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The Catcher in the Eye: Stem Cells as a Therapeutic for Glaucoma

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Modern management of glaucoma involves a wide arsenal of tools, most of which are designed to lower the intraocular pressure (IOP) of the eye. After all, elevated IOP is the only modifiable risk factor for glaucoma. However, lowering eye pressure does not directly reverse retinal ganglion cell (RGC) degeneration nor typically restore vision. Consequently, there has been growing momentum to identify cell-based therapies to ultimately treat and reverse neuronal degeneration. There certainly has been considerable work done to understand retinal pigment epithelium and photoreceptor replacement for age-related macular degeneration,[1] and many of the lessons learned regarding safety and the development of large-scale good manufacturing practices can be applied for cell-based therapies for glaucoma. While there are several targets under development for cell-based therapies such as sustained release of ciliary neurotrophic factor (CNTF; ClinicalTrials.gov NCT01408472, NCT02862938, and NCT04577300),[2] here we aim to focus on stem cell-based strategies involving trabecular meshwork (TM) replacement, RGC rejuvenation, and RGC replacement. Our goal is to discuss several recent strategies using stem cells as a therapeutic for glaucoma and the potential clinical implications of basic research. Moreover, we examine the effect of predatory “stem cell clinics” that promise vision restoration using approaches with limited scientific validity, and we discuss how ophthalmologists play an important role in protecting our patients.

A major hallmark of primary open angle glaucoma (POAG) is trabecular meshwork dysfunction, where aqueous humor outflow is disrupted resulting in elevated IOP. While topical medications lower aqueous production or improve outflow, these do not directly restore TM function to a healthy state. Trabecular meshwork dysfunction in POAG may be in part due to decreased cellularity of the TM beams.[3] Therefore, a strategy that repopulates the drainage angle with functioning TM cells may be fruitful approach. Using mouse models and human donor ex vivo cultures, several recent studies showed that TM stem cells home to the angle and restore function to lower IOP,[4–8] with several studies demonstrating decreased RGC death.[4,5] Interestingly, in one study, the mice treated with transplanted TM cells retained organized organelle structures and did not demonstrate fusion of adjacent trabecular beams or shrinkage of the intertrabecular space compared to mice treated with saline alone, suggesting the TM transplanted cells may maintain and restore TM structure.[7] There still remains considerable research before translation into human eyes, such

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as optimizing induction conditions, cell number and concentration, route of transplantation, and cell integration and proliferation.[9]

There has also been significant research done to identify ways, using a gene agnostic approach, to promote RGC rejuvenation. One strategy utilized the Yamanaka transcription factors (*Oct4*, *Sox2*, *Klf4*, and c-*Myc*), which are factors used to reprogram adult differentiated cells into "youthful" pluripotent stem cells. In one study, investigators used an intravitreal injection of adeno-associated viral vectors that expressed the Yamanaka factors *Oct4*, *Sox2*, and *Klf4* (OSK) in mice before undergoing optic nerve crush injury. This group did not include the fourth Yamanaka factor, *c-Myc*, which is oncogenic, but the expression of OSK promoted a "youthful" mRNA profile without loss of cellular identity or induction of teratogenicity or pluripotency. In essence, this strategy resets the epigenome and the DNA methylation age, thus permitting neuronal regeneration. This study showed that expression of the OSK factors could induce axonal regeneration in mice.[10] The mice also demonstrated improved visual acuity—as measured via an optomotor response assay and a pattern electroretinography (PERG) response—similar to mice without optic nerve damage suggesting possible restoration of electrophysiological function, although the strategy did not rescue RGC death.[10] With such candidates, there is cautious optimism for RGC rejuvenation, but much work is needed to demonstrate translatability of these models to humans as well as replication of these findings in other models of glaucoma and ageing-related vision loss.[11] Additional work is also needed to understand the safety and potential side effects of deleterious gain- or loss-of-function mutations or off-target effects with this strategy.

Finally, a stem cell strategy that targets RGC replacement may bring us closer to the holy grail of vision restoration in glaucoma. Currently, there is evidence for several stem cell candidates such as human embryonic stem cells (hESCs) and induced pluripotent stem cells (iPSCs), the latter of which could be beneficial because they do not require immunosuppression if the cells are autologous.[12,13] Mesenchymal stem cell (MSC) transplantation has also shown promise as these secrete neuroprotective factors such as brain-derived neurotrophic factor (BDNF) and CNTF,[14] and human Müller stem cells (hMSC) can differentiate into RGCs in the presence of fibroblast growth factor 2 and NOTCH inhibition.[15] Nevertheless, one major barrier for RGC replacement is ensuring that the cells have the necessary survival and growth factors to allow for correct axonal growth out of the eye and to appropriate visual targets in the brain.[16] Furthermore, we must ensure that the transplanted RGCs form synapses with the appropriate partners within the diseased adult retina and visual targets in the brain, as various subtypes of RGCs encode different information.[17] Early work in mouse models have demonstrated that RGCs may be able to seed correctly and have their axons grow toward the optic nerve,[18] and enzyme digestion of the inner limiting membrane may facilitate RGC integration in an *ex vivo* model.[19] There are also major initiatives to understand and overcome these barriers to ultimately translate these findings for humans, such as the National Eye Institute (NEI)-funded Audacious Goals Initiative to pursue vision restoration through regeneration of RGCs and photoreceptors.[20]

As stem cell treatments continue to develop and gain more visibility in the public eye, it is imperative that as treating ophthalmologists, we understand our roles in educating

patients regarding what are safe, evidence-based trials. A recent case series reported that several patients had major vision loss including blindness after undergoing bilateral intravitreal injections of autologous stem cells for age-related macular degeneration.[21] Two of these patients found the stem cell clinic after seeing a listing on ClinicalTrials.gov and believed they were participating in a rigorous clinical trial. While this website is a very important repository, it can give patients a false sense of security. ClinicalTrials.gov does not distinguish for-profit versus not-for-profit trials, and a listing on the website does not indicate US Food and Drug Administration approval. Our role as ophthalmologists is to help our patients discern the scientific validity, preclinical data, and rigorous trial design underlying a stem cell clinical trial. We play a critical role in educating patients to protect them from experiencing vision loss and financial hardship through ill-advised participation in poorly designed clinical trials with limited-to-no scientific basis.

This is without a doubt an exhilarating time to be an ophthalmologist who cares for patients with glaucoma. We stand at the cusp of a wave of new technology—not only cell-based therapies but also technologies such as gene therapy and neuroprotective and/or neuroenhancement strategies—that may stop the progression of glaucoma and even restore vision loss. Nevertheless, even with great optimism that such therapies will reach the patient, we must remain cautious and ensure that patients are well-informed and only participate in safe, well-designed clinical studies. In other words, we are our patients' best advocates, and we must be their "catchers in the rye" to preserve their sight and avoid the proverbial cliff that is vision loss.

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