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The use of autologous mesenchymal stem cells in complications of diabetes mellitus, in particular diabetic retinopathy: inputs and insights

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Abstract

The review provided reveals the analysis of the available scientific literature on the feasibility of using cellular technologies, such as, autologous mesenchymal stem cells (MSCs) for diabetic retinopathy treatment. The results indicated the viability of cellular technologies in clinical ophthalmology with respect to anatomical features and immune privilege of the organ of vision. Additionally, feasibility, safety, and optimization of pathogenetic therapy for MSC transplantation expands the prospect of their use in late complications of type 1 and type 2 diabetes mellitus, in particular, diabetic retinopathy.

Key words: mesenchymal stem cells, diabetic retinopathy

Introduction

Autologous mesenchymal stem cells (MSCs) reported as a considerable advance in biomedical cell therapy provide for the feasibility and safety of using cell technologies, in particular, in various fields of medicine, including ophthalmology [1,2]. The evidence represented in experimental studies in the direction of cellular technologies, repeatedly point to the advantages of the eye over other organs. It mostly relates to the presence of certain amount of non-invasive methods for diagnosing the organ of vision, the minimum risk of systemic complications (formation of tumors) due to hemato-ophthalmological barrier. Additionally, various mechanisms of immunological tolerance, the presence of a low immune response in the anterior segment of the eye, which is carried out according to a specific type of "immune deviation associated with the anterior chamber", which allows the use of not only allogeneic, but even more autologous MSCs without the threat of rejection in the recipient's body [2,3].

Mesenchymal stem/stromal cells include a group of multipotent cells extracted from various tissues of the body, in particular from bone marrow, adipose tissue, dental pulp, neonatal umbilical cord, amniotic membrane, amniotic fluid, placenta [4,5]. The unique fenomena of MSCs origined from the above biological tissues. When transplanted, MSCs demonstrate the ability to inhibit inflammation in case of tissue damage, secrete growth factors leading to tissue repair, and differentiate into any types of cells (nerve, bone, fat, etc.) depending on recipient tissue [6].

When transplanted, the nonspecific immunosuppressive therapy and the risk of transplant material rejection are excluded, the minimal susceptibility to malignant tissue degeneration and easy collection of biological material, and compliance with ethical standards are presented [7-10].

The clinical application of this line of cells in ophthalmology today is mainly experimental, especially in situations of late irreversible stages of degenerative processes in the photoreceptor layer of the posterior segment of the eye [11,17]. The reason for this is the insufficient in vivo potential of progenitor cells (ciliary body epithelium, iris pigment epithelium, Müller cells) capable of differentiating into retinal cells to replace a defect in such pathologies as age-related macular degeneration (AMD), retinitis pigmentosa (RP), diseases Stargardt and Leber's congenital amaurosis (AL), which lead to a significant decrease in visual function and, as a result, disability of the working population worldwide [12]. As known, the pathologies like ganglion-photoreceptor-pigment interface is first of all damaged, followed by activation of a cascade of irreversible complications: neuroinflammation, microglia, gliosis [13-15].

The failure of various traditional therapeutic methods for retinal diseases dictates the development of various methods of regenerative therapy. Recent achievements in the field of gene therapy, neuroprotection, anti-VEGF (vascular endothelial growth factors) and stem cell therapy make it possible to slow down the process of progressive vision loss [16]. The benefit of gene therapy is the recovery of certain types of degenerative retinal diseases associated with certain recessive gene defects. The therapeutic efficacy of neuroprotection is aimed at preventing the cascade of reactions leading to damage to retinal and optic nerve neurons [17-18]. Finally, anti-VEGF therapy is the gold standard for the treatment of neovascular age-related macular degeneration (AMD), diabetic retinopathy (DR), in particular in diabetic macular edema (DME), and neovascular retinal diseases [19]. The targeted role of in vitro cell therapy in these diseases of the retina lies in the possibility of their use in late incurable stages of apoptosis of the neuroepithelium and the inner layer of the retina, i.e. triggering the mechanisms of reversibility of the death of neuronal cells in the retina and optic nerve [20]. Pathological complications of the retina occured in diabetes type 1 and type 2 affect neurons in the light-receiving and light-transmitting layer of the posterior segment of the eye, which combines DR with degenerative diseases of the retina [21].

The global prevalence of DR impressed by almost 200 million people suffering from eye complications due to diabetes mellitus. The proliferative stage of DR and DME is a particular threat to visual functions [22].

At the basis of pathogenetic processes, the main role belongs to the long-term state of hyperglycemia of the body and, resulted in prolonged hypoxia of the retina, sequented to gross violation of the homeostasis of retinal vessels. The outcome of such transformations of the microcirculation of the retina, mostly the vascular wall, is the development of microaneurysms, exudations, activation of neovascularization causing secondary ischemia of the retina, which exacerbates the processes of neurodegeneration, gliosis, and neuroinflammation [23,24].

Routine pathogenetic methods of treatment for the above conditions, such as retinal photocoagulation (panretinal and focal) in the proliferative stage of DR and macular edema, and intravital administration of anti-VEGF (bevacizumab, ranibizumab and aflibercept) significantly reduce retinal edema and cause regression of neovascularization [17,22]. However, the implementation of these techniques is accompanied by the risk of possible complications and adverse reactions: recurrence of a bleeding episode, subcapsular cataract, steroid-induced glaucoma, endophthalmitis, intraocular inflammation, rhegmatogenous retinal detachment, traction retinal detachment, which entails additional economic costs [25,26].

Drawbacks of existing methods motivate the search for the best ways to treat DR, taking into account modern scientific achievements, including in the field of stem cell therapy, has great promise and relevance, especially in terms of restoring damaged retinal architectonics [27].

Thus, the aim of the study is to analyze the available scientific literature reported about using cell technology, in particular MSCs, to optimize the treatment of DR.

Material and methods

The search conducted based on medical and biological publications in "PubMed", the "Biotechnology" section, created by the National Center for Biotechnology Information (National Center for Biotechnology Information). The search allowed identifying the studies on the issue of potential use of stem cells / progenitor cells in DR. It addressed the therapeutic efficacy by having four areas of application such as precursors of photoreceptors and other retinal neurons, also, Muller / glia stem cells - the ancestors of glia and retinal neurons, pigment epithelial stem cells, endothelial, myeloid cells - precursors, adult stem cells, induced pluripotent stem cells (iPSCs). The cells mentioned can contribute to the microvasculature of the retina, thereby exerting vasculo- and neurotrophic effects [22].

Results

As the therapeutic efficacy of stem cells depends on many factors: donor-recipient matching, tissue of origin, MSC cultivation protocol we underlined the following. When chose a donor tissue, it is mandatory to consider the characteristics of the obtained stem cells, affecting the level of therapeutic efficacy: the ability to proliferate and get aged, paracrine activity, the simplicity of collection method, and its option effective, as well as the route of transmission of the cell material. Accounting these aspects, MSCs of the bone marrow, adipose tissue and umbilical cord meet pointed conditions. Therefore, the issue of MSC integration into the retinal tissue has a number of unresolved issues that require further study and research [5].

As additional problem we defined the favorable mode for the delivery of MSCs to the retina. Previously mentioned the results obtained in preclinical trials, which found low efficiency of MSCs on ganglion cells and photoreceptors when administered systemically. Regarding the method of local injection of MSCs, a review showed the performed preclinical trials with preference of intravitreal transplantation of MSCs, given their ability to synthesize neurotrophic factors that prolong the survival of ganglion cells, regenerate axons, thereby slowing down the rate of loss of the latter [22]. With the background of prolonged ischemia of the retinal tissue and a decrease in the secretion of growth factors, MSCs can replenish their volume by producing two categories of neurotrophic factors. Some stimulate cell proliferation (transforming growth factor-alpha (TGF-α), TGF-β, hepatocyte growth factor (HGF), epidermal growth factor (EGF) and fibroblast growth factor-4 (FGF-4), others are responsible for maintaining angiogenesis, (VEGF, interleukin-8 (IL-8) and insulin-like growth factor-1 (IGF-1) [10]. The rat models demonstrated the trophic effect of the retinal neuroepithelium by experiment on laser-induced glaucoma and damage to the visual nerve induced. The damage caused by intravitreal transplants of dental pulp MSCs (DPSC), simultaneous cultivation of porcine

retinal cells and human MSCs differentiated in the Transwell system (brain-derived neurotrophic factor (BDNF) and ciliary neurotrophic factor (CNTF) in the eyes of rats with chronic hypertension with intravitreal transplanted MSCs (brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF) [12].

Thus, these studies have shown the possibility of successful use of autologous MSCs to improve retinal gliosis through their differentiation, which significantly increases the thickness of the macula and improves visual functions [11].

In modulating angiogenesis, MSCs play an important role in diabetic retinopathy (DR), which is characterized by the triggering of the formation of disordered and physiologically defective blood vessels. This leads to a violation of the histology of neurons in functionally significant areas of the retina and irreversible loss of vision. Experimental intraperitoneal administration of MSCs from the human amniotic membrane to mice inhibited neovascularization due to the expression of transforming growth factor beta (TGFβ), subconjunctival administration of bone marrow MSCs resulted in corneal wound healing and suppression of the formation of new vessels due to VEGF inhibition [28-29]. In an induced model of mice with DR, when adipose tissue MSCs were injected into the vitreous body, the researchers observed a decrease in the activity of the VEGF receptor 2 due to an increased expression of thrombospondin-1 (TSP1), which led to the suppression of angiogenesis [20].

With the background of early stages of DR, the use of MSCs makes interest because of the ability to replace lost pericytes of the retinal microvascular bed due to the existing morphological similarity of mesenchymal cells. This assumption appeared during the experimental intravitreal administration of human MSCs in diabetic mouse models, where an improvement in the physical properties of the retina was noted [22, 30].

Regarding the preservation of the survival of photoreceptors after the introduction of MSCs, positive experimental results were obtained in rat models with induced retinitis pigmentosa, retinal degeneration, and diabetic retinopathy, which demonstrate the neuroprotective effect of stem cells administered by subretinal or intravitreal injections [31].

Naturally, each mode of injection is associated with certain risks and side effects; therefore, optimization of procedures is required to minimize the consequences, such as secondary glaucoma, epiretinal membrane, differentiation into myofibroblast-like cells with subsequent development of fibrosis, proliferative retinopathy, traction retinal detachment, neovascularization [27].

Another advantage of the use of MSCs is associated with the production of extracellular vesicles, secreted bilipid-layered nano-microvesicles containing functional molecules (lipids, proteins, RNA, etc.). With subsequent endocytosis, retinal cells provide the content of the necessary biochemical subunits, which suppresses cell apoptosis, promotes inhibition of pro-inflammatory mediators and stimulates retinal regeneration. Experimentally, in DR, there is a positive effect of neuroprotection and regeneration of the retina from the movement of miRNA-222 in exosomes secreted by MSCs from adipose tissue into different layers of the retina in three ways (intravenous, subconjunctival, intraocular), damaged and deficient miRNA-222 expression resulted in persistent hyperglycemia [32]. This direction has the prospect of development due to the low risk of a number of complications: the quality of transplantation, immunogenic and oncogenic risks [27].

Studies reviewed evidenced the additional mechanism that provides the protective function of cells; we are talking about the transfer of functional mitochondria into damaged target cells via tunneling nanotubes [33]. Such structures have active intercellular communication and are able to transfer cytosolic material to ganglion cells. These data were obtained in rat models with induced inflammation and glaucoma [17]. As is known, mitochondrial dysfunction is observed in many diseases of the retina, including DR, and treatment with this method will help to suspend and restore the function of ganglion cells [34].

With regard to the immunological reactivity of the organ of vision, there is scientific information on an interesting mechanism of the immune response that is triggered by the introduction of MSCs: suppression of the proliferation of T-cells, B-cells and natural killer cells, inhibition of differentiation and maturation of monocyte-derived dendritic cells, and promotion of the formation of regulatory T cells. It is based on the ability of MSCs to release mediators, including cytokines, chemokines, and some metabolites (IDO, IL-6, PGE2 and TGF-β1), which provide an immunomodulatory effect, thereby causing protection of the hemato-retinal barrier, infiltration of immune cells and subsequent tissue inflammation. (edema, violation of the MCC, growth of microglia). The significance of the immunosuppressive role lies in the phagocytic absorption of the retinal tissue of apoptotic MSCs, which results in the production of indoleamine-2,3-dioxygenase (IDO), which provides an anti-inflammatory function [21].

In international practice, the therapy of ocular pathology remains in process of testing at the stage of clinical trials, in particular DR, is being tested with retinal stem cell transplantation. Clinical trials in humans are carried out with retinal stem cell transplantation using pluripotential stem cells (PSCs) and iPSCs, which are morphologically similar to photoreceptors and retinal pigment epithelial cells (RPE) [35]. Following this, in 2017, Japan researchers presented two cases of transplantation of MSCs into the retinal pigment epithelium obtained from iPSCs, the cell layer was previously monitored for the absence of genetic breakdowns and anomalies, in patients with wet macular degeneration after removal of the neovascular membrane. At an intermediate stage of this clinical study, the authors proved the survival of induced retinal pigment epithelial cells during the first year after transplantation, improvement in visual acuity and the absence of complications. This study and follow-up of patients is in progress [35].

Since 2012, the biotechnology company SmartCell, based on the Institute of Advanced Medicine VIRTUS, has been developing and implementing unique cellular technologies. They reported AMK (platelet automesoconcentrate), which is a cellular preparation containing growth factors, in particular, bioactive substances that stimulate the process of regeneration of damaged tissues, the growth of new vessels, and as a result, improvement of local blood circulation. That were isolated in the laboratory from the patient's blood platelets used in regenerative medicine, in particular in diabetic retinopathy, to start the natural process of tissue and organ repair in diabetes mellitus. [32].

Bhattacharya, 2017, prospective clinical study provided an evaluation of changes in visual functions, the degree of DME and the state of microcirculation of retinal vessels after transplantation of MSCs in patients with non-proliferative and proliferative stages of DR by intravenous administration. The study revealed the ability of MSCs to control the processes of phagocytosis and reduce inflammation of the retinal tissue. The indicators of the two groups were experimentally compared, without the participation of the placebo group, which is the main drawback of this study [35]. Summarizing the results

of the studies, it was concluded that ABMSCs have an anti-inflammatory effect, reducing the thickness of the macula that controls inflammation. With respect to improvement in BCVA and electrophysiological function (data not shown), MSC-derived neurotrophic factor [36] and control of inflammation may be indicative results. Although several studies have obtained damaged stem cells from people with diabetes [36,37], enough cells have been successfully extracted for transplantation to demonstrate their efficacy. Thus, ABMSCs extracted from diabetic patients may be suitable seed cells for DR.

Baek, 2011, long-term clinical study (NCT01736059) reported the intravitreal injections of bone marrow CD34+ MSCs are administered to subjects with irreversible visual loss due to retinal degenerative disease or retinal vascular disease, including DR. Nirwan, 2019, (NCT03403699) examined the ability of iPSCs to generate endothelial cells and pericytes in areas with capillary degeneration seen in DR [38].

In support of this assumption, recently obtained autologous MSCs from bone marrow were found to be beneficial in patients with NPDR, with significant improvement in macular thickness and improved best-corrected visual acuity (BCVA) from baseline [39].

Overall, the calculation of integral hematological parameters found as no less important before the start of the study and in dynamics, which makes it possible to predict the results after transplantation of autologous MSCs and the state of the body's immunological reactivity [40].

Conclusion

Overall, the review in the field of application of biomedical cellular technologies, in particular, autologous MSCs for the treatment of late complications of diabetes type 1 and type 2 , such as diabetic retinopathy, which is currently one of the leading causes of blindness worldwide, found the technology as perspective.

The presented experimental and clinical cases of achieving an optimal result in transplantation of autologous MSCs explain sufficient potential in improving the homeostasis of the retinal microvasculature and the pathomorphological picture of the neuroretinal interface at all stages of DR. That does not exclude the stage of proliferation, as well as an increase in the state of the body's immunological reactivity, including including the organ of vision, provided that international ethical standards are observed when using cellular technologies.

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