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Ophthalmological Metabolic Diseases and Stem Cells

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ABSTRACT

Ocular pathologies are, without a doubt, one of the most complicated at the time of regulating medical therapy. Being one of the most relevant sense organs (if not the most important) the use of stem cells in the treatment of metabolic diseases that were previously considered to be slow-progressing, significant improvement can now be achieved.

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INTRODUCTION

Diabetic retinopathy (DR) has been considered for a long time as a microcirculatory retinal disease caused by the deleterious metabolic effects of hyperglycemia. Mesenchymal stem cells have the ability of cloning to form adherent fibroblastic cells that express the unique properties and abilities of the cell surface phenotype. Previous studies have demonstrated consistently the capacity of MSCs to differentiate into nervous system cells (NSCs) in vitro by the combination of reverse transcription-polymerase chain reaction (RT-PCR) and immunofluorescence studies. Lately, it has been demonstrated that NSCs originating from MSCs have a neuroprotective effect by increasing the number of surviving retinal ganglion cells and significantly reducing the progression of DR. These results aim that transplantation of NSCs could be a novel strategy for the treatment of neurodegeneration in DR. In future studies, it will be necessary to ensure the safety of this procedure in large animal models that closely mimic the human eye before performing them in humans. [1,2,3]

Stem Cell in Diabetic Neuropathy

Diabetic neuropathy is a loss of sensory function beginning distally in the lower extremities that is also characterized by pain and substantial morbidity and is one of the most prevalent complications among diabetic patients with chronic hyperglycemia. Microvascular factors, metabolic regulations, unregulated glucose level, increased glycated hemoglobin level, oxidative and nitrosative stress, and reduced blood flow rate (due to the accumulation of ROS) are some factors which are attributed to the incidence of Diabetic neuropathy. ROS and reactive nitrogen species reduce blood flow leading to microvascular ischemia, which finally disrupts the function of the nerve. Prolonged hyperglycemia also promotes the production of AGEs which after binding to RAGEs trigger an inflammatory response and enhance oxidative stress, leading to degeneration of Schwann cells. These cells not only insulate neurons but also regulate nerve regeneration, and any oxidation-mediated loss in their function promotes Diabetic neuropathy among diabetic patients. [3,4,5,6,7]

Hyperglycemia and dyslipidemia, together with altered insulin signalling, lead to several pathological alterations in neurons, glia and vascular cells that can lead to nerve dysfunction and ultimately, neuropathy, including DNA damage, endoplasmic reticulum stress, mitochondrial dysfunction, neurodegeneration and loss of neurotrophic signalling, and can trigger macrophage activation. The importance of these pathways in the development of neuropathy varies with cell type, disease profile and time, as distinct cell types are more or less susceptible to injury depending on the metabolic impairments; to develop an efficient therapy against Diabetic neuropathy, the treatment procedure should address the mediation of the advanced glycation end products (AGEs), because they disrupt the defense mechanism and assist the destruction of beta langerhans cells culminating in the insulin deficiency, reason

why stem cell therapy seems like a good option due its regenerative properties. For example: Mesenchymal stem cells release exosomes that transfer miRNAs and other bioactives molecules to endothelial cells promoting angiogenesis; has neurotrophic activity by the action of these factors: nerve growth factor, brain-derived neurotrophic factor, glial cell line-derived neurotrophic factor, vascular endothelial growth factor, insulin-like growth factor-1, neurotrophic factor 3 and neurotrophic factor 4; and they modulate immune responses via paracrine and cell–cell contact effects as well as through extracellular vesicles. [2,7,8,9,10,11]

Glaucoma and stem cells.

Glaucoma is a neuropathy of the optic nerve and one of the major causes of blindness in the world population. Although its aetiology is multifactorial and not yet fully understood, it is known that the visual impairment is a result of the damage to the retinal ganglion cells (RGCs). These are cells located in the innermost layers of the retina and their axons form optic nerves. [12]

Therapy of stem cells can definitely improve the effect of clinical treatment on glaucoma and visual acuity. But stem cells also face a number of peculiar problems about safety and efficiency. [13]

MSCs are able to suppress effector T cells in a juxtacrine manner (through the program death (PD) ligand: PD receptor interaction) or in a paracrine manner, via the production of soluble immunoregulatory factors (transforming growth factor-β (TGF-β), HGF, nitric oxide (NO), indoleamine 2,3-dioxygenase (IDO), interleukin 10 (IL-10), interleukin 1 receptor antagonist (IL-1Ra),[44,45] heme oxygenase- (HO-) 1, and prostaglandin E2 (PGE2)); these transplantation of MSCs and their secretomes efficiently attenuate glaucoma progression. Beneficial effects of MSCs in the glaucoma treat- ment mainly relied on their capacity for neurotrophin pro- duction, differentiation into functional RGCs, and crosstalk with retinal residential RSCs and TM cells. [15]

Therapeutic potential of DP-MSCs in glaucoma treatment. Dental pulp represents valuable and easily accessible sources for DP- MSCs which are able to differentiate into functional retinal ganglion cells (RGCs) under appropriate culture conditions (a). Intravitreally transplanted DP-MSCs produce several neurotrophic factors (platelet-derived growth factor (PDGF), nerve growth factor (NGF), brain- derived neurotrophic factor (BDNF), ciliary neurotrophic factor (CNTF) and glial cell line-derived neurotrophic factor (GDNF) which promote survival of RGCs and induce regeneration of injured axons. [16]

Nerve growth factor has demonstrated the enhancement expression of bcl-2 (An antiapoptotic protein) and attenuated expression of Bax (An proapoptotic protein); reducing palmitic acid-induced injury in retinal ganglion cells apoptosis. [17]

Brain derived neurotrophic factor binding to its receptors (tropomyosin receptor kinase B (TrkB) and the pan-neurotrophin (p75NTR) induces activation of c-jun and suppression of caspase-2, which prevents apoptosis and promotes survival of RGCs. [18]

Platelet-derived growth factor (PDGF) and ciliary neurotrophic factor (CNTF) reduce the apoptotic loss of RGCs by increasing phosphorylation and activation of STAT-3 which downregulated the expression of proapoptotic Bax and consequently reduced apoptotic loss of RGCs. [19]

Brain-derived neurotrophic factor (BDNF) increases the regeneration of the RGCs. TGF-Beta and the Hepatocyte Growth Factor (HGF) attenuates the inflamation. [20,21]

Cardio-vascular problems in ophthalmology and stem cells.

Stem cells for treatment of retinal vein occlusion.

Retinal vein occlusion is a disease characterized with hemorrhages, macular edema and finally retinal ischemia; which can be presented in two different anatomical sites; central retinal vein or branch retinal vein. In both, the clinic is decreased visual acuity, unilateral generally. [22]

Epidemiologically speaking it is more common between the sixth and seventh decade of life. And the risk increases with age, however, this pathology can affect young patients with some hypercoagulability disorder (thrombophilias, wegener's granulomatosis). The occlusion can be classified in turn, as ischemic or not. In the pathogenesis of this vascular disease we can find three theories: a) external compression of the vein, b) venous disease (vasculitis), or finally c) thrombosis. The most common risk factor is a diagnosis of systemic hypertension. Nowadays the most accepted diagnosis method is retinal angiography. [22]

Currently the treatment of this ophthalmological emergency, has been based on laser photocoagulation when it has not progressed to retinal neovascularization. [23,24]

Other treatment modalities that focus on avoiding progression of macular edema are intravitreal corticosteroid injection, or anti-VEGF (anti vascular endothelial growth factor therapy). [24,25]

The administration of intravitreal ranibizumab three monthly injections, presents improvement in visual acuity and macular edema (48% of patients in central retinal vein occlusion group and 69% in branch retinal vein occlusion). Vitreoretinal surgery reserves for advanced occlusive disease. [25]

The therapeutic value of different types of stem cells (multipotent mesenchymal, cardiac and pluripotent embryonic stem cells). Firstly the endothelial progenitor cells have been isolated using immunotypic surface proteins or by the mononuclear fraction of blood and in vitro culture. [26]

In the literary review it was found that the outgrowth of endothelial cells was the only type of stem cells who has potential reversing ischemic retinopathy. The haematopoietic stem cells show compromising results with the neovascularization in the ischaemic retina, specially the differentiated ones (CD34þ). Myeloid progenitors defined as CD44 with hyaluronic acid receptor cells became microglia. [27]

An important advance in the treatment of retinal vein occlusion is the combination of anti-VEGF with mesenchymal stromal cells (MSCs). In this study they used rabbit adipose tissue MSCs with encapsulated anti-VEGF. [25]
In the final results they found limited retinal detachment and edema retinal vascular attenuation compared with the group that only received balanced salt solution [56]. Compromising results expected in humans, not without first seeking the efficacy and safety of this treatment modality. [25]
In other studies it is compared the efficacy of early endothelial progenitor cells (eEPC) versus growing endothelial cells (OEC). The immunophenotype was also distinct, with only eEPCs expressing hematopoietic markers whereas OECs highly expressed endothelial markers. [26]
Besides, the OECs have higher proliferation potential and are more sensitive to angiogenic factors; and these cells can be identified as integrated 72 hours after intravitreal injection. [26,27]

Cytotherapy with stem cell in ischemic retinopathy shows promising results; the continuous study and assessment of the efficacy of this treatment modality is very relevant, especially due to the side effects of conventional treatments like cataract formation and ocular hypertension in young patients with intraocular applied steroids. [26,27]

Treatment of ophthalmological infectious diseases

Infectious ophthalmological problems have a wide range of etiological agents; among them parasites, viruses, bacteria and fungi. It is well known that broadly the solutions of these kind of unfortunate conditions require broad spectrum antibiotics, surgery, pharmacs or aggressive therapies that hopelessly results in tissular damage which decreases the eye functions occasionally ending in visual impairment and once in a while in blindness; also untimely treatment, or not treatment at all, can lead to the same resolutions. Furthermore conventional therapies are not enough, and based stem cells treatment could offer better outcomes due to the microbial clearance properties, modulation of tissue remodeling and the immunomodulatory effects of the stem cells.
Mesenchymal stem cells (MSCs) exhibit direct antimicrobial properties which are mediated by the secretion of antimicrobial peptide LL-3, hepcidin and beta-defensins. [28,29,30]

The LL-37 peptide is secreted by many types of cells, including neutrophils, macrophages, natural killer (NK) cells, epithelial cells of the skin, airways, eyes and intestinal tract. Also, the expression of the peptide LL-37 is controlled by inflammatory pathways. LL-37 binds and neutralizes bacterial lipopolysaccharide. Some highlights of this peptide are: a broad spectrum of antimicrobial activity, several immunomodulatory effects, anticancer activities, and also chemotactic and pro-angiogenic properties.[31,32,34]

Hepcidin antibacterial protein HAMP has indirect microbicidal properties; the major function of hepcidin is to suppress ferroportin-mediated export of iron affecting almost all microorganisms, cause generally they use iron to sustain their growth; therefore, restricting circulating levels of iron presents a significant host response to systemic infection. [33]

LL37 and beta-defensin-2 have an indirect antimicrobial effect competitively binding to CD14 or TLR4, thereby indirectly inhibiting LPS-induced reactions downstream.
Beta-defensins are effective against almost all bacterial pathogens and are induced in response to bacterial LPS, TNF-α and pro-inflammatory mediators (like interleukins [IL-1 β] and interferons). [34,35]

Stem cells for treatment of retinal diseases.

In recent years, there have been giant advances in therapy of ophthalmology diseases, specifically on those who affect retina. [36]

There are numerous advantages over using mesenchymal stem cells in the eye. Due to their size, the required amount of these cells is quite low, which is good considering their cost. The approach is surgical and it is very simple both to carry out the procedure and to monitor the transplanted cells by means of well-known imaging methods. Therapy is usually one-sided because the opposite eye is used for control. In addition, the immunological privilege of the eye makes immunosuppression unnecessary in these patients. [37]
In experimental studies on degenerated retinas, stem cells have had positive effects such as: creating new intercellular connections, promoting cell regeneration and improving visual function, to name a few. Due to the potential of these cells to differentiate into retinal neural cells and photoreceptors, they can make the repair process possible. Experimental studies have shown that stem cells are highly compatible with retinas and can adapt to different types of cells of the retina, for example: Müller, amacrine, bipolar, horizontal and glial cells and to photoreceptors. [37]
The results obtained with stem cell transplants have been satisfactory, in order to determine this, improvements were observed in the function of the photoreceptors and a greater visual performance. [37]

In other studies, improvements in visual function and visual field were observed after the use of RPE cells derived from human ESC in rats, however more evidence should be gathered on their long-term effectiveness. [37]

The use of hESCs in degenerative retinal pathologies have had satisfactory results. [38]

Although it takes time for these cells to mature, differentiate and be able to act at the level of the retina to be able to reverse the histological changes, significant and very encouraging changes have been observed regarding the use of these cells, such as the disappearance of edema. and hemorrhage in the area of the fovea centralis. [39]

However, it should be taken into account that immunosuppression therapy is necessary in the implantation of these cells. [39]

The hiPSCs were used in order to form RPE cells. The hiPSCs showed their typical potential by means of traditional pluripotent stem cell markers known as OCT4 and SOX2. [40] Using different growth and maturation factors, the cells were led to the differentiation of the hiPSCs. By means of different methods (such as culturing 3D spheroids) it helped to maintain the properties and functions of hiPSC-RPE. [40]

Different in vitro studies showed that hiPSC-RPE cells had the ability to avoid apoptosis of retinal cells and decreased the loss of photoreceptors. Studies suggest that transplantation of hiPSC-RPE cells is a highly viable therapeutic strategy to preserve the structural and functional characteristics of the photoreceptors and the integrity of the retina. [40]

The same transplant but applied subretinal is a therapy for retinal degeneration, however, this must be tested to assess the true long-term effects. [40]

Stem cells for treatment of optic nerve disease/neural regeneration

Loss of visual function can occur due to different affectations of the optic nerve. There are various ways in which the optic nerve can give rise to various pathologies (intraorbital, intracranial, intrinsic or systemic disorders). [41]

The potential of human embryonic stem cells (hESC) in transplantation therapies is well known. These cells are widely used in retinal repair but have also started to be used in optic nerve diseases. [42]

Some studies found improvement in acuity and peripheral vision, but changes in the optic nerve head were not associated with vision improvements. [43]

It is thought that this result may be related to an increase in mitochondrial function and may be related to incorporation of cells developed in the ganglion cell layers and the optic nerve. [43]

Recent research suggests that vascular conditions of the optic nerve and retina could benefit from intravitreal RPCs obtained from hiPSCs. [44]

IPSC-derived PNs are also believed to provide a type of neuroprotective support as mentioned above. Various mechanisms helped the authors attribute the benefit to the optic nerve to the secretion of neurotrophic factors, which in turn is supported by the in vitro release of CNTF, FGF2, and IGF-1 by iPSC-derived PNs. [45]

The use of mesenchymal stem cells (MSCs) has great potential in the treatment of optic nerve injuries. Because they are self-renewing cells that with the right conditions can differentiate into any tissue through signaling. [46]

They have been shown to have a predilection for tissues originating from the mesoderm. MSCs are immunomodulatory, anti-inflammatory and with the ability to restore neurological disorder, facilitating improved function of the organ in question. and they also exhibit neurogenic potential. [47]

Although different cell sources have been tried for this purpose MSCs are probably one of the most viable options. These cells have been shown to have a neuroprotective effect which is associated with platelet-derived growth factor, NGF, BDNF, neurotrophin secretion - as well as the role of inflammation in optic nerve regeneration. [45]

It is important to mention that MSCs are immunoprivileged cells, and they do not cause rejection. It has been proposed that cryopreservation may be the key to better bioavailability of these cells. [46]

The use of rMSC after optic nerve injury promoted sustained neuroprotection of RGC. The lack of recovery of visual behavior in some patients indicates that the RGC require a greater amount of stimuli to establish stable reconnections and that the recovery of visual function is greater. [47]

Cell replacement therapy has made tremendous progress over the years. Although RGC needs to be differentiated, this is only the first step. [48]

The adaptation process has been described as follows: to integrate with the presynaptic amacrine and bipolar cells in the retina (to integrate the visual reflex), the axons must grow through the damaged or diseased optic nerve and connect properly with the appropriate targets -in the geniculate nucleus and other regions of the brain. But this process needs to be described in more detail. [48]

Stem cells and disease characterization and 3d printing

The ability to reprogram human somatic cells to induce pluripotent stem cells (iPSC) offers an excellent opportunity to generate human disease models with primary cells. Reprogramming somatic cells into induced pluripotent stem cells (iPSCs) is achieved by transduction using a defined set of transcription factors: Oct4 (Pou5f1), Sox2, Klf4, and c-Myc (OSKM) in mice humans. [49,50]

In general, reliable disease models helps in obtaining better understanding of disease mechanisms, and in particular leds to the development of new therapeutic interventions and personalized treatments for a specific case, as it allows us to observe the progress of the disease in a specific biological model, which give us the possibility of testing a therapy specially designed for a patient. [51,52]

Up-to-date, the majority of our knowledge about disease states comes from in vivo animal models, nevertheless this involves various ethical problems and despite the similarities with other mammals, the human being has important differences that should be considered when generating diagnostic methods, new treatments or novel interventions. [50,52]

The gap between cell line studies and in vivo modeling has been narrowing thanks to progress in biomaterials and stem cell research, however, it has been exceedingly difficult to model disease at the tissue level. In fact, the development of reliable 3D culture systems has enabled a rapid expansion of sophisticated in vitro models. Here we focus on some of the latest advances and future perspectives in 3D organoids for human disease modeling. [51]

Human induced pluripotent stem cell derived organoid culture has been shown superior in mirroring functionality, architecture, and geometric features of tissues seen in vivo. Is important to highlight recent advances in the 3D organoid technology for use in modeling complex hereditary diseases, cancer, host-microbe interactions, and possible use in translational and personalized medicine where organoid cultures were used to uncover diagnostic biomarkers for early disease detection via high throughput pharmaceutical screening. Human induced pluripotent stem cell derived organoid culture may better illustrate the processes involved due to similarities in the architecture and microenvironment present in an organoid, which also allows drug responses to be properly recapitulated in vitro. [52]

The potential applications of 3D printing in ophthalmology are extensive. 3D printing enables cost-effective design and production of instruments that aid in early detection of common ocular conditions, diagnostic and therapeutic devices built specifically for individual patients, 3D-printed contact lenses and intraocular implants, models that assist in surgery planning and improve patient and medical staff education, and more. Advances in bioprinting appears to be the future of 3D printing in healthcare in general, and in ophthalmology in particular, with the emerging possibility of printing viable tissues and ultimately the creation of a functioning cornea, and later retina. It is expected that the various applications of 3D printing in ophthalmology will become part of mainstream medicine. [53]

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