cell technologies, which are based on the use of stem cells. To date, various cell populations have been studied for this purpose. The most physiologically justified is the use of stem cells of the pancreas itself and their further differentiation into β-cells. This review is devoted to new methods of diabetes therapy with the use of cellular technologies and the prospects of using cells such as C-kit-positive cells, desmin-positive stellate cells and some others for the cell therapy of diabetes mellitus.
***Keywords**:* diabetes mellitus, stem cells, differentiation, pancreas, cell technology.

Introduction. Diabetes mellitus (DM) is one of the most important problems of modern medicine due to a steady increase in the number of patients in most countries of the world. According to forecasts, by 2030 the number of people suffering from diabetes mellitus will increase to 552 million [1]. DM is a chronic disease in which autoimmune processes destroy the insulin-producing β-cells of the pancreas. The main way to correct hyperglycemia in patients with insulin-dependent diabetes is the administration of exogenous insulin. However, insulin therapy does not allow to restore normal physiological regulation of blood glucose level and eliminate the risk of possible complications [2]. Depending on the nature of its development, DM is classified into two types. In type 2 diabetes, the tissues of the body lose sensitivity to insulin, the function of which is to regulate the level of blood glucose. This most common (up to 80-90% of cases) type of diabetes mellitus, which is also called insulin-independent, develops mainly in old age and is characterized by a relatively easy flow [3].
In type 1 diabetes, autoimmune lesions of beta cells of the pancreas are observed. This type of diabetes leads to a full lifelong dependence on insulin injections - at the moment this is practically the only way to treat this serious illness. The patient should constantly monitor the level of glucose in the blood and, depending on the "jumps" of glucose level, adjust the doses of insulin independently. In any case, the patient develops complications: dysfunction of the kidneys and the cardiovascular system, eye damage (diabetic retinopathy), necrotic tissue damage. The result is a significant reduction in the quality of life of patients, and often disability and early death [3].
The development of severe and irreversible complications that determine the quality of life of patients allows us to classify diabetes as a disease with medical-social significance. Significant economic losses of the state, related to the costs of treatment of the disease and its complications, early disability of patients with disability, mortality in working age are a weighty argument in determining the social significance of the DM problem.
Treating Diabetes Mellitus. At present, the only possible way to cure patients with type 1 diabetes is the transplantation of pancreatic islets, as well as the organ itself [3]. Transplantation of the whole organ is an effective way to achieve and maintain a long-term physiological glucose level in the blood. However, this method is rarely used to treat diabetes due to various risks associated with performing a surgical procedure [4]. Transplantation of the islets of the prostate requires a minimally invasive surgical procedure [5]. Nevertheless, at present, this procedure can not be considered a standard of treatment, because it has its drawbacks. First of all, this is a problem of lack of donors, as well as the need for lifelong immunosuppression. One of the most obvious ways to obtain the large number of islets required for transplantation in diabetes is the use of Langerhans islets derived from other mammalian species. Most attempts in this area have been directed toward the use of porcine pancreatic islets [6-8]. The main problem with the use of xenogenic material, in addition to the risk of zoonosis, is the development of an immunological response to graft rejection [9]. To overcome the problem of the immunogenicity of porcine cells, donor cells were immunized. Thus, the pancreas (macroencapsulation) or individual islets (microencapsulation) of the recipient are placed in the capsule from the semipermeable membrane [10]. Semipermeable the membrane interferes with the contact of the transplanted material with the immunocompetent cells of the recipient, but the diffuse supply of nutrients to the cellular material, the secretion and the yield of insulin are preserved [11]. However, this method has its drawbacks: capsules are perceived by the recipient organism as foreign body; there is a pronounced proliferative reaction around the capsules which leads to inadequate nutrition of the islets; cell apoptosis and islet cell death [12].
Another reason of restraining the clinical use of porcine islet cells is the detection in the cells of these animals of the endogenous retrovirus (ERV), which potentially can infect the cell lines with human [13, 14]. However, at present there is no information about the disease of patients who have undergone xenotransplantation of porcine islet cells earlier. Serologic studies in recipients, conducted 4-7 years after xenotransplantation of pigs islands, did not find marker genes of ERV infection [15].
In recent years, studies have been conducted on the possibility of using bone marrow, hematopoietic, multipotent mesenchymal stromal cells (MMSC), cells producing insulin as a result of differentiation or genetic modification of bone marrow and MMSC for correction of diabetes mellitus [16-19].
Pancreas stem cells. From the physiological point of view, the most suitable are the stem cells of the pancreas itself. However, in this case, the problem that hinders the use of stem cells in regenerative medicine is the complexity of their identification and isolation because of the lack of clear information about their phenotype. To date, one of the most promising markers of precursor cells of pancreatic endocrinocytes is the receptor of the stem cell factor C-kit, or CD117, since it is located on the cell membrane and can be used as a marker for their isolation. C-kit is a transmembrane receptor protein tyrosine kinase, which is encoded in rodents by the dominant allele white-spotting (w), located on the 5 chromosome; the human homologue is located on 4 chromosomes (4 qll-12). This receptor is also called CD 117, stem cell factor receptor (SCF-R), Kit / SCF-R, receptor for the growth factor of mast cells (cell growth factor receptor (MGF) receptor) [20, 21].
C-kit-positive cells were found in 14-16-week-old human fetuses in pancreatic islets that, when cultured in the presence of an exogenous stem cell factor (SCF), began to synthesize glucagon and insulin. It was shown that SCF / C-kit interaction can play an important role in the differentiation of human pancreatic endocrine gland cells at a period of 14-16 weeks. gestation [22]. Expression of C-kit was also found in the islets of the pancreatic rat gland [23]. In addition, it was found that the first C-kit-positive cells appear in the epithelium of the ducts at a period of 8.5 weeks. gestation, further formed C-kit-positive islets, reminiscent of the islets of Langerhans, which persist after birth. It is interesting that at a time of 11.5 weeks. intrauterine development in the islets, cells were found that simultaneously synthesized both insulin and glucagon, as well as remaining in the islets after birth. The authors suggest that the population of C-kit-positive cells can serve as a common source of both β- and α-cells, which first synthesize glucagon, and then insulin [24]. When studying the regeneration of the prostate after the ligation of the duct system, the appearance of C-kit-positive cells in the ducts and islets of Langerhans with maximal expression of the marker for 3 days is also shown. experiment [25]. In experimental alloxan diabetes in the islets of the pancreas in rats, C-kit-positive cells synthesizing insulin appear after a day of experimental hyperglycemia, and these cells are present in the prostate gland at all experimental times. It has been shown that C-kit-positive cells participate in the correction of morphological changes in the islets and the level of glucose in the blood of rats in experimental diabetes (ED) by differentiation into β-cells through the stage of glucagon-producing cells [26]. Thus, C-kit-positive pancreatic cells are the main candidates for the role of stem cells of the prostate - the precursors of β-cells. An interesting fact is that with ED, along with an increase in the expression of C-kit, desynine-positive stellate cells appear in the acini and islands of the pancreas.

These cells, by their phenotype and properties, are very similar to stellate cells of the liver. The cells of both populations accumulate vitamin A, secrete a wide range of growth factors, synthesize the macromolecules of the intercellular substance. In the literature, there is evidence that these cells can be a source of development of endocrine cells [27]. It was shown that with ED, the stellate cells increased quantitatively, however, in these cells, hormone secretion was not detected. According to the authors, stellate cells provide the necessary microenvironment for the differentiation of C-kit-positive cells into endocrine cells. Thus, the authors make the assumption that with ED there is activation of stellate cells of the prostate, which begin to synthesize growth factors and cytokines. The synthesized growth factors interact with the receptors of the progenitor cells, in particular the C-kit stem cell receptor. This interaction leads to differentiation of C-kit + cells into β-cells through the stage of glucagon-producing cells [28].
The ability of C-kit-positive cells to differentiate into α- and β-cells of the pancreas allows us to state that this marker is the is true for the progenitor cells of endocrinocytes. This opens the way for the development of new methods for the treatment of Type I diabetes mellitus by transplantation of C-kit-positive pancreatic cells, which will synthesize hormones and contribute to the correction of disorders of carbohydrate metabolism. In addition, the available data on the change in the population of stellate cells of the prostate at ED suggest that simultaneous transplantation of stellate cells of the pancreas and C-kit + cells may be more effective than isolated transplantation of only C-kit-positive cells. Thus, the use of C-kit-positive pancreatic cells can be one of the promising methods of cell therapy for diabetes.

Differentiation of pluripotent stem cells. As was mentioned above, transplantation of donor β-cells is the only successful practice of diabetes treatment for now. After such transplantation, the patient becomes independent of insulin injections for several years. Problems of this therapy are associated with the quality and quantity of donor material, not to mention the tissue incompatibility of the recipient and the donor. After the transplant, patients need to take drugs that suppress the activity of the immune system, moreover, after some time, the transplant rejection still occurs. Another obstacle is the ethical problems associated with the use of embryonic tissues [29].
However, there is another technic that allows us to way the issue out: β-cells of the pancreas can be obtained *in vitro* (in the laboratory) from cell cultures (Figure 1). Their source can be pluripotent human stem cells, that is, "primary" undifferentiated cells, from which all cells of our organs and tissues are derived. To obtain β-cells, both embryonic stem cells and induced pluripotent stem cells can be used, which are obtained from ordinary adult somatic cells by "reprogramming" them [29].

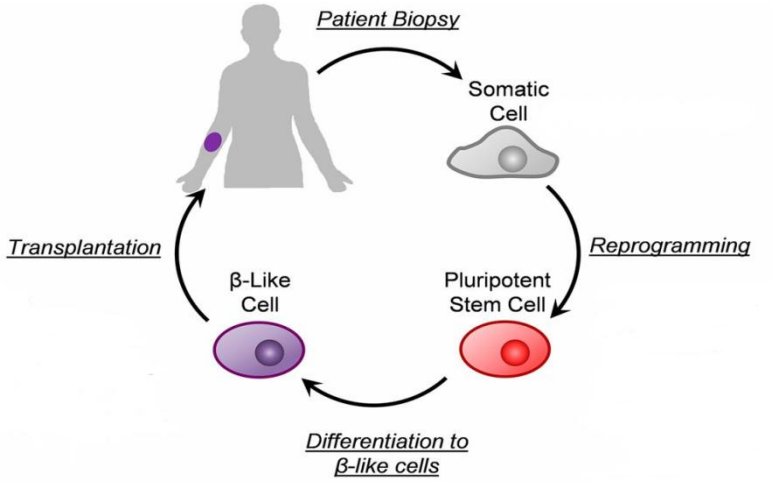

Figure 1 - In vitro derivation of β-cells from pluripotent SCs obtained from somatic cells

Technologies for producing induced pluripotent stem cells are known and well developed. But to get mature β-cells from them is much more difficult, because for this it is necessary literally in a Petri dish to reproduce the most complicated processes occurring during the embryonic development of a person, using signal molecules and chemical compounds that direct the development of cells in the right direction [30].
The list of outstanding scientific studies of the past year published by the journal *Science* includes the work of two research groups: the Harvard Stem Cell Institute (USA) and the Medical School of Massachusetts University in Worcester (USA), under the direction of D. Melton and the University of the Province of British Columbia (Canada) and BetaLogics (USA), led by T. Kiefer, devoted to *in vitro* technologies for producing β-cells of the pancreas [30-31]. Taking as a starting material the stem cells of the human embryo, as a result, the scientists received cells exhibiting all the basic qualities of β-cells.

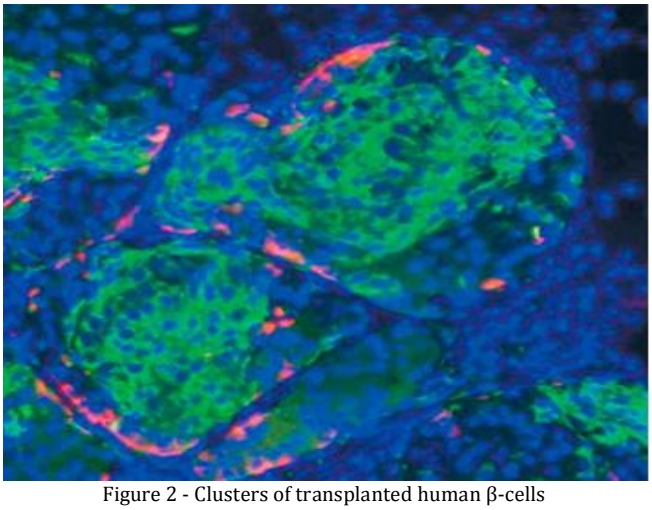

Figure 2 - Clusters of transplanted human β-cells

Fluorescence microscopy: two weeks after implantation into a renal capsule (a fibrous layer of connective tissue around the kidney) of a lab mouse, a "diabetic patient", of β-cells obtained "in vitro" from human embryonic stem cells. It can be seen that the transplanted cells formed clusters and began to produce the hormone insulin. Insulin and glucagon (the hormone of the alpha cells of the islets of the pancreas of Langerhans) are colored with antibodies in green and red, respectively; The DNA of the cell nuclei is a DAPI fluorescent dye in blue [31].

That is, they "worked" certain genes and there were specific proteins, so these cells were able to produce insulin in response to the presence of glucose. Transplanted to laboratory mice from a clean line serving as an experimental model of diabetes mellitus, these cells functioned normally and compensated for the initial absence of insulin (Figure 2) [30-31].

The tremendous advantage of this method is that with its help it is possible to obtain functioning β-cells in a rather large amount. In the final process, up to 300 million cells can be obtained from a single 0.5 liter culture bottle - this number is enough to compensate for the missing insulin in one person weighing about 70 kg. Or for screening among 30 thousand individual chemical compounds - potential medicinal substances, if you use cells not for "direct use", but for pharmacological studies.

It is obvious that the described technologies need to be improved. In particular, the development of detailed protocols for the production of β-cells from induced pluripotent stem cells is required. This will allow not only in any period of the patient's life and practically from any cells of his own organism, if necessary, to obtain the necessary amount of β-cells, but will also solve the problem of immunological incompatibility of the donor and recipient. However, another problem remains: since type 1 diabetes is an autoimmune disease, the new β-cells will again be attacked by the immune system, as once their "native" cells of the patient. Therefore, the transplanted cells must be learned to protect! Only in this case such treatment can become accessible and widely applicable, because the use of immunosuppressants is justified only in the most severe cases.

Now various options for such protection are being developed. For example, it is possible to cover cells with a special hydrogel, but in this case it will be much more difficult to remove them from the body if necessary. In addition, there is as yet no way to prevent their encapsulation in the same way as other foreign bodies in the body, which will block the inflow of nutrients from the transplanted cells [32]. Now there is a search for chemicals suitable for the manufacture of hydrogel, which will not cause such an effect.

Another solution was offered by competitors of the Melton team - the American company ViaCyte. Its essence is to put a pool of immature β-cells inside the body in a biocompatible shell: it is assumed that the precursors of β-cells will gradually mature there and function successfully. Such a device has already been created; moreover, the company has already launched the first phase of clinical trials. But although the results of similar studies on animals look promising, there are concerns about the effectiveness of this method.

Treating DM with stem cells. A functioning transplant in a patient with type 1 diabetes mellitus can eliminate episodes of hypoglycemia, correct the level of glycated hemoglobin (HbA1c), reduce or completely eliminate the risk of secondary complications associated with this disease and, in the most optimal cases, allows achieving independence from insulin. According to the data provided in the Collaborative Islet Transplant Registry (CITR) [33], the independence of insulin in terms of 3 years after transplantation is constantly improving. 27% in the early stages (1999-2002), then 37% in the middle stage (2003-2006), and 44% in the last years (2007-2010). Unlike blood, skin or intestines, the tissues of which are characterized by a relatively high rate of cell replacement, β cells of pancreatic islets are an inactive cell population, while in annual mice the proliferation rate of these cells is 0.1-0.3% per day. In humans, the natural expansion of the β-cell pool occurs in the neonatal period, gradually fading out in early childhood; in adults, increased β-cell replication can occur in certain physiological and pathological conditions, such as pregnancy, or in the development of insulin resistance caused by obesity [34]. Thus, in patients with diabetes (diabetes mellitus), special drugs can be used to increase the number of β cells in ex vivo for transplantation, and endogenous cell proliferation can be stimulated in vivo in order to increase the β-cell pool. In fact, in patients suffering from CD1, β-cell regeneration was observed both at the time of diagnosis and several years after the detection of the disease.

At Harvard University, in conjunction with the Department of Molecular and Cell Biology, Professor Yuval Dor and his colleagues observed a significant increase in the mitotic index of β-cells after mild traumatization of the pancreas by resection of 50-70% of the organ or selective genetic ablation (lat ablatio - removal) of β-cells. Transfection of various molecules involved in the regulation of the cell cycle, such as cyclin-dependent kinases and cyclins, into pancreatic islets of rodents and humans under ex vivo conditions, leads to an increase in the rate of replication of β-cells, however prolonged expression of these molecules also increases the risk of oncogenesis. A safer option is to add various growth factors to the cell culture, such as growth hormone (GH), glucagon-like peptide-1 (GLP-1) or hepatocyte growth factor (HGF), which are known to increase the rate of β-cell replication rodents [35]; but, unfortunately, increased proliferation is accompanied by loss of β-cells of their basic properties, such as the ability to express Pdx-1 (the gene responsible for the synthesis of insulin localizing in the short arm of chromosome 11) or insulin [36]. According to preliminary clinical efficacy studies conducted with patients receiving GLP-1, in vivo therapy with long-acting GLP-1 analogues is believed to stimulate the replication of β-cells in patients with type 2 diabetes [37]. However, it is necessary to obtain long-term results proving the presence of such a positive effect in patients. It has also been shown that the proliferation of β-cells can be influenced by a new hormone-betatrophin, which is expressed in the liver and adipose tissue. Short-term expression of betatrophin in the liver in mice causes significant proliferation of β-cells, an increase in β-cell mass and improves glucose tolerance [38]. Considering the question of clinical use, it should be said that a second-generation human β-cell line is being developed using the reversible "immortality" methods of cells, which avoids the risk associated with the use of cells massively treated with genes potentially associated with oncogenesis. Another completely different point of view is the assumption that in such states as pregnancy or obesity, the mechanism responsible for the growth of the number of β-cells is neogenesis, and not proliferation. The proof is the pathoanatomical study of Butler A. Ye. and his co-workers. The subject of the study was the human pancreas taken during or after pregnancy. In the study, an increase in the number of new small islands was observed, rather than an increase in the replication of β-cells, an increase in the size of islands, or a change in the severity of apoptosis. Butler A. Ye., And his colleagues also observed an increase in the number of insulin-positive cells in the ducts during the study, which indicates the ability of the duct cells under different conditions to differentiate into β-cells or that the stem pancreatic progenitor cells are located in the ducts pancreas. In this study, the authors also observed an increased rate of proliferation of β-cells. Accordingly, replication and neogenesis are not mutually exclusive processes, and contribute to maintaining the required mass of the β-cell pool after birth. In 2009, Patrick Collombat studied the ability of α-cells to transform into β-cells due to the expression of the Pax4 gene, capable of accelerating the conversion of mature α-cells to β-cells. The presence of such an opportunity in humans has not been established, and the results of experiments with chemically-induced diabetes mellitus in lower primates have not revealed the ability of β-cells to regenerate.

Conclusion. Attempts to cure diabetes by inducing functioning insulin-producing cells have never stopped. Despite the existence of problems in the development of new methods for the treatment of diabetes mellitus, there is now a real possibility of using cell therapy in the near future for the treatment of diabetes mellitus. The main issues requiring further studies are the procedure for isolating cells, which can be converted into β-cells, and developing methods for the expansion of those cells in culture to produce necessary amount for the transplantation procedure. In any case, already available technologies inspire hope that the problem of treatment of diabetes will soon be solved. The use of β-cells derived from the patient's stem cells, even with the continued use of immunosuppressants, can be a huge relief for patients with severe diabetes that constantly face life-threatening changes in blood sugar levels.

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ҚАНТ ДИАБЕТІН ЕМДЕУДЕ БАҒАНАЛЫ ЖАСУШАЛАР ТЕХНОЛОГИЯСЫН ҚОЛДАНУДЫҢ ПЕРСПЕКТИВАЛАРЫ

Түйін: Қант диабеті - қазіргі ғасырдағы медицинаның ең үлкен проблемаларының бірі. Аталған аурудың мәселесін шеше алатын жолдардың бірі ретінде бағаналы жасушаларды қолдану ұсынылуда. Осы мақсатқа орай, қазіргі уақытта бүкіл әлемде бағаналы жасушалардың көптеген түрлері зерттелді. Ұйқы безінің өзіндік бағаналы жасушаларын тікелей пайдалану және оларды инсулин синтездеуші β-жасушаларға дифференциялау қолайлы әдіс болып танылуда. Бұл мақала қант диабетіне қарсы қолдануға болатын жасушалық терапияның жаңа әдістерін сипаттауға арналған.
Түйінді сөздер: қант диабеті, бағаналы жасушалар, клеткалық дифференциация, ұйқы безі, клеткалық технологиялар

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ПЕРСПЕКТИВЫ ИСПОЛЬЗОВАНИЯ ТЕХНОЛОГИЙ СТВОЛОВЫХ КЛЕТОК ДЛЯ ЛЕЧЕНИЯ САХАРНОГО ДИАБЕТА

Резюме: Сахарный диабет является одним из огромных проблем медицины в текущем веке. Одним из многообещающим решением проблемы данного заболевания может быть использование технологии стволовых клеток. В данное время, во всем мире были изучены различные виды клеточных культур. Сравнительно самым подходящим является прямое использование стволовых клеток самой поджелудочной железы и их дальнейшее дифференциация в β-клетки. Данная статья посвящена новым методам клеточной терапии против сахарного диабета.
Ключевые слова: сахарный диабет, стволовые клетки, дифференциация, поджелудочная железа, клеточная технология.