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PROSPECTS FOR CELL THERAPY IN OPHTHALMOLOGY 2. POTENTIAL OF STEM CELLS FOR TREATMENT OF RETINAL PATHOLOGIES

Heřmánková B., Holáň V.

Institute of Experimental Medicine, Academy of Sciences of the Czech Republic, Department of Transplant Immunology, Vídeňská 1083, 142 20 Praha 4, Head of Department prof. RNDr. Vladimír Holáň, DrSc.

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Mgr. Barbora Heřmánková
Institute of Experimental Medicine, Academy of Sciences of the Czech Republic, Department of Transplant Immunology, Vídeňská 1083, 142 20 Praha 4,
email: barbora.hermankova@biomed.cas.cz

SUMMARY

Retinal diseases represent a large group of hereditary and acquired diseases that often lead to loss of vision. There is currently no effective treatment of retinal degeneration, only supportive therapy is used for treating numerous diseases. Perspective treatment of retinal diseases represent a cell therapy using stem cells. Suitable candidates for the stem cell therapy are mesenchymal stem cells due to their differentiating properties, protective effect and also immunomodulation.

Key words: retinal disease, therapy, stem cells, mesenchymal stem cells

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INTRODUCTION

The retina is one of the most important parts of our eye, the main function of which is receiving and pre-processing incoming light signals. It is composed of ten layers of different cells which are in constant mutual communication and transmit signals to one another. The first layer, located furthest from incoming light, is the retinal pigment epithelium (RPE), followed by a layer formed by photoreceptors – rods and cones, the external limiting membrane, the outer nuclear layer, the outer plexiform layer, the inner nuclear layer composed of bipolar, horizontal and amacrine cells, followed by the inner plexiform layer, the ganglion cell layer, the nerve fibre and ganglion cell axon layer and finally the internal limiting membrane. Damage to any of these layers leads to a disruption of function and homeostasis of the entire retina, which in many cases causes deterioration of vision up to blindness (1). At present there is no effective possibility of treatment for retinal degeneration, only medicaments which retard the development of degenerative diseases are administered. A certain hope for the treatment of retinal pathologies is offered by cell therapy based on the application of stem cells. Three types of stem cells come into consideration for cell therapy: embryonic stem cells (ESC) obtained from the blastocyst of an embryo, stem cells isolated from the tissue of an adult organism and "induced pluripotent stem cells" (iPSC) prepared in a laboratory by the introduction of specific genes into somatic cells of the adult organism.

Stem cells and therapy

The most frequently damaged retinal cells are the photoreceptors, RPE and ganglion cells. An ideal solution would be their replacement with healthy cells and subsequent renewal of interactions between the individual layers. A prospect for cell therapy of retinal pathologies lies in stem cells, which would replace a specific lacking or damaged cell type.

Embryonic stem cells

ESCs are pluripotent cells capable of developing into any cell type of the adult organism. Their disadvantage is frequent and uncontrolled growth, the possibility of formation of teratomas in the organism, and their use is also limited by ethical problems in connection with their origin and preparation (1, 4).

Induced pluripotent stem cells

As a result iPSCs, which are artificially prepared from somatic cells of the organism with the help of the introduction of genes for the transcription factors Oct4, Sox2, Klf4 and cMyc, have been demonstrated to be a more promising candidate for cell therapy. Somatic cells modified in this manner acquire the properties of stem cells and the ability to differentiate into all embryonic lines in a process known as reprogramming. These stem cells have brought great hope in the possibility of preparing cells of a given individual with subsequent autologous use in therapy. However, it has been demonstrated that the expression of other genes also may occur in the reprogrammed cells together with the influence of introducing genes for transcription factors. It has been observed that upon autologous transplantation, the use of cells modified in this manner has led to an activation of the immune system. The use of iPSCs is also limited by problems with the incomplete reprogramming of cells and the possibility of

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a transmission of foreign genes with the help of viral vectors. It has also been demonstrated that iPSCs may form teratomas in the organism, similarly as in the case of ESCs (21).

Stem cells of the adult organism

For the above reasons, the most suitable type for cell therapy of retinal pathologies appears to be stem cells isolated from the tissue of the adult organism, within which we can include for example haematopoietic stem cells, stem cells occurring specifically in individual tissues or mesenchymal stem cells (MSC). MSCs may be transplanted without genetic modification, are able to migrate to the place of damage and differentiate themselves into a range of different cell types, including retinal cells. To date no formation of teratomas following their transplantation into the organism has been determined. MSCs have been demonstrated practically in all tissues of mesodermal origin, and are most frequently isolated from bone marrow or fat tissue (1, 19). Numerous studies have already confirmed the suitability of use of MSCs in the treatment of corneal damage (7, 11).

Protective effect of MSCs

Stem cells can mediate a therapeutic effect partially by direct differentiation into cells of the afflicted tissue or through the production of a range of growth and trophic factors. The paracrine effect of the stem cells influences the environment of the damaged tissue, protects it and activates repair mechanisms. MSCs inhibit damaging inflammatory reaction in the place of damage, and amongst other factors neurotrophic factors such as brain-derived neurotrophic factor (BDNF), ciliary neurotrophic factor (CNTF), glial cell line-derived neurotrophic factor (GDNF) or basic fibroblast growth factor (bFGF). In the case of several pathologies linked with retinal damage, increased survival of cells was demonstrated upon the effect of neurotrophic factors produced by MSCs (19). As a result, one of the current directions of research is an endeavour to ensure a safe and effective method of transporting neuroprotective cells to the place of tissue damage and secure the long-term production of neurotrophic factors in the place of damage (3).

Table no.1 - Specific markers of retinal cells

Retinal cells	Typické znaky
Undifferentiated progenitor cells	Pax-6 Six-3
Retinal pigmented epithelium cells	RPE65 Bestrofin CRALBP Cytokeratin 8
Photoreceptor cells	Rodopsin Rekoverin CRX
Bipolar cells	Chx10 Protein kinase C-α
Ganglion cells	Thy-1

Immunomodulation properties of MSCs

In addition to their protective effect, MSCs also have the ability of immunomodulation, suppress the activation and function of cells of natural and adaptive immunity, and support the rearrangement of the immune response to anti-inflammatory (15). MSCs can act on the cells of the immune system both through inter-cellular contact and through the help of soluble immunomodulation molecules such as indoleamine dioxygenase (17), nitrous oxide (22), prostaglandin E2 (6), transforming growth factor-β (23) and others.

Differentiation of MSC in vitro

It has been demonstrated that in addition to osteogenic, chondrogenic and adipogenic differentiation, MSCs are also capable of differentiating into cells expressing attributes of retinal cells. In the case of MSCs isolated from the conjunctiva, expression of signs typical of photoreceptors and bipolar cells (18) was determined following cultivation on nanofibre scaffolds using taurine (table no. 1). Differentiation of rat MSCs into cells expressing typical attributes of photoreceptors was demonstrated also following the use of taurine, activin A and epidermal growth factor (14).

In addition to differentiation into cells with attributes of photoreceptors, MSCs are also capable of differentiation into RPE cells and expressing attributes typical of these retinal cells such as bestrophin or RPE65 (24) (table no. 1). Expression of attributes specific for RPE cells was also determined in human MSCs cultivated together with isolated human RPE cells (10, 16). Similar results have also been described in the case of rat MSCs, in which differentiation into RPE cells was induced by cultivation conditions reminiscent of the development of these cells within the framework of the retina (8). These experiments demonstrate the potential of MSCs to differentiate into retinal cells and thus support the prospects for the use of MSCs in the treatment of retinal pathologies.

Retinal pathologies

Retinal pathologies rank amongst very serious diseases, often leading as far as loss of sight. At present the methods of therapy used are very invasive and linked with serious side effects, furthermore for many retinal pathologies only supportive therapy exists, which attempts to alleviate the consequences of the pathology. As a result MSCs, through their properties of differentiation, protection and immunomodulation, represent promising candidates for cell therapy of thus far untreatable retinal pathologies.

Hereditary retinal pathologies

Amongst the most common hereditary retinal pathologies is retinitis pigmentosa (RP). This pathology incorporates a range of genetic defects, in which there is damage and subsequent necrosis of rod cells. In the later phase there is also degradation of cone cells and RPE cells, leading to total blindness. At present there is not successful treatment for this disease (19). In an experimental model of chemically induced RP, it was determined that following subretinal application these cells can be found in the outer layer of the retina, whe-

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re they differentiate into cells expressing attributes of RPE cells and photoreceptors (9) (table no. 1). Other authors have confirmed the extended survival of photoreceptors following the transplantation of MSCs isolated from bone marrow on a model of a mouse with an eliminated gene for rhodopsin. MSCs are integrated not only into the RPE layer, but also into the neural and glial layers of the retina. An important factor in this case was mainly the production of neurotrophic factors by the applied MSCs (2). At present three clinical trials are under way using MSCs in the treatment of RP, focusing for example on the selection of the most suitable method of cell application and the safety of use of MSCs (19).

Another hereditary pathology is Stargardt's disease, which is the most common retinal pathology occurring at an early age. This pathology causes necrosis of RPE cells due to an accumulation of lipofuscin, leading to the degradation of photoreceptors in the area of the macula and loss of central vision (4). On an experimental model of a laboratory rat it was observed that only 2 weeks after subretinal application of MSCs their integration into the retina took place, with formation of cells expressing attributes of photoreceptors (14) (table no. 1).

Ischemic retinal pathologies

Diabetic retinopathy (DR) is a retinal pathology in which the vascular supply of the retina is damaged, and in its advanced stage can lead to irreversible loss of sight. It affects up to 60% of patients with diabetes mellitus. In the initial phase there is a weakening of the walls of the blood vessels, with the formation of micro-aneurysms in their walls. Insufficient oxygen supply to the cells causes necrosis of endothelial and pericyte cells, with vascular occlusion which prevents sufficient nutrition, resulting in hypoxia to ischemia. This process is further accompanied by the production of angiogenic factor and the formation of new blood vessels. In the newly formed blood vessels ruptures and haemorrhages take place into the vitreous body, which together with the formation of fibrous scars leads to disorders of vision and in the final form to blindness. At present the methods used in therapy are intravitreal application of corticoids, laser photocoagulation or vitrectomy. However, these methods are very invasive and are linked with serious complications (3).

In a model of diabetes in a laboratory rat, it was demonstrated that following intravenous application of MSCs these cells reached the damaged retina, where they differentiated into astrocyte cells and cells expressing rhodopsin. At the same time this group demonstrated that MSCs reduced the level of glucose in blood and regenerated the breached barrier between blood and the retina (25). Similar results were determined following the application of human fat MSCs into the vitreous body in a rat with induction of diabetes. Following application, MSCs were found mainly in the surrounding area of the retinal capillaries, where there was a suppression of expression of inflammatory symptoms and an increased survival of retinal cells (20).

Other retinal pathologies

The most common cause of visual disorders and blindness, not only in the Czech Republic, is age-related macular degeneration (ARMD), which occurs in patients older than 50 years. It affects the photoreceptors and RPE layer in the place of the macula, which leads to a loss of central vision. ARMD occurs in dry (atrophic) and wet (exudative) forms. In dry form, amorphous deposits accumulate in the retina, leading to a degradation of the RPE. Wet form is less common, but more dangerous, involving choroidal neovascularisation, in which subsequent haemorrhage and fibrosis may cause damage to the macula. Both types of the pathology entail damage to the photoreceptors, whereas the inner part of the retina remains undamaged. These pathologies suggest that a potential therapy could be replacement of the damaged cells. At present wet form is treated by photodynamic therapy, as well as blockage of vascular endothelial growth factor, whilst there is currently no effective treatment for dry form (3, 4). On a model of retinal degeneration in a laboratory rat it was demonstrated that subretinally applied MSCs replaced pigment cells and restored the integrity of the individual layers of the retina (5).

Glaucomas are a group of chronic degenerative diseases, in which there is a slow, progressive degeneration of the ganglion cells of the retina, leading as far as irreversible loss of sight. At present treatment is focused only on reducing intraocular pressure and slowing the progression of the pathology. New therapies propose the application of lacking neurotrophic factors such as BDNF, GDNF or CNTF (13). However, in order to attain the required effect their repeated application is necessary, as a result of which a more suitable solution would be the application of MSCs producing these factors directly into the place of damage. Studies on an experimental model of glaucoma have demonstrated that following injection administration of MSCs into the vitreous body, the production of lacking neurotrophic factors takes place in the place of damage, which results in reduced necrosis of ganglion cells in the retina. However, no ability of MSCs to differentiate and express attributes typical of retinal cells has been demonstrated here (12, 26) (table no. 1). The first clinical trial using MSCs from bone marrow in the treatment of glaucoma began in 2013 (19).

Mechanical damage to the retina

The retina can also be damaged mechanically upon injury or penetration of a foreign body into the eye. Usually upon contusion swelling occurs, which soon subsides without long-term consequences. However, if the macula of the retina is directly injured, retinal detachment and deterioration of vision may occur. A further means of damage to the retina is direct effect of ultraviolet radiation, which causes degeneration and apoptosis of the photoreceptors, leading to irreversible loss of sight. In an experimental model of a retina damaged by light radiation in a laboratory rat, it was demonstrated that subretinal transplantation of MSCs isolated from bone marrow suppressed apoptosis of the photoreceptors and alleviated the consequences of retinal damage (27). Expression of bFGF and BDNF was determined in the place of application of MSCs, which had a protective influence on the damaged cells and supported their regeneration. However, no differentiation of MSCs into photoreceptors or other retinal cells was demonstrated here (27).

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CONCLUSION

With regard to their properties, MSCs are demonstrated to be very suitable candidates for cell therapy in the case of retinal pathologies. However, many issues still require clarification and need more detailed study before their clinical utilisation. To date not all the mechanisms of the effect of MSCs in the place of damage have been clarified, neither have the ability of MSCs to survive and differentiate in vivo or the possibility of interconnection of individual cells and the regeneration of the entire integrity of the retina. A fundamental role may also be played by the quantity of applied MSCs and the attendant selection of their most appropriate and safest application. For full clarification of the given issue it is necessary to conduct further experimental and pre-clinical trials.

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