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Regenerative Medicine

The use of mesenchymal stem cells for the treatment of progressive retinal diseases: a review

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Some ocular diseases, such as dystrophies, retinal and macular degeneration, optic nerve atrophy, and Stargardt disease, are progressive and irreversible. In this review, we focus on the use of mesenchymal stem cells (MSCs) in the treatment of these diseases. In animal studies, MSC transplantation significantly delayed retinal degeneration, led to the regeneration of cone cells, and supported the survival of retinal ganglion cells and axon regeneration. In clinical practice, patients with Behcet's disease with retinal vasculitis who received MSC injections experienced a decrease in retinal vasculitis but no improvement in vision acuity. Nonetheless, there is no evidence that MSCs are carcinogenic, and they even reduce the size of tumors *in vitro*. Furthermore, MSCs do not trigger the immune response.

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The therapeutic potential of stem cells is already widely studied in ophthalmic diseases, especially in disorders that lead to a progressive and irreversible loss of vision. Among them, the following deserve special attention: optic nerve atrophy, dystrophies, retinal and macular degeneration, and Stargardt disease.

Optic nerve atrophy

Causes of optic nerve atrophy include optic neuritis, excessive pressure, glaucoma, chronic retinal degenerative processes, toxic substance intake, pathological changes taking place in the orbit or in the cranial cavity, injuries and genetic burden [1]. The classical treatment for optic nerve atrophy mainly consists in preventing and minimizing the deterioration of vision using conservative or surgical means. However, in the case of optic nerve atrophy resulting from injuries or genetic burden, the loss of vision is inevitable. Hereditary optic nerve atrophy cannot be treated. Apart from mesenchymal stem cell (MSC) therapy, the only hope for these patients is gene therapy [2], which is still not a reality because the genes responsible for the disease have not been completely identified.

Dystrophies

Progressive cone-rod dystrophies are a large, heterogeneous subgroup of genetically conditioned retinal diseases (retinopathies), characterized by a gradual degeneration of cone and/or rod construction and function [3,4]. Cone dystrophies can affect all three classes of cones or only some of them [5].

Retinal degeneration

Retinal degeneration is a wide group of disorders associated with abnormal retinal cell function [6]. The most common retinal dystrophy is retinitis pigmentosa (RP). In this type of dystrophy, photoreceptor cells are gradually deposited to form clusters of pigment [6]. In the early stages of RP, the cells responsible for night vision are

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damaged. The next stage involves the loss of peripheral vision and, finally, an almost complete loss of vision [6]. The disease is also often accompanied by photophobia. There is no effective treatment for RP, but the following substances are used in its management: vitamin A [7,8], vitamin E [8], lutein [9,10], omega-3 acids [11–13] and calcium channel blockers [14]. The proper selection of optical aids is still the most effective therapy for RP. Retinopathies of premature, diabetic and hypertensive natures can also be distinguished.

Macular degeneration

Macular degeneration is a chronic, progressive eye disease occurring mostly in people over 50 years of age [15]. This condition is characterized by damage to the macula, the central part of the retina, and results in the deterioration or total loss of central vision [15]. The treatment options for this disorder are very limited. In some cases, such as in exudative age-related macular degeneration, a pharmacological treatment with antiangiogenic drugs is possible [15].

Stargardt disease

Stargardt disease is classified as a rare, mainly autosomal recessive disease, which damages the central part of the retina [16]. It can occur as a result of mutations in the *ABCA4* gene, which encodes a transport protein for vitamin A, and less frequently in the *CNGB3* or *ELOVL4* genes [1]. The first clinical symptom of this disease is a rapidly progressing bilateral reduction in visual acuity, which usually occurs in people aged 8–25 years [16].

The treatment for most of these diseases is mainly focused on the use of optical aids, orientation and mobility training, and a limited number of pharmacological agents. However, these drugs merely inhibit the development of the disease and only a few cases allow for vision improvement.

Therapeutic properties of Wharton's jelly-derived MSCs isolated from the umbilical cord

Several types of cells have been considered in the experimental therapy of ophthalmic diseases, including embryonic stem cells (ESC), limbal stem cells of the corneal epithelium, retinal pigment epithelial cells and MSCs. Acquiring stem cells from embryos and fetuses is burdened with numerous doubts and reservations of ethical and legal natures. In addition, there is a danger of carcinogenesis due to the pluripotent properties of ESCs, which can form teratomas – tumors made of different types of tissue – in the recipient's body [17]. On the other hand, the use of mature cells, such as corneal (limbal) progenitor cells and retinal pigment epithelial cells, is associated with limited autologous (own) cell numbers and potential complications at the site of cell collection. For allogeneic applications, in which the cells are typically sourced from deceased donors, it is necessary to enclose the cells in casings made from materials such as alginate to avoid an adverse immune response in the recipient. None of these problems and limitations apply to MSCs obtained from Wharton's jelly of the umbilical cord (umbilical cord-derived MSCs [WJ-MSC]).

The immunological privilege of MSCs isolated from Wharton's jelly

Currently, the use of WJ-MSCs is possible almost exclusively in an allogenic system, in which the recipient is not a donor at the same time. With the growing popularity of stem-cell banking, the potential for autologous use is increasing. MSCs obtained from extra-embryonic tissues, such as amnion, placenta and umbilical cord, partially retain pluripotent properties [18].

The unique features of Wharton's jelly MSCs make them attractive for allogeneic transplantation. First, WJ-MSCs are immune privileged. Even though they express low levels of major histocompatibility complex (MHC) I, there is no full activation of alloreactive lymphocytes due to the lack of co-stimulatory molecules (such as CD40, CD80 and CD86) and an unusually high level of the immune inhibitors IDO and PGE2 [19]. In addition, WJ-MSCs synthesize the G6 subtype of the HLA antigen (not detected in MSCs isolated from the bone marrow [BM-MSCs]), which seems to be involved in protecting the fetus from the mother's immune system [20]. Moreover, MHC class II antigens are not observed on their surface. Consequently, WJ-MSCs are very well tolerated by the recipient's immune system in allogeneic transplantations from unrelated donors. Furthermore, WJ-MSCs do not trigger an immune response after xenogeneic transplantation to recipients of different species [19]. Additionally, WJ-MSCs injected intravenously did not change the total number of $CD3^+$, $CD4^+$ and $CD8^+$ T cells, and did not increase IgG and IgM levels in patients with heart failure, compared with the control group [21].

The introduction of allogeneic MSCs into the recipient's body does not trigger an immune response, which means that the risk of adverse reactions is extremely low. Additionally, the collection and isolation of WJ-MSCs does not require additional medical procedures, as in the case of BM-MSCs, where bone marrow collection is required.

MSC differentiation & neuroprotective properties

Just like mesenchymal cells isolated from other tissues, WJ-MSCs cultured *in vitro* differentiate into osteoblasts, adipocytes, chondrocytes, endothelial cells, skeletal muscles and cardiomyocytes [22]. In addition, WJ-MSC can transform into different nerve cells, including dopaminergic neurons [23], cholinergic neurons [24], Schwann cells [25] and oligodendrocytes [26]. In a preclinical study on stroke, WJ-MSCs implanted in the brain of rats differentiated into endothelial cells and neurons [27]. Therefore, WJ-MSCs can potentially contribute to the reconstruction of the nervous system by differentiating into specialized cells and allowing for the replacement of disease-damaged neurons or oligodendrocytes. Additionally, studies have shown that BM-MSCs can differentiate into photoreceptors [28] and retinal pigment epithelial cells [29].

WJ-MSCs can also produce and secrete proteins that stimulate tissue regeneration. WJ-MSCs can produce angiogenic factors (such as CXCL2, CXCL5 and FGF9). More importantly, WJ-MSCs can secrete neurotrophic factors, including neurotrophin-3, midkine and glial cell-derived neurotrophic factor, and they do so at higher levels than BM-MSCs [30]. In *in vitro* experiments, paracrine factors produced by WJ-MSC have been shown to increase the survival and proliferation of primary cortical and cerebellar neurons [31].

Preclinical studies demonstrating the beneficial effects of MSCs in retinal diseases

In vivo studies in a rat model of retinal degeneration showed that subretinal MSC transplantation significantly delayed retinal degeneration and supported normal retinal function in syngeneic [32], autologous [33] and xenogeneic systems [34]. MSCs transplanted together with the cornea significantly extended graft survival time [35]. After transplanting MSCs to the damaged area of the retina, these cells differentiated into retinal nerve cells and synthesized the tissue-specific proteins rhodopsin, calbindin and glial fibrillary acidic protein [36]. Furthermore, in a rhodopsin knockout mouse model of RP, the injection of MSCs led to the regeneration of cone cells [37].

MSC implantation under the retina, and not into the vitreous cavity, was more beneficial and resulted in improved vision in a rat model of RP [38].

In rats with optic nerve injuries, dental pulp-derived MSCs injected into the vitreous cavity supported the survival of retinal ganglion cells and axon regeneration [39]. Similarly, cells isolated from Wharton's jelly reduced the percentage of apoptotic cells and exerted a neuroprotective effect on retinal ganglion cells, especially in the first phase of optic nerve injury in rats [40]. This effect was short lived, suggesting that multiple injections of cells would be most effective. Other experiments using WJ-MSCs indicate that these cells may also support the regrowth of retinal ganglion cells after optic nerve injury [41]. These results indicate that WJ-MSCs can be used as an effective therapy in some forms of retinal degeneration and for optic nerve regeneration.

The use of MSCs for retinal diseases in clinical trials

In view of the above, it seems reasonable to use MSCs to treat ophthalmic diseases. Table 1 shows a list of the registered clinical trials using MSCs for this purpose.

To date, only the results of trial NCT00550498 have been published [42]. In this study, three patients with advanced Behcet's disease with retinal vasculitis and complete loss of vision received 1.8×10^6 autologous BM-MSCs per kg of bodyweight. The authors reported a significant decrease in retinal vasculitis, which was due to the stem cell infusion and not the drugs used (cyclophosphamide + prednisolone + azathioprine). This was evidenced by the lack of effect in the second eye, which did not receive stem cells, and in which a strong inflammation was observed. Nevertheless, despite a decrease in retinal vasculitis, no improvement in vision was observed. This might indicate a dependency of the therapeutic effect on the severity of the disease. For future studies, the authors suggest including only patients within a less advanced stage of the disease and in whom the MSCs could still be beneficial for the reversal of the retinal degeneration process.

Attempts at treatments for cone-rod dystrophy were probably part of the first scientific programs seeking a treatment method for RP. Stem cell therapy for this disease has also been investigated. Since 2005, researchers at the University of Sao Paulo, Brazil (clinical trial number: NCT01068561) have investigated the use of autologous stem cells to treat RP. In this study, 10^7 autologous mononuclear cells isolated from the bone marrow were injected into the vitreous cavity of five patients [43]. No side effects associated with cell application were observed, but unfortunately the therapeutic effect of the cell therapy was not confirmed. Most of the cells used in the treatment, however, were hematopoietic cells, and according to various sources, MSCs constitute only 0.02–0.0017% of all mononuclear cells in bone marrow aspirate [44]. Therefore, the lack of a therapeutic effect in this study may be due

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Table 1. Clinical trials registered at www.clinicaltrials.gov that assess the use of mesenchymal stem cells in ophthalmologic diseases.

Disease	Cell type	Source	Cell dose	Route of administration	Clinical trial number
Optic nerve inflammation; retinitis pigmentosa; macular degeneration; glaucoma	BM-MSC	Auto	NS	IVIT; iv.; ST; IO	NCT01920867
Macular degeneration	BM-MSC	Auto	NS	IVIT	NCT02016508
Macular degeneration	BM-MSC	Auto	10^7 in 0.1 ml	IVIT	NCT01518127
Optic nerve inflammation	NS	Auto	2×10^6/kg	iv.	NCT02249676
Optic nerve inflammation	WJ-MSC	Allo	NS	NS	NCT01364246
Limbal stem cell deficiency	BM-MSC	Allo	NS	NS	NCT01562002
Behcet's disease	BM-MSC	Auto	$3–5 \times 10^6$ in 0.1–0.3 ml	IVIT	NCT00550498
Ischemic retinopathy	BM-MSC	Auto	10^7 in 0.1 ml	IVIT	NCT01518842
Retinitis pigmentosa	BM-MSC	Auto	10^7 in 0.1 ml	IVIT	NCT01068561
Retinitis pigmentosa	BM-MSC	Auto	10^7 in 0.1 ml	IVIT	NCT01560715
Retinitis pigmentosa	BM-MSC	NS	10^6 in 0.1 ml in PBS	IVIT	NCT01531348
Retinitis pigmentosa	BM-MSC	Auto	NS	NS	NCT01914913

Allo: Allogeneic; Auto: Autologous; BM-MSC: Bone marrow-derived mesenchymal stem cell; IO: Intraocular; iv.: Intravenous; IVIT: Intravitreal; NS: Not specified; PBS: Phosphate buffered saline; ST: Sub-tenon; WJ-MSC: Wharton's Jelly-derived mesenchymal stem cell.

to an insufficient number of MSCs. Additionally, it is possible that the autologous MSCs used in this study could have the same genetic defect as the patients' retinal cells, and thus they would not have positive and long-lasting effects.

In Thailand, researchers at Mahidol University in Bangkok in cooperation with the Ministry of Health have been conducting a clinical trial (NCT01531348) since 2012. About 10^6 BM-MSCs were administered to the inside of the eyeball in patients previously invited by the center in Bangkok. The results of the study have not yet been published.

Additional information on the use of MSCs and other cells in the treatment of ophthalmic diseases can be found in the review articles by He *et al.* [45] and He *et al.* [46].

The risk of complications after MSC administration

Risk of tumors

MSCs can be maintained *in vitro* for 20–30 passages, depending on the culture conditions and the cell isolation site [47]. The genetic stability of MSCs during *in vitro* culture has been confirmed in several experiments. Data collected from karyotyping, comparative genomic hybridization, *in situ* hybridization of subtelomeric regions and the analysis of SNPs have shown a lack of the chromosomal aberrations that may lead to neoplastic transformation [48,49]. Like other types of cells, MSCs undergo aging (senescence) in long-term *in vitro* culture, which leads to an inhibition of their proliferative potential. However, the unique feature of MSCs is their high resistance to neoplastic transformation, unlike other cell types, which undergo spontaneous mutations [50].

The safety of using MSCs in passages 3–13 was verified in a series of experiments in animal models, including immunodeficient Nude/SCID mice, miniature pigs, rabbits and monkeys [51]. The experiments consisted in the subcutaneous administration of MSCs. As a result of the cell administrations, no formation of tumors was observed during several months of observation. Injecting MSCs mixed with K562 leukemia cells or Kaposi's sarcoma cells significantly reduced the tumor-cell proliferation potential, which indicates the anticancer properties of MSCs [52,53]. The anticancer properties of MSCs probably derive from the immunomodulatory and chemotactic influence MSCs have on the immune system components [54].

Research on the clinical use of MSCs has been conducted for several years. To date, there are no reports of neoplastic processes resulting from MSC administration, despite the similarities between ESCs and MSCs. In addition, in a very detailed study performed on 340 patients with orthopedic injuries who were given *in vitro*-grown MSCs for tissue regeneration, there was a lack of neoplastic processes at the sites of MSC injection [55]. The lack of neoplastic process development may be due to the reduced expression of some of the embryonic markers

present on WJ-MSCs. In the case of human cells, it is the expression of Dnmt3b and Tert, which correlates with the ESC expression pattern [56]. In addition, the safety of the *in vivo* use of WJ-MSCs regarding teratoma formation has been confirmed using animal models, including rats and immunodeficient mice [57,58]. Moreover, some studies have confirmed the anticancer properties of WJ-MSCs. Among these, Ayuzawa *et al*. were able to reduce the growth of a human breast cancer tumor, both *in vitro* and *in vivo* in a xenogeneic system using a mouse model [59]. The antitumor properties of WJ-MSCs seem to be effective not only against breast cancer cells, but also against ovarian and bone cancer cell lines [60]. Recent publications suggest that WJ-MSCs exert their antitumor effect through cell–cell interactions and humoral factors (induction of apoptosis, cycle arrest and autophagy) [60,61]. These cells express a high level of inflammatory response mediators, such as IL-8, IL1B and IL6 [62], which may affect the chemotaxis of the immune cells toward the tumor. At present, there are at least 65 clinical trials (www.clinicaltrials.com) using WJ-MSCs, which have been isolated and expanded *in vitro*, and none of these trials has reported any adverse effects due to MSC injection, including carcinogenesis. The most important analysis documenting the safety of the systemic delivery of MSCs in the clinic is the work of Lalu *et al*. [62]. They assessed the safety of MSC use through a meta-analysis of studies using MSCs, which included over 1000 patients. The authors searched for key data in three databases: MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials (data until June 2011). The meta-analysis included prospective clinical trials, in which MSC infusions were administered intravenously or intra-arterially. The analysis included 36 trials containing data for 1012 participants and assessing the effectiveness of MSC infusions for the treatment of brain ischemia, Crohn's disease, cardiomyopathy, myocardial infarction and graft-versus-host disease. No significant association was found between MSC treatment and the toxicity of infusions, internal organ infection, deaths or cancer.

Retinal detachment

Intravitreal injections of MSCs have been linked to a risk of fibrosis and tractional retinal detachment [64]. However, this complication was also reported after intraocular injections of bevacizumab, and the authors of this case report suggest that this may be a consequence of the natural history of this disease rather than an adverse event caused by the injection [65].

Immunogenicity

Despite overall high safety, it should be mentioned that although these cells do not activate allogeneic lymphocytes *in vitro* (due to low expression of allogeneic MHC molecules), the situation can be different after their transfer into inflammatory environment of the diseased eye. In the presence of proinflammatory cytokines, the expression of MHC molecules is significantly increased, the secretory profile of allogeneic MSCs is changed and their therapeutic properties can be different than in the case of the use of autologous MSCs. For this reason, therapeutic use of allogeneic cells still requires in-depth molecular studies and careful safety assessment.

Conclusion

The positive results obtained from the use of MSCs in rat models of ocular diseases suggest that this treatment can also be beneficial in humans. Studies in humans have had little success so far, probably due to the overly advanced stage of the disease in the treated patients. An earlier administration of cells may improve the results, but the risk of accelerated vision loss due to adverse effects should be excluded first.

Future perspective

Recently, a new treatment modality has emerged, which can decrease the potential risks associated with cell therapies. Cell-free stem cell therapy involves the use of microvesicles and exosomes released by MSCs, and its therapeutic potential has been demonstrated in animal models of renal disease [66,67]. Further studies on cell-free therapy using extracellular vesicles may reduce risk of retinal detachment. Other important fields for future studies are interactions between different types of stem cells and the use of substances, which may improve of clinical outcome, such as quercetin [68–71], luteolin [72,73], apigenin [73] or resveratrol [74–77].

Authors' contributions

Study conception and design were carried out by A Borkowska-Kuczkowska, B Świątkowska-Flis and D Sługocka. Acquisition of data was carried out by D Sługocka, A Borkowska-Kuczkowska, B Świątkowska-Flis and D Boruczkowski. Analysis and interpretation of data was done by A Borkowska-Kuczkowska, B Świątkowska-Flis, D Sługocka and D Boruczkowski. Drafting of manuscript was done by A Borkowska-Kuczkowska, B Świątkowska-Flis and D Sługocka. Critical revision was carried out by D Boruczkowski.

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Executive summary

Background

- Stem cell therapy has been investigated in the treatment of several irreversible ophthalmic diseases.

Therapeutic properties of Wharton's jelly-derived mesenchymal stem cells isolated from the umbilical cord

- Mesenchymal stem cells (MSCs) obtained from Wharton's jelly (WJ-MSCs) are free from the problems associated with other cells considered in the treatment of ophthalmic diseases, including embryonic stem and mature cells.

The immunological privilege of MSCs isolated from Wharton's jelly

- WJ-MSCs are immune privileged, and thus are well suited for allogeneic transplantation.
- They express high levels of the immune inhibitors IDO and PGE2, and synthesize the G6 subtype of the HLA antigen, which is involved in protecting the fetus from the mother's immune system.
- WJ-MSCs also do not elicit an immune response when used in xenogeneic transplantations.

MSC differentiation & neuroprotective properties

- WJ-MSCs can differentiate into nerve cells when cultured *in vitro* and can potentially contribute to the regeneration of the nervous system.
- WJ-MSCs also secrete angiogenic and neurotrophic factors, which have been shown to increase the survival and proliferation of primary cortical and cerebellar neurons *in vitro*.

Preclinical studies demonstrating the beneficial effects of MSCs in ophthalmologic diseases

- In rat and mouse models of ophthalmic diseases, the administration of MSCs significantly reduced retinal degeneration, led to the regeneration of cone cells, resulted in improved vision, and improved the survival of retinal ganglion cells and axon regeneration.

The use of mesenchymal stem cells in clinical trials

- There are several clinical trials investigating the use of MSCs to treat ophthalmic diseases.
- The therapeutic effect of MSC therapy has not been confirmed in the studies published so far.
- The lack of success in clinical trials may be due to the low number of MSCs used and to the advanced stage of disease in the patients.

The risk of complications after MSC administration

- MSCs are very resistant against neoplastic transformation.
- In animal experiments, the subcutaneous implantation of MSCs did not result in tumor formation, even after several months of observation.
- Studies have shown that MSCs can reduce tumor cell proliferation potential.
- In a meta-analysis that included over 1000 patients, no significant correlations were found between MSC therapy and the toxicity of cell infusions, internal organ infection, deaths or cancer.

Conclusion

- The positive results of MSC therapy in animal models suggest that this treatment can also be beneficial in humans, although so far MSC treatment in humans has had little success.

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