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Editorial

Gene therapy for glaucoma: A paradigm shift in treatment

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Since time immemorial one of the leading causes of irreversible blindness, has been Glaucoma. Glaucoma is rightly said to be the silent killer of sight as it has affected more than 70 million people globally. Glaucoma characteristically is progressive optic neuropathy, with degeneration of retinal Ganglion cells resulting in contraction of visual field and subsequently leading to irreversible blindness.[1,2] Glaucoma has innumerable risk factors out of which the only modifiable risk factor is Intra Ocular Pressure, and surprisingly all the current therapies focus on only reducing the Intra ocular pressure thereby slowing down the progression of the disease only. There is at present no treatment that can directly target the mechanism of optic nerve damage.

In recent years, Gene therapy has emerged as a very promising avenue for treating the root cause of Glaucoma. It has the potential to halt the progression of the disease by taking into account its genetic and molecular roots.

1. Current Glaucoma Therapies

Glaucoma is not a single disease entity rather a spectrum of eye diseases that causes irreversible damage to the Optic nerve and retinal Ganglion cells, resulting in loss of visual field.[3] Certain forms of Glaucoma like POAG (Primary Open Angle Glaucoma) and PACG (Primary Angle Closure Glaucoma) are characterized by increase in the IOP, while Normal Tension Glaucoma occurs even in the absence of elevated IOP. Regardless of the types, progressive loss of RGCs (Retinal Ganglion Cells) lead to characteristic loss of visual field.

Current therapies, including Anti- Glaucoma Medications, Laser Therapies and Surgical Interventions, all aim at lowering the IOP thereby slowing the progression of disease. Medications like PG analogues (Prostaglandin analogues), Beta blockers, Carbonic anhydrase inhibitors, Rho kinase inhibitors, Alpha agonists etc can reduce the IOP but have side effects and patient compliance issues.[3] Surgical options like Trabeculectomy and Minimally Invasive Glaucoma Surgery (MIGS) are quite effective but have their own set of complications.[4] Therefore, there is an urgent need for treatment to be aimed at basic pathophysiology of Glaucoma in Genetic and Molecular level for better outcomes.

2. Gene Therapy

Gene Therapy will be offering a metamorphic approach to treat Glaucoma. It works by targeting specific genes and their molecular mechanisms responsible for disease progression. It is mainly based on concepts of Introducing, Modifying and/or Silencing the genes within the patient's cells so as to correct the genetic defects and alter the disease pathways. Initial success has been seen in cases of

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Leber's Congenital Amaurosis,[5] which gives us the hope for Glaucoma management via gene therapy.

3. Mechanisms of Gene Therapy in Glaucoma

There are primarily three approaches in Gene Therapy – Lowering IOP, Protecting RGCs, and promoting Optic nerve regeneration.

1. Lowering intra ocular pressure- The most basic approach in treating Glaucoma is by increasing the Aqueous humor outflow, thereby lowering IOP. Recently Researchers have identified that, by using Adeno- associated virus (AAV) vectors to deliver therapeutic genes to the Trabecular Meshwork, has resulted in increased outflow of aqueous humor and sustained IOP reduction in animal models.[5] Even delivery of Rho kinase (ROCK) gene has been shown to relax the TM and improve outflow facility, offering a novel method to reduce IOP.[6]
2. Neuroprotection of RGCs- The very basic pathophysiology of Glaucoma lies in the fact that the vision loss is due to degeneration of Retinal Ganglion Cells, therefore, protecting these cells is critical.[6] In Gene therapy, main aim is to deliver genes encoding neurotrophic factors that support the survival and function of RGCs. Two such Neurotrophic factors i.e. BDNF (Brain Derived Neurotrophic factor) and CNTF (Ciliary Neurotrophic Factor) have shown promising results in animal models of glaucoma.[7,8] In these models, AAV (Adeno-associated Virus) mediated delivery of BDNF and CNTF has helped in preserving RGCs thereby, halting the disease progression.[9]
3. Optic Nerve Regeneration- A very common saying in OPD to patient with advance Glaucoma with Glaucomatous Optic atrophy goes this way, "Sorry, your Optic nerve has been dried up in Glaucoma. Whatever vision is lost in glaucoma, won't get recovered". But in recent studies of Gene Therapy, options for regeneration of the Optic nerve are being explored in order to restore vision. These therapies focus on stimulating the intrinsic growth capacity of RGCs and promoting axon regeneration. For example, in experimental glaucoma models, overexpression of the Transcription factor SOX 11 has been shown to further improve the axon regeneration thereby, enhancing the visual functions.[10] In very similar pattern, targeting the Phosphatase and Tensin homolog (PTEN) pathway, which is associated with inhibition of axon regeneration, has shown promising results in enabling RGCs to regrow damaged axons.[11]

Success of gene therapy lies on the founding stones of Identification of key genetic targets implicated in Pathogenesis of the disease. Several such genes have been studied by researchers in this context.

1. MYOC (Myocilin)- It has been found that mutations in the MYOC gene are mainly associated with Autosomal Dominant POAG, leading to accumulation of misfolded Myocilin protein in the Trabecular Meshwork. This reduces the aqueous humor outflow, thereby elevating intraocular pressure. Use of RNAi (RNA interference) for silencing MYOC gene has shown to have effectively reduced IOP in animal models[11]. AAV vectors have been used to deliver short hairpin RNAs (shRNAs) that target and silence mutant MYOC, providing sustained IOP reduction.[12]
2. OPTN (Optineurin)- Optineurin has been linked with role of Autophagy and Inflammation in cellular processes. It has been seen to be associated with Normal Tension Glaucoma (NTG), where the RGCs death occur even with normal IOP. Gene therapy aimed at correcting OPTN mutations or modulating its activity could provide a therapeutic approach for NTG patients.[13]
3. WNT Signaling Pathway- Dysregulation of the WNT signalling pathway has been associated with Glaucoma. Gene Therapy strategies that can activate WNT signalling pathway, could represent novel approach for reducing IOP since enhancing WNT signalling in Trabecular Meshwork have shown to improve aqueous humor outflow.[14]
4. S1P (Sphingosine-1-Phosphate)- Another key pathway involved in regulation of aqueous humor outflow is S1P signalling pathway. One potential gene therapy target has been studied, by inhibition of S1P signalling, there is marked reduction of IOP by increasing aqueous humor outflow in experimental models.[15]
5. Other key genes related to Glaucoma- WDR36, CYP1B1, PITX2, FOXC1, PAX6, LTBP2, LOXL1, NTF4.

4. Viral Vectors and Delivery Systems

Gene Therapy is presently at its baby steps. The most challenging aspect of gene therapy is the efficient and safe delivery of the therapeutic genes in to the target cells. And for this noble job, viral vectors have been used effectively. Particularly the Adeno-associated viruses have been the most efficient delivery vehicles. It is mainly due to their ability to transduce a variety of cell types with minimal immune responses. Moreover, AAV vectors have been particularly suitable for ophthalmic applications due to their propensity to provide long lasting expression of therapeutic genes with favourable safety profile.[16,17]

Various studies on preclinical models have shown that AAV- mediated gene delivery has resulted in sustained IOP

reduction and neuroprotection.[18] Other viral vectors, like Lentiviruses and adenoviruses, have also been investigated. But they have been shown to have high risk of inflammatory response as well as high immunogenicity.

Apart from viral vectors, non-viral delivery systems have also been explored, which includes nano-particles, liposomes, and polymer-based delivery platforms. These vectors have the advantage of minimal immunogenicity and capability of repeated administrations. Yet, their efficiency in delivering genes to target ocular tissues remains low in comparison to viral vectors, and further research is awaited in this direction for better glaucoma therapy.

5. Clinical Trials and Future Directions

It is quite evident that Gene Therapy for Glaucoma is still in the experimental stage. Yet several preclinical studies have yielded promising results. The clinical trials are expected in near future soon. The key areas that the researchers are working are – Optimisation of gene delivery method, identification of new therapeutic targets, and ensuring long term safety profile.

One of the most promising developments is the potential use of CRISPR-Cas9 gene editing technology to correct mutations associated with glaucoma. CRISPR-Cas 9 allows for precise editing of the genome, offering the possibility of directly correcting mutations in genes such as MYOC or OPTN. This technology could provide a one-time cure for inherited forms of glaucoma, significantly reducing the burden of disease.[19]

At present, there are two approved ocular human gene therapy products available, Macugen^{TM} and Luxturna^{TM}. And the most striking part of the story is that Macugen^{TM} is one of the first approved gene therapy products and the first anti-angiogenic agent approved by the FDA.

As gene therapy technology continues to advance, the possibility of combining gene therapy with other emerging treatments, such as stem cell therapy and regenerative medicine, may further enhance outcomes for glaucoma patients. These combined approaches could provide a multifaceted strategy to not only halt the progression of glaucoma but also restore lost vision in advanced cases.

6. Challenges and Ethical Considerations

Gene therapy is presently is like the red beautiful rose, attractive but has thorns. It is presently having several challenges, like the delivery system. Ensuring that the therapeutic genes reach the target cells in sufficient quantities is very essential for successful management of glaucoma. Long term safety of the gene therapy has to be scrutinized closely as the introduction of foreign genetic material can cause harsh immune reactions, off target effects and most importantly tumorigenesis.

Ethical considerations are also important, particularly regarding access to gene therapy treatments. Affordability becomes the biggest issue in low- and middle- income countries where Glaucoma is prevalent, since developing and administering gene therapy is pretty costly in present day scenario. Moreover, the irreversible nature of gene therapy interventions needs careful scrutiny and consideration of patient consent, particularly in cases of inherited forms of glaucoma.

7. Conclusion

Gene therapy holds great promise for revolutionizing the treatment of glaucoma by addressing the underlying genetic and molecular mechanisms of the disease. By targeting specific genes involved in IOP regulation, neuroprotection, and optic nerve regeneration, gene therapy offers the potential to modify disease progression and preserve vision. While challenges remain, ongoing research and technological advancements in gene delivery systems and gene editing technologies like CRISPR-Cas9 suggest that in near future Glaucoma would be readily be managed by gene therapy. If this becomes a success, then it can transform millions of lives by offering a ray of hope, when Glaucoma won't be called as irreversible cause of blindness, rather just another cause of reversible blindness like Cataract or Refractive error.

8. Conflict of Interest

None.

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