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Е.Ю. Шаповалова, С.А. Василенко, И.О. Аврамцев

Ордена Трудового Красного Знамени Медицинский институт имени С.И. Георгиевского, Симферополь, Россия

ТЕРАПЕВТИЧЕСКИЙ И РЕГЕНЕРАТИВНЫЙ ПОТЕНЦИАЛ МЕЗЕНХИМАЛЬНЫХ СТВОЛОВЫХ КЛЕТОК, ПОЛУЧЕННЫХ ИЗ ЖИРОВОЙ ТКАНИ, В ЛЕЧЕНИИ САХАРНОГО ДИАБЕТА 1 И 2 ТИПА (ОБЗОР ЛИТЕРАТУРЫ)

Ye.Yu. Shapovalova, S.A. Vasilenko, I.O. Avramtsev

The Order of Red Banner of Labor S.I. Georgievsky Medical Institute, Simferopol, Russia

Regenerative Potential of Adipose-Derived Mesenchymal Stem Cells in The Treatment of Type 1 And Type 2 Diabetes Mellitus (Review)

Резюме

Работа посвящена анализу терапевтического потенциала мезенхимальных стволовых клеток, полученных из жировой ткани, при лечении сахарного диабета 1 и 2 типа и его осложнений. Приведены краткие сведения о распространенности заболевания, рассмотрены основные существующие подходы к лечению сахарного диабета, направленные на поддержание нормального уровня глюкозы и гликированного гемоглобина, обосновано использование мезенхимальных стволовых клеток, полученных из жировой ткани. Основной недостаток инсулинотерапии, заключающийся в неспособности имитировать физиологическую регуляцию гликемического профиля и полностью устранять сосудистые осложнения у пациентов, стал поводом для поиска более совершенных методик, использующих регенеративный потенциал мезенхимальных стволовых клеток, полученных из жировой ткани. Описаны морфологические и иммуногистохимические особенности данных клеток, охарактеризован широкий спектр факторов роста и сигнальных молекул, определяющих их иммуномодулирующие, антиоксидантные и антиапоптические свойства. Паракринное влияние мезенхимальных стволовых клеток, полученных из жировой ткани, может быть использовано при трансплантации островков поджелудочной железы для повышения их выживаемости. Способность сохранять остаточную массу β-клеток пациента, а также восполнять их количество путем дифференцировки в инсулинпродуцирующие клетки обусловливает использование данных клеток при лечении сахарного диабета 1 типа. В то же время положительное влияние на механизмы инсулинорезистентности, стимуляция гликогенеза и регуляция гликемического профиля характеризуют их перспективность для терапии сахарного диабета 2 типа. Полипотентность и пластичность мезенхимальных стволовых клеток, полученных из жировой ткани, позволяют применить их для лечения диабетических осложнений: трофических язв, диабетических ретино- и нефропатии. Обсуждается состояние клинических исследований, направленных на получение доказательных данных об эффективности и безопасности мезенхимальных стволовых клеток, полученных из жировой ткани, при терапии сахарного диабета 1 и 2 типов.

Ключевые слова: *мезенхимальные стволовые клетки, полученные из жировой ткани, сахарный диабет, диабетические осложнения, лечение*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract

The article is devoted to the analysis of the therapeutic potential of mesenchymal stem cells obtained from adipose tissue in the treatment of diabetes mellitus types 1 and 2 and their complications. Brief information on the prevalence of the disease is provided, the main existing approaches to the treatment of diabetes mellitus aimed at maintaining normal glucose and glycated hemoglobin levels are considered, the use of mesenchymal stem cells obtained from adipose tissue is based. The main disadvantage of insulin therapy is the impossibility of imitation the physiological regulation of the glycemic profile and completely eliminating vascular complications in patients. This fact became the reason for searching for more advanced techniques using the regenerative potential of mesenchymal stem cells obtained from adipose tissue. The morphological and immunohistochemical features of these cells are described; a wide range of growth factors and signaling molecules determining their immunomodulatory, antioxidant and antiapoptotic properties is characterized. The paracrine effect of mesenchymal stem cells obtained from adipose tissue can be used in transplantation of pancreatic islets to increase their survival. The ability to preserve the residual mass of the patient's β-cells, as well as to supply their number by differentiating into insulin-producing cells determines the use of these cells in the treatment of type 1 diabetes mellitus. At the same time, a positive effect on the mechanisms of insulin resistance, stimulation of glycogenesis and regulation of the glycemic profile characterizes the demand for them in the treatment of type 2 diabetes mellitus. Pluripotency and plasticity of mesenchymal stem cells obtained from adipose tissue allow their use in the treatment of diabetic complications: trophic ulcers, diabetic retinopathy and nephropathy. The state of clinical trials aimed at obtaining evidence-based data on the efficacy and safety of mesenchymal stem cells obtained from adipose tissue in the treatment of types 1 and 2 diabetes mellitus is discussed.

Key words: *mesenchymal stem cells, adipose tissue, diabetes mellitus, diabetic mellitus complications*

Conflict of interests

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DM — diabetes mellitus, HbA1c — glycated hemoglobin, IPC — insulin-producing cells, MSC –mesenchymal stem cells, ASC — adipose-derived stem cells (mesenchymal stem cells derived from adipose tissue)

Introduction

The progressive growth rate of diabetes mellitus (DM) incidence has allowed this disease to be assigned the status of an epidemic [1-3]. According to the Federal Register of Diabetes Mellitus in the Russian Federation as of January 1, 2021, the number of DM patients has doubled compared to the year 2000 and approached 5 million (4,799,522). The majority of patients with Type 1 Diabetes Mellitus (T1DM) are of working age, with a peak prevalence at 30--39 years, whereas the largest number of patients with Type 2 Diabetes Mellitus (T2DM) are aged over 65 years [2, 4]. Such a distribution of patients leads to significant economic costs and social burden, including expenses for medical care, reduced working capacity, and the need for social protection measures.

As is well known, DM refers to a group of diseases characterized by multiple etiologies and heterogeneity of development. According to the 2019 WHO classification, several types of DM are distinguished, the main ones being Type 1 DM (T1DM), Type 2 DM (T2DM), hybrid forms of diabetes, other specific types, unclassified diabetes, and hyperglycemia first detected during pregnancy. Despite the different pathogenetic mechanisms underlying these diseases, it is generally recognized that the primary characteristic common to all forms of DM is hyperglycemia resulting from the destruction or dysfunction of pancreatic β-cells [5]. The necessity of maintaining normal glucose and glycated hemoglobin (HbA1c) levels in T1DM leads to lifelong dependence on insulin therapy. Hypoglycemic agents are primarily used for T2DM therapy; however, about 14–25 % of patients eventually require exogenous insulin injections [2, 6]. For a long time after the discovery of insulin by Frederick Banting and Charles Best in 1921, insulin therapy remained the only treatment for T1DM, and all research efforts were directed toward improving insulin production technology, optimizing delivery methods, and glycemic self-monitoring techniques [7]. However, exogenous insulin cannot mimic the physiological regulation of the glycemic profile and completely prevent the development of vascular complications. Moreover, the development of macro- and microangiopathies is associated with low levels of C-peptide secreted by the islet β-cells, which could potentially be compensated by the use of long-term functioning, hormonally active β-cells [8, 9].

Pancreatic islet transplantation and the introduction of the so-called Edmonton Protocol into practice have allowed for the successful restoration of endogenous insulin production. Adequate glycemic control achieved immediately after transplantation was maintained for one year in 44 % of recipients [10]. However, the cumulative incidence of unsuccessful islet transplantations over a 5-year long-term retrospective period exceeded

70 % [11]. Furthermore, this procedure is limited due to the lack of a sufficient number of donor cells and the necessity of immunosuppressive therapy for their survival [12].

In recent decades, mesenchymal stem cells (MSCs) have been considered a promising source of insulin-producing cells (IPCs) due to their multipotency, sufficient quantity in the human body, and immunomodulatory properties [13, 14]. Current achievements in this field are mainly aimed at optimizing the control of T1DM progression. Additionally, it has been established that MSCs can improve insulin resistance in peripheral tissues through the secretion of paracrine factors via extracellular vesicles — exosomes [15, 16].

Sources and Morphological Features of Adipose-Derived MSCs (ASCs)

The most popular sources of MSCs are adipose tissue, red bone marrow, umbilical cord, and dental pulp [6, 17, 18]. Adipose-derived MSCs (ASCs), compared to other MSCs, possess a similar proliferative potential and differentiation capacity; however, they have advantages due to the accessibility and less invasive nature of their harvesting [19]. Moreover, it has been noted that adipose tissue contains a higher concentration of MSCs than other sources [20, 21]. ASCs include MSCs from brown and white fat, as well as visceral and subcutaneous fat. The latter includes cells of the dermal layer of the skin, particularly the dermal papilla and interfollicular dermis, as well as hypodermal cells [16, 20, 21]. A particularly abundant source of ASCs is subcutaneous fat obtained through liposuction [22]. The extracted tissue samples undergo enzymatic separation and are seeded in Petri dishes with a specific nutrient medium containing glucose and penicillin [18, 23]. Cultured cells are washed with phosphate-buffered saline, after which they are identified based on their ability to differentiate into osteogenic, chondrogenic, and adipogenic lineages [23]. Morphologically, ASCs are fibroblast-like, spindle-shaped cells with light, euchromatic oval nuclei. These cells exhibit adhesiveness to plastic and are characterized by a set of specific surface markers, the main ones being CD73, CD90, and CD105, while CD36 and CD49d are unique to ASCs [19]. At the same time, they must be negative for markers of hematopoietic and endothelial cells, as well as MHCII, c-kit, Lin, and HLA-DR [6, 14, 19, 24]. ASCs from the dermis and hypodermis are capable of differentiating into keratinocytes, dermal fibroblasts, melanocytes, and endothelial cells [16]. There is evidence confirming the ability of ASCs to differentiate into neurons, smooth myocytes, cardiomyocytes, and hepatocytes — i.e., derivatives of ectodermal, mesodermal, and endodermal sources [15, 25]. It has been noted that ASCs obtained from brown fat are characterized by higher proliferative properties and differentiation potential than ASCs from white adipose tissue [20, 25].

ASCs are being extensively studied for the treatment of a wide range of diseases: multiple sclerosis, myocardial infarction, liver cirrhosis, muscular dystrophy, and trophic ulcers. Their ability to replace damaged β-cells and regulate blood glucose levels is considered a means of restoring the insulin-producing function of the pancreas [15]. The implantation of autologous cells significantly reduces the probability of their rejection, eliminating the need for long-term immunosuppressive drug therapy. Furthermore, using one's own ASCs resolves a complex of ethical issues arising from the use of donor or embryonic stem cells and simplifies the legal aspects of the procedure, which are encumbered by numerous regulatory requirements. However, despite the advantages of autologous ASC therapy, its effectiveness may be reduced due to the influence of the diabetic microenvironment [15]. The persistent hyperglycemic environment in DM can reduce the differentiation potential of ASCs, their proliferation rate, and their immunomodulatory effects [18, 26]. Donor age also influences the proliferation intensity of ASCs: cells from donors under 30 years of age exhibit higher proliferative activity and differentiation rates compared to ASCs from older donors [20]. To date, there is no consensus regarding the optimal delivery method for ASCs from the standpoint of therapeutic effect. Existing methods involve the administration of in vitro differentiated IPCs intravenously, into the portal vein, the thymus, or the subcutaneous adipose tissue of the patient [19, 27].

Therapeutic Potential of ASCs for the Treatment of Type 1 Diabetes Mellitus

The ability of ASCs to differentiate into IPCs was first discovered in 2003, and in less than 20 years, their effect on pancreatic β-cell function has become the subject of extensive preclinical and clinical trials, many of which have entered Phase II [14]. The therapeutic effect of ASCs is attributed to a combination of several effects, primarily their property of replacing damaged β-insulocytes and normalizing blood glucose levels. Genes responsible for the embryonic development of the pancreas are involved in the complex process of ASC differentiation into IPCs [18]. In a study conducted by Dai P. et al. on dogs, the reprogramming process of ASCs into IPCs was induced by a combination of genes Pbx1, Rfx3, Pdx1, Ngn3, Pax4, and MafA [28]. The listed genes were synthesized and ligated into the linear shuttle adenoviral vector pAdTrack-CMV (BglII and HindIII restriction sites), after which the construct was recombined with pAdEasy-1 in E. coli to form the adenoviral vector pAdEasy-Pbx1-Pdx1-Ngn3-Pax4,

co-expressing multiple genes [27]. Using the RedTrack-CMV adenoviral shuttle vectors as mediators, the adenoviral vector pAdEasy-Rfx3-MafA was generated using the same method [28]. The resulting vectors were used to transduce ASCs cultured in Petri dishes, leading to their reprogramming into IPCs [25]. PCR analysis of the obtained IPCs established the expression of β-cell marker genes, including Neurogenin-3 (Ngn-3), Homeobox protein Nkx6.1, V-maf musculoaponeurotic fibrosarcoma oncogene homolog A (MafA), and Insulin-1 (Ins-1), and a glucose-stimulated insulin secretion (GSIS) test was performed [18]. To enhance insulin synthesis potential, ASCs undergo genetic modification. Specifically, ASCs overexpressing glucagon-like peptide-1 (GLP-1) and FGF21 have been described; these, being metabolically active hormones, stimulate higher insulin secretion and optimize carbohydrate metabolism [15]. The binding of insulin to its tyrosine kinase receptor triggers a cascade of intracellular phosphorylation reactions: insulin receptor substrate (IRS) proteins, activation of phosphatidylinositol 3-kinase (PI3-kinase), and serine-threonine kinase (Akt). The realization of this signaling pathway stimulates multiple biological reactions, including the translocation of glucose transporter type 4 (GLUT4) in the liver, muscles, and adipose tissue, glucose uptake, increased glycogen synthesis in the liver and muscle tissue, and reduced insulin resistance [29]. Similar to the mechanism of glucose uptake by cells via the GLUT4 transporter, insulin stimulates the translocation to the membrane of several long-chain fatty acid transport proteins: CD36 (cluster of differentiation 36), FATP1 and 4 (fatty acid transport protein family members), and FABPpm (plasma membrane-associated fatty acid-binding protein). It is known that free fatty acids activate several serine kinases (IKK and JNK), which subsequently phosphorylate and degrade insulin receptor substrate-1 (IRS-1), a key protein in insulin signal transduction. There is an opinion that this molecular mechanism may be responsible for insulin resistance associated with hyperlipidemia. Thus, the induction of adipogenesis, linked to the capacity for fatty acid uptake, is an important factor in maintaining systemic insulin sensitivity [30]. Alongside this, adipose tissue produces a number of biologically active substances that regulate energy homeostasis, lipid, and glucose metabolism, such as leptin, adiponectin, resistin, and tumor necrosis factor-alpha (TNF-α). An imbalance of these factors can also provoke the development of insulin resistance or impaired insulin secretion [29] **(Figure 1)**.

In addition to differentiation into IPCs, ASCs activate a paracrine signaling system by secreting a wide spectrum of growth factors, including transforming growth factor (TGF-β1, TGF-β3), granulocyte colony-stimulating factor (G-CSF), basic fibroblast growth factor (b-FGF), vascular endothelial growth factor (VEGF), nerve growth factor (NGF), insulin-like growth factor (IGF), hepatocyte growth factor (HGF), von Willebrand factor (VWF), and others. The secretome of ASCs also contains a range of anti-inflammatory, antioxidant, and anti-apoptotic signaling molecules, which promotes the regeneration of endogenous β-cells and the preservation of their functional mass [19, 22, 25]. ASCs demonstrate a significant immunomodulatory effect by inducing M2 macrophage polarization [31]. As is known, macrophage phenotypes M1 and M2 represent two extremes of activation. The M1 phenotype releases a range of cytokines with pro-inflammatory, antimicrobial, and antitumor activity, while M2 macrophages are an alternatively activated type exerting anti-inflammatory, regenerative, angiogenic, and immunomodulatory effects. Macrophages constitute a significant proportion of immune cells in adipose tissue, reaching 40–50 % in obesity.

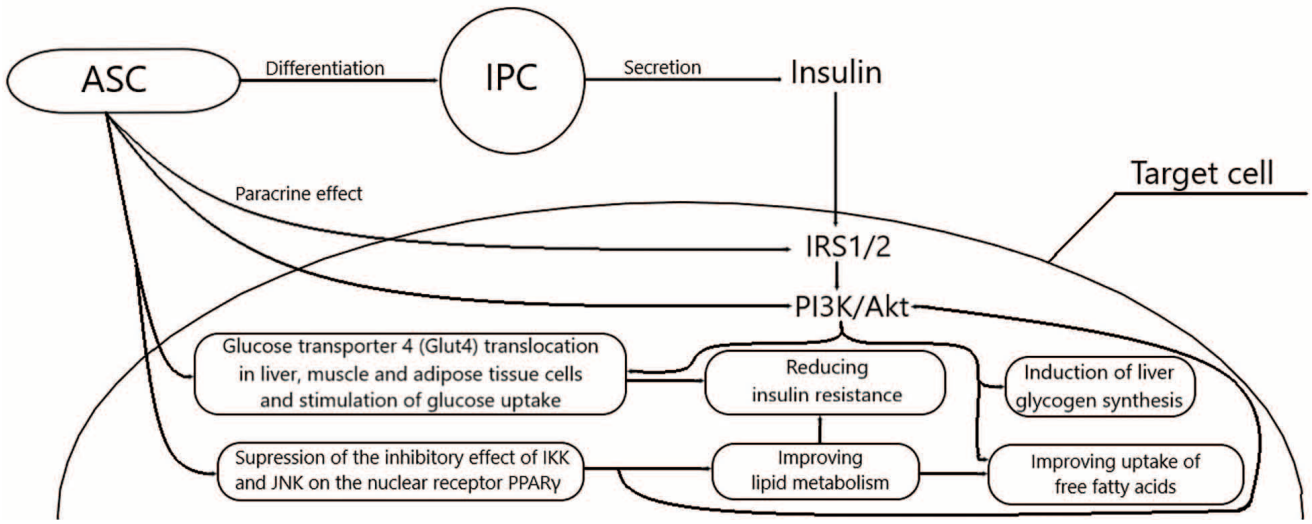

Figure 1. *ASC effect on carbohydrate and lipid metabolism and insuline resistance*

Normally, M2 macrophages predominate, maintaining tissue homeostasis, whereas in obesity, pro-inflammatory M1 macrophages dominate, contributing to the development of chronic inflammation and insulin resistance. The diabetic environment also shifts the balance of macrophages towards M1, exacerbating organopathology [32]. The polarization process of macrophages is regulated by multiple signaling cascades, including the PI3K/AKT, JAK/STAT, NF-κB, Wnt, and Notch signaling pathways. The STAT6 pathway has been established to play a key role in the activation of M2-type macrophages. Experimental studies have revealed the presence of a number of proteins, DNA, mRNA, and microRNAs within ASC exosomes that influence the differentiation and activity of M1/M2 macrophages. For instance, ASC exosomes contain MFGE8 — a glycoprotein that ensures the clearance of apoptotic cells and exhibits anti-inflammatory properties by stimulating M2 macrophage polarization. Cytokines from ASC exosomes exert a similar influence. For example, prostaglandin E2 reduces the expression of M1 markers and increases the expression of M2 markers. Interleukin-6 (IL-6) increases the expression of the IL-4 receptor and STAT6 phosphorylation, stimulating M2 polarization. IGF-2 induces a decrease in inflammatory cytokines and enhances the expression of several genes, such as methyl-CpG-binding protein 2 (Mecp2), an inhibitor of macrophage inflammation. MicroRNAs and long non-coding RNAs from ASC exosomes can activate the transcription of genes that ensure the phenotypic transformation of macrophages from the M1 type to M2. Furthermore, it has been noted that ASC exosomes restore the structure and function of macrophage mitochondria, increase ATP production, and reduce oxidative stress. There is an opinion that the immunomodulatory action of ASCs is based on a mechanism affecting CD4+ T-lymphocytes, involving the induction of apoptosis and cell cycle arrest through the activation of JNK signaling pathways and mitochondrial apoptosis **(Figure 2)**.

In experiments, ASCs inhibited the proliferation of dendritic cells and autoreactive T-lymphocytes. Their interaction with these immunocytes led to a decrease in the level of pro-inflammatory cytokines, e.g., interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and an increase in the level of anti-inflammatory cytokines, such as interleukin-10 (IL-10), prostaglandin E2 (PGE2), and indoleamine 2,3-dioxygenase (IDO). These properties of ASCs have enabled their use as a means of protecting transplants and the patient's own β-cells from inflammatory reactions and autoimmune damage. It is important to emphasize that ASCs positively influenced revascularization processes, which is a critically important factor considering the high risk of cultured islet death due to ischemia [14, 15].

Such effects of ASCs were demonstrated in an experiment on mice: upon co-transplantation of islets with ASCs, significantly less loss of their mass was observed (1.1 ± 0.81 % and 2.7 ± 1.9 % for co-cultured mouse and human pancreatic islets, respectively, versus 22.1 ± 10.5 % using the same technique without ASCs). Despite the fact that the restoration of normoglycemia was temporary, co-transplantation showed higher rates of its restoration with ASC co-transplantation (22.3 ± 4.7 days compared to the control group — 38.5 ± 7.6 days) [33]. Thus, it was noted that the use of ASCs reduces the required mass of transplanted islets and improves their insulin-producing function.

The successful results of experiments obtained in animals prompted investigations into the efficacy and safety of ASC use in humans. In a prospective trial from

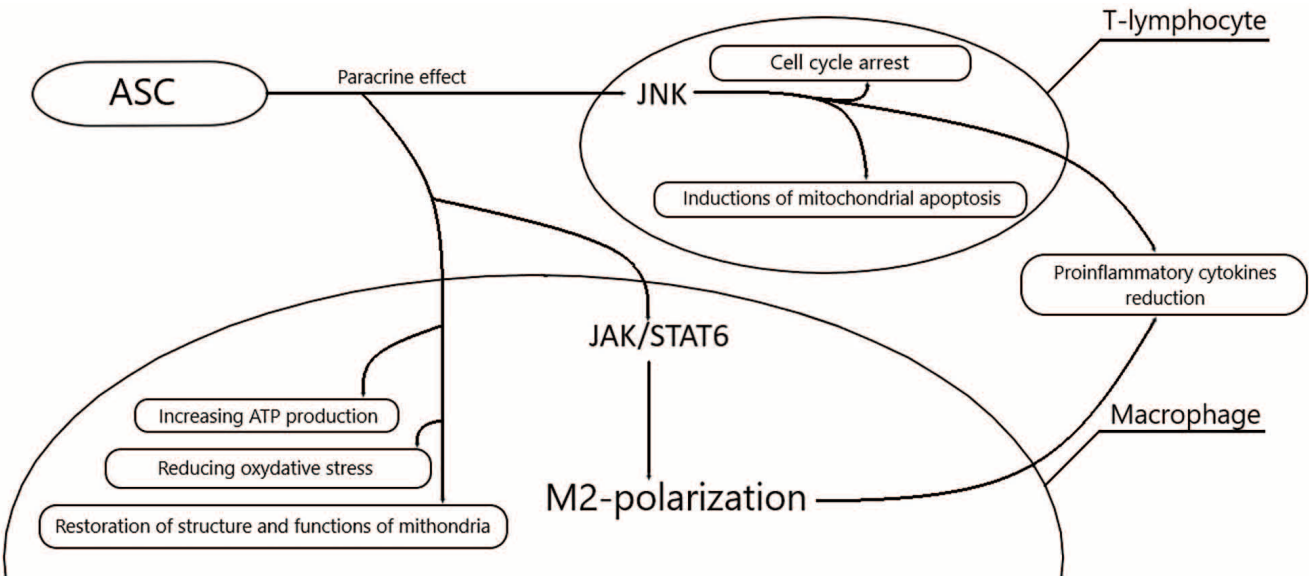

Figure 2. *Immunomodulatoryeffect of ASC*

2015-2021 involving 8 patients with newly diagnosed T1DM, a single intravenous infusion of allogeneic ASCs at a dose of 1 million cells/kg combined with daily vitamin D2 administration resulted in a significant reduction in exogenous insulin requirement almost threefold after 3 months (0.22 ± 0.17 vs. 0.61 ± 0.26 units/kg in the control group) [27]. This positive effect remained stable for 12 months. An increase in basal C-peptide was noted after 6 months; however, subsequently, its levels equalized with those of the control group [34, 35].

Regenerative Potential of ASCs in the Treatment of Type 2 Diabetes Mellitus

Recently, the possibility of using ASCs in the therapy of T2DM, characterized by the development of insulin resistance in insulin-sensitive tissues and pancreatic β-cell dysfunction, has been studied. Several scientific concepts explaining the mechanisms of insulin resistance formation have been proposed: ectopic lipid accumulation in peripheral tissues, a pro-inflammatory environment, endoplasmic reticulum stress, mitochondrial dysfunction, and oxidative stress. Among the possible mechanisms of the positive influence of ASCs in T2DM are the regeneration of pancreatic β-cells, increased glucose utilization in the liver and optimization of hepatic metabolism, anti-inflammatory effects, and increased insulin sensitivity [15]. The mechanism of reducing insulin resistance upon ASC transplantation is hypothesized to be realized through several key events: phosphorylation of the IRS-1 substrate is activated, ensuring effective signal transduction into the cell; expression of the Akt2 gene, which regulates the phosphoinositide pathway of insulin signal transduction, is increased; and translocation of the GLUT4 glucose transporter to the membranes of muscles and adipose tissue is enhanced, increasing its uptake. Thus, the introduction of ASCs enhances the cascade of reactions in the insulin pathway, restoring normal tissue response to insulin action [15, 19]. The high plasticity of ASCs allows them to differentiate into vascular endothelial cells, improving the blood supply to the pancreas [19, 22, 25]. The anti-inflammatory effect is expressed in a significant decrease in the concentration of tumor necrosis factor α (TNF-α), interleukins 6 and 1β (IL-6, IL-1β) [15, 36]. It is assumed that TNF-α and IL-6 are directly involved in the formation of insulin resistance. One probable mechanism is the ability of TNF-α to inhibit the activity of the nuclear receptor PPARγ (peroxisome proliferator-activated receptor gamma), which controls lipid metabolism and maintains high tissue sensitivity to insulin [37] (Fig.1). Furthermore, it is noted that increased expression of TNF-α is observed in obese humans and rodents, which stimulates lipolysis, raises the level of free fatty acids, and disrupts normal insulin signaling, thereby exacerbating the state of insulin resistance [19, 37]. In an experimental rat model with induced T2DM, the administration of ASCs resulted in a statistically significant reduction in hyperglycemia and HbA1c, which persisted for 6 weeks. Histological analysis revealed an increase in the number of islets β-cells and their VWF content, with a simultaneous decrease in the activity of caspase-3, a crucial pro-apoptotic factor [38]. In another study on rats with induced T2DM, it was shown that ASCs pre-treated with the neuropeptide Orexin A exerted a greater therapeutic effect than ASCs without Orexin A. This phenomenon is presumably explained by the fact that Orexins A and B, being stimulators of white adipogenesis, positively influence lipid homeostasis and insulin sensitivity in rodents [15, 37].

Use of ASCs for the Treatment of Diabetic Complications

Currently, the regenerative potential of autologous and allogeneic ASCs in DM and its complications is being studied in several investigations, which include the treatment of skin wounds and trophic ulcers, diabetic retinopathy, and nephropathy. The safety and tolerability of ASC transplantation are being assessed, along with dose determination, frequency of administration, and the early efficacy of this procedure [39, 40, 43]. ASCs can both differentiate into epithelial cells and paracrinely stimulate their proliferation, inhibit inflammation, promote vascularization, and collagen synthesis [14, 15, 19, 40, 41]. In a study conducted by Woo S.H. et al., for the treatment of skin wounds, ASCs were combined with elastin-like polypeptides containing the arginine-glycine-aspartic acid motif — polymers derived from human elastin, possessing a structure that mimics fibronectin-integrin interactions in the extracellular matrix [39]. The experimental results showed that the combined use of ASCs with these polypeptides positively affects wound healing and enhances angiogenesis [39]. Quiñones E. D. et al. compared the efficacy of 2D and 3D culture methods for ASCs in terms of the functionality of their exosomes. It was established that MSCs cultured in 3D spheroids have a higher level of secretion of trophic factors (IL-11, VEGF, bFGF) and overall therapeutic potential than MSCs in monolayer culture. This is likely due to the fact that MSCs located in the central core of the spheroid are less susceptible to hypoxic and mechanical stress. Furthermore, a phenomenon of cell self-activation with increased PGE2 production is suggested, which enhances the anti-inflammatory immunomodulatory potential [40]. Bour F. et al. proposed another combined approach to treating diabetic wounds using a three-dimensional matrix scaffold derived from dermis together with ASCs. This method demonstrated

increased collagen secretion, expression of TGF-ß, bFGF, VEGF, and other regenerative genes, as well as improved stereological, biomechanical, and tensiometric characteristics overall, alongside decreased expression of TNF-α, IL-1ß, and numerical density of neutrophils and macrophages in the experimental groups [41]. Ma T. et al. created a model of a bilayer cell patch containing epidermal stem cells and angiogenic ASCs for the treatment of diabetic wounds [42]. The use of ASCs for diabetic retinopathy has been proposed: these cells can differentiate into pericytes and endothelial cells and delay the breakdown of the blood-retinal barrier. Intravitreal administration of ASCs in diabetic mice prevented capillary loss by 50 %. Moreover, a reduction in the expression of inflammatory factors characteristic of this disease was observed [20]. Diabetic nephropathy is one of the main causes of death in patients with T1DM and T2DM. Morphologically, it is characterized by glomerular enlargement, damage to podocytes and the glomerular basement membrane, and damage to the renal tubular apparatus. In vivo studies have shown that the application of exosomes produced by ASCs and containing microRNAs (*miR-150, miR-134, miR16-5p, miR-26a-5p*) significantly alleviates the course of the disease. Specifically, the ability of miR-26a-5p to inhibit podocyte apoptosis and counteract oxidative stress in the kidneys has been noted [19, 43]. The combined use of ASCs with antioxidants demonstrated a good therapeutic effect in treating liver and kidney dysfunctions in rats with T1DM and a significant ($p < 0.05$) improvement in urea, uric acid, and creatinine levels compared to control groups [44].

Safety of ASC Application

Federal Law of the Russian Federation No. 180-FZ of June 23, 2016, "On Biomedical Cell Products" legalized the use of cell technologies in medical practice in Russia. The use of adult ASCs resolves the ethical contradictions associated with the inadmissibility of terminating the development of a human embryo when obtaining embryonic stem cells. In accordance with the Order of the Ministry of Health of the Russian Federation dated June 4, 2015, adipose tissue is included in the approved list of transplantable objects (Order of the Ministry of Health of the Russian Federation No. 306n/3 dated June 4, 2015, "On Approval of the List of Transplantable Objects"). Thus, defining the legal status of ASCs expands the boundaries of their use for clinical research. However, despite the high regenerative potential of ASCs and the approved legal documents permitting their use, cell therapy is still far from widespread implementation in practical medicine. Some publications report possible negative effects and technical difficulties associated with this direction. To achieve therapeutic efficacy, a high concentration of MSCs, ranging from 1×10^6 to 1×10^8 cells, is required, which is obtained through prolonged cultivation. The manipulative stress to which ASCs are subjected during passaging leads to the accumulation of chromosomal abnormalities. Research results reveal statistically significant DNA damage in ASCs starting from the fifth cell passage [45]. Consequently, to ensure the maximum possible safety of clinical trials involving ASCs, strict monitoring of cytogenetic anomalies in cell culture is necessary. Experimental data indicate that stem cells share similarities with clonogenic tumor cells. There is an opinion that MSCs may act as the cellular origin of tumors or enhance existing precancerous tendencies due to the generation of growth factors. It is indicated that the probability of malignant transformation of human MSCs can reach 45.8 %. It should be noted that transformed MSCs are capable of participating in the creation of the stroma and the tumor-associated vascular network [46]. However, unlike transformed cancer cells, MSCs demonstrate both pro- and anti-tumor properties. Thus, patient biology is a key factor largely determining the therapeutic effect and the body's response. The structure and frequency of side effects when using autologous MSCs were analyzed in a multicenter study involving 2,372 patients with degenerative joint diseases: a total of 325 adverse events were registered, accounting for about 14 %. The vast majority of these effects were associated with pain syndrome due to the progression of the underlying disease. Cases of neoplasms accounted for 0.3 %, which is somewhat lower than the average rate in the general population [47].

The use of multipotent cells presents researchers with the task of controlling their differentiation pathway to avoid the emergence of undesirable cell lineages. The ability of ASCs, besides the chondrogenic, osteogenic, and adipogenic lineages, to differentiate into myofibroblasts with subsequent development of fibrous tissue is well known. A case of chronic kidney disease progression 5 months after ASC therapy due to massive fibrosis of glomeruli and interstitial tissue has been described [48].

Various cultivation conditions contribute to the heterogeneity of MSCs in terms of morphology, cell membrane receptor profile, and secretome. For instance, it has been found that culturing MSCs under normoxic conditions induces a senescent morphology characterized by increased cell volume. The use of large MSCs for cell therapy leads to their entrapment in non-target organs with capillary diameters smaller than the size of the MSCs (e.g., lungs, brain) and can be complicated by vascular obstructions and stroke [49]. It is evident that to enhance the safety and efficacy of MSC use, the development of a standardized cultivation protocol and the production of a homogeneous cell population with optimal sizes are necessary.

Allogeneic MSCs pose a certain risk associated with the potential presence of viral DNA or mycoplasma contamination, which could negatively affect the recipient's health and reduce the effectiveness of the transplantation [50]. Thus, strict adherence to biosafety rules during cell cultivation is a mandatory condition for the use of ASCs in clinical practice.

Conclusion

In summary, it should be noted that the use of ASCs opens new perspectives in the regenerative therapy of Type 1 and Type 2 Diabetes Mellitus. This method contributes to the improvement of glycated hemoglobin and C-peptide parameters, reducing patient dependence on exogenous insulin. The therapeutic effect of ASCs, confirmed by the results of preclinical and clinical studies, is determined not only by differentiation into insulin-producing cells but also by the paracrine secretion of a broad spectrum of cytokines, immunomodulatory, and angiogenic factors. The regenerative potential of ASCs allows for their use in combating diabetic complications. However, before their application becomes a widely used technique, a larger body of scientific data confirming the safety and efficacy of this therapy must be accumulated.

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Информация об авторах

Шаповалова Елена Юрьевна — д.м.н., профессор, заведующая кафедрой гистологии и эмбриологии Ордена Трудового Красного Знамени Медицинского института имени С.И. Георгиевского, Симферополь, e-mail: shapovalova_l@mail.ru, ORCID ID: https://orcid.org/0000-0003-2544-7696.

Василенко Светлана Анатольевна ✉ — старший преподаватель кафедры гистологии и эмбриологии Ордена Трудового Красного Знамени Медицинского института имени С.И. Георгиевского, Симферополь, e-mail: sweta_181171_@rambler.ru, ORCID ID: https://orcid.org/0000-0002-7965-2639.

Аврамцев Игорь Олегович — студент Ордена Трудового Красного Знамени Медицинского института имени С.И. Георгиевского, e-mail: iropbcharkov1@gmail.com, ORCID ID: https://orcid.org/0009-0003-4119-3005.

Information about the authors

Yelena Yu. Shapovalova — MD, Professor, Head of the Department of Histology and Embryology of the Order of the Red Banner of Labor, S.I. Georgievsky Medical Institute, Simferopol. e-mail: shapovalova_l@mail.ru, ORCID ID: https://orcid.org/0000-0003-2544-7696.

Svetlana A. Vasilenko ✉ — Senior Teacher of the Department of Histology and Embryology of the Order of the Red Banner of Labor, S.I. Georgievsky Medical Institute, Simferopol, e-mail: sweta_181171_@rambler.ru, ORCID ID: https://orcid.org/0000-0002-7965-2639.

Igor. O. Avramtsev — student of the Order of the Red Banner of Labor at the S.I. Georgievsky Medical Institute, e-mail: iropbcharkov1@gmail.com, ORCID ID: https://orcid.org/0009-0003-4119-3005.

✉ Автор, ответственный за переписку / Corresponding author