Epigenetic Implications in Glaucoma Neurodegenerative Disease

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Glaucoma, a complex and multifactorial neurodegenerative disorder, is a leading cause of irreversible blindness worldwide. Despite significant advancements in the understanding of its pathogenesis and management, early diagnosis and effective treatment of glaucoma remain major clinical challenges. Epigenetic modifications, encompassing deoxyribonucleic acid (DNA) methylation, histone modifications, and non-coding RNAs, have emerged as critical regulators of gene expression and cellular processes.

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1. Introduction

Glaucoma is one of the leading causes of irreversible blindness worldwide; it is a neurodegenerative disease characterized by progressive retinal ganglion cells (RGCs) loss and optic nerve neuroretinal rim degeneration that can lead to severe visual field loss [1]. The global prevalence of glaucoma is 3.54%, with the highest prevalence in Africa. The number of people affected by glaucoma worldwide (aged 40–80 years) will be 111.8 million in 2040 [2]. There are several risk factors for glaucoma onset. Among these are increased intraocular pressure (IOP), family history of glaucoma, genetics, age, gender, race (non-white ethnicity), environmental influences, myopia, pseudoexfoliation, disc hemorrhages, vasospasm, systemic hypotension/hypertension, corticosteroid use and smoking [3][4][5]. Currently, the pathogenesis is not fully clear (i.e., mechanical/ischemic insult, oxidative stress, neuroinflammation, etc.) [6].

Despite this multiplicity of risk factors, IOP is the only one on which therapeutic action is possible nowadays. In order to lower IOP, medications, laser therapy, or surgery can be employed. However, several studies highlighted that even glaucomatous patients with IOP within the normal limits will progress in losing RGCs. In addition, novel approaches promoting neuroprotection are now emerging [7][8]. Moreover, among the risk factors, in addition to IOP, those that play a key role in the development of glaucoma are genetics and environmental influences [9]. In that regard, there is an emerging area of scientific research, called epigenetics, that shows how environmental influences affect gene expression. Epigenetics should be recognized as an important element of glaucoma pathogenesis and development [10][11]. Epigenetics, in addition to genetics and environmental factors, influences the signaling pathways that are responsible for disease progression [10][11].

In recent years, in fact, there has been an increase in studies on the role of epigenetics in glaucoma that is now considered as an important causal factor in glaucoma. It is known that 16–20% of the risk of primary open-angle glaucoma (POAG) is imputable to genetic factors, and first- and second-degree relatives of affected patients are both at risk [12][13]. The genes involved in the pathogenesis of early-onset glaucoma are OPTN, MYOC, CYP1BI, PAX6, PITX2 and FOXC1; however, mutations in these Mendelian genes account for ≤10% glaucoma cases worldwide. Environmental factors that affect IOP include physical activity, ω-3 and ω-6 fat intake, yoga, and lifting weights [10].

Epigenetics can influence the regulation of gene expression with different mechanisms; the three most known and studied ways through which it acts are DNA methylation, histone modification and micro-ribonucleic acids (also called miRNAs). A better understanding of the mechanisms of glaucoma development may provide a therapeutic strategy that is truly effective in blocking or reverting the progression of the disease.

2. Epigenetic Implications in Glaucoma Neurodegenerative Disease

Glaucoma is characterized by a progressive loss of retinal germ cells (RGCs) and their axons, which frequently occurs in tandem with elevated intraocular pressure. Evidence from studies conducted on mice, using saline injections as non-glaucomatous controls, unilaterally induced increased intraocular pressure for 21 days by injecting microbeads into the anterior chamber of the eye [14]. Dual adeno-associated viruses (AAVs) were injected intravitreally along with Sox2 and Klf4 genes (OSK) in mouse retinal ganglion cells to restore youthful DNA methylation patterns, and transcriptome expression was induced for an additional 4 weeks, followed by a notable decrease in axonal density and the number of RGCs at the 4-week time point. When compared to glaucomatous eyes that were given AAVs without any OSK induction (−OSK), the glaucomatous eyes that received OSK treatment (+OSK) displayed an axon density that was comparable to the non-glaucomatous eyes [14][15].

The concept of “reprogramming” epigenetic information to regenerate tissues or bodily functions represents an innovative frontier, promising to revolutionize the treatment of many ailments, including vision loss. The idea of restoring genetic information to regenerate visual function could pave the way for more effective and less invasive treatments than those currently available. The complex dynamics of epigenetics must be addressed, to understand how epigenetic information is acquired, modified, and transmitted during the cellular reprogramming process. Additionally, ensuring that epigenetic reprogramming is safe and free from risks is necessary, avoiding potential unwanted side effects or complications [16][17][18][19][20].

Another significant challenge concerns the long-term effectiveness of treatments based on epigenetic reprogramming. It is crucial to understand whether the induced epigenetic changes can persist over time and whether vision restoration can be long-lasting or require long-term supportive therapies [21].

Glaucoma epigenetics research has yielded significant insights into the molecular mechanisms underlying the disease, offering novel perspectives on its pathogenesis and potential therapeutic targets. Understanding the

results of such research in the context of previous studies and working hypotheses provides a comprehensive view of glaucoma etiology and progression [22].

Firstly, the identification of epigenetic modifications, including changes in DNA methylation, histone modifications, and non-coding RNA expression, has enhanced the understanding of glaucoma pathophysiology. These alterations, observed in various ocular tissues and bodily fluids of glaucoma patients, suggest a widespread dysregulation of gene expression networks, contributing to disease onset and progression [23].

From the perspective of previous studies, the findings of glaucoma epigenetics research underscore the multifactorial nature of the disease. Previous investigations have primarily focused on genetic factors and intraocular pressure as key determinants of glaucoma. However, epigenetic modifications provide additional layers of regulation that intersect with genetic predisposition and environmental factors, shaping the complex landscape of glaucomatous neurodegeneration [24].

Moreover, the implications of these findings extend beyond glaucoma to other neurodegenerative disorders. Epigenetic dysregulation is increasingly recognized as a common feature underlying various neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, and multiple sclerosis. Shared epigenetic signatures across these conditions highlight potential common pathways and therapeutic targets that warrant further exploration [25][26].

In the broadest context, glaucoma epigenetics research highlights the interconnectedness of molecular pathways underlying ocular health and disease. It underscores the importance of considering epigenetic factors in the development of personalized medicine approaches for glaucoma management. By targeting specific epigenetic modifications, it may be possible to modulate gene expression patterns and mitigate neuronal damage, paving the way for more effective therapeutic interventions [26].

The compelling investigation conducted by Pan et al. [27] delineates a genetic etiology underlying normal-tension glaucoma (NTG) and delineates the role of a mutated histone methyltransferase in NTG [28][29][30]. The researchers identified a Japanese family spanning three generations afflicted with NTG and harboring a splicing mutation within the methyltransferase-like 23 (METTL23) gene, responsible for encoding a histone arginine methyltransferase. The autosomal dominant inheritance pattern associated with the METTL23 c.A83G mutation was evident in all six affected family members. This mutation led to aberrant splicing of METTL23 mRNA. Haploinsufficiency of the gene resulted in reduced protein levels and abnormal subcellular localization. Mechanistically, METTL23 catalyzed the methylation of H3R17 in the retina. The estrogen receptor pS2 was identified as a downstream target of this methylation activity, exerting negative regulation on NF-κB signaling [31][32][33][34].

Using a variety of methodologies, including Mettl23-knock-in and -knockout mice, as well as induced pluripotent stem cells (iPSCs) derived from patients with normal-tension glaucoma (NTG), the researchers demonstrated the crucial role of METTL23 in the survival of retinal ganglion cell (RGC) soma and the protection of the optic nerve. Nevertheless, it is plausible that additional factors may influence the phenotype associated with METTL23

heterozygosity [35]. For instance, a METTL23 c.84+60delAT variant, which promotes exon 2 skipping, was more prevalent in NTG patients; however, it was also detected in controls (1.4% of NTG patients and 0.6% of controls), suggesting that METTL23 splice variants may exhibit variable pathogenicity [35][36].

Epigenetics encompasses alterations in gene expression or cellular phenotype without modifying the DNA sequence, influenced by factors like environment, lifestyle, and aging. Various factors may contribute to the association of cataract, which involves lens clouding due to protein aggregation, and glaucoma, characterized by optic nerve damage. Cataracts and glaucoma correlate with oxidative stress, inducing epigenetic changes like DNA methylation and histone modifications, as well as with chronic inflammation, aging, genetic predisposition, and environmental factor links to both conditions, altering epigenetic regulation and gene expression.

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