Alternate Causes for Pathogenesis of Exfoliation Glaucoma

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Exfoliation glaucoma (XFG) is the most recognizable form of secondary open-angle glaucoma associated with a high risk of blindness. This disease is characterized by white flaky granular deposits in the anterior chamber that leads to the elevation of intraocular pressure (IOP) and subsequent glaucomatous optic nerve damage. Conventionally, XFG is known to respond poorly to medical therapy, and surgical intervention is the only management option in most cases.

Keywords: exfoliation ; miRNA ; autophagy ; mitochondrial dysfunction ; blood–aqueous barrier

1. Potential Role of miRNAs in Exfoliation Glaucoma (XFG)

MicroRNAs are small, noncoding RNAs, 21–25 nucleotides in length, that regulate gene expression by binding to the 3′-untranslated region (UTR) of specific messenger RNAs (mRNAs) for degradation or translational repression [1][2][3][4][5]. The expression of miRNAs is often typical for a particular tissue or during essential cellular processes [1][2][3][4][5][6]. A single miRNA can modulate the expression of multiple mRNAs that regulate various physiological processes such as hematopoiesis, proliferation, tissue differentiation, cell-type identity maintenance, apoptosis, signal transduction, and organ development by regulating the expression of various genes [6][7][8][9]. They may exist in a stable state within cells or outside cells in biological fluids, including plasma and aqueous humor (AH), vitreous humor, serum, saliva, urine, and tears, and can exist as exosomes or be bound to carrier proteins [10][11]. Previous studies have reported that the expression of miRNAs can be involved in senescence or age-related neurological disorders, diabetes, degenerative arthritis, carcinomas, and cataracts [6][11][12][13][14][15][16][17][18][19][20][21][22][23][24][25][26][27]. In glaucoma, miRNAs can regulate extracellular matrix (ECM) metabolism by regulating TGF-β and can regulate stiffness by the accelerated maturation of ECM proteins, altering the trabecular meshwork (TM) contractile properties, thus accelerating or inhibiting TM cell senescence, or by modulating oxidative- and mechanical-stress-induced damage [10][12][28] in the cell/tissue. Alterations in the miRNA levels may indicate pathogenic processes underlying disease or a stage transition of the specific disease. Thus, miRNAs serve as valuable noninvasive biomarkers for various diseases and help to prognosticate the severity of diseases that are caused by the modulation of the specific processes that they regulate [5][17].

The role of miRNAs in glaucoma remains unclear, with several studies reporting miRNAs specifically expressed in the AH or serum in eyes with glaucoma [5][11][13][29][30]. Drewry et al. found three miRNAs (**miR-125b-5p**, **miR-302d-3p**, and **miR-451a**) and five miRNAs (**miR-122-5p**, **miR-3144-3p**, **miR-320a**, **miR-320e**, and **miR-630**) to be significantly differentially expressed in the AH of primary open-angle glaucoma (POAG) and XFG eyes, respectively, compared to controls [31]. Pathway analysis revealed that these miRNAs are involved in potential glaucoma pathways including tight junctions and TGF-β signaling, all of which are known in XFS pathogenesis. Another study, however, found no difference in miRNA expression between the different kinds of primary glaucoma, though **hsa-miR-6722-3p**, **hsa-miR-184**, and **hsa-miR-1260b** were more frequently found in XFG and POAG, respectively [32]. Another study identified higher levels of expression of 20 miRNAs in XFG and POAG patients than in controls, with 6 out of the 20 miRNAs (**miR-637**, **miR-99b-3p**, **miR-4725-3p**, **miR-4724-5p**, **miR-4358**, and **miR-433-3p**) elevated in both plasma and AH [33]. It was found that 12 out of 84 miRNAs to be upregulated in XFG. Out of these 12, 3 miRNAs (**hsa-miR-122-5p**, **hsa-miR-124-3p**, and **hsa-miR-424-5p**) were involved in pathways, namely, TGF-β1, fibrosis/ECM, and proteoglycan metabolism with common effectors such as SMAD3/2 [34]. Phenotype comparisons with fibrosis-related miRNA gave similar results, with **hsa-miR-19a-3p** and **hsa-miR-30a-5p** related to proteoglycans being significantly downregulated in ocular hypertension (OHT) compared to XFG. Flaky aggregates are visibly seen deposited on the lenses of XFS/XFG patients. With its monolayer structure and direct exposure to ultraviolet radiation, the lens capsule epithelium is a significant subject for exploring complex elements, including genetics and environmental influences in XFS. Tomczyk-Socha et al. reported the upregulation of **miR-125b** in the lens capsules of XFS patients when compared to controls (cataract), with no significant upregulation in the XFG patients [35].

It is believed that concentrating on the polymorphisms in the miRNA biogenesis pathway and their dynamic interaction with the genes under specific environmental triggers could uncover data for disease anticipation and pharmacogenomics in exfoliation syndrome (XFS) [35][36][37]. Recently, various studies have reported differential miRNA expression status in the AH and trabecular meshwork, two anatomical structures that are closely related to glaucoma, and linked them to the apoptosis of retinal ganglion cells and IOP [11][28][29]. Fewer studies, however, have reported polymorphisms in miRNA [36][37][38][39]. One study reported rs1057035 polymorphisms in the 3′-UTR of the *DICER* gene to be associated with a decreased risk of XFG, and rs55671916 in the 3′-UTR of the exportin 5 (*XPO5*) gene with an increased risk of XFG [40][38]. As per the miRNASNP database, the polymorphism rs11382316 results in a gain of function of **miRNA-3161** in the genes caveolin-1 (*CAV1),* cytochrome P450 family 1 subfamily B member 1 (*CYP1B1*), and *CACNA1A,* and a loss of function of transforming growth factor-beta receptor 3 (*TGFBR3*). This result seems to further support a previously reported implication of the *CACNA1A* gene in XFS susceptibility [41].

Given the significance of ECM elements to the ordinary physiology of the outpouring pathway, miRNAs that control ECM metabolism could be reasonable targets to impact AH dynamics in exfoliation syndrome (XFS) eyes. The best-described group of miRNAs that directs ECM digestion is the miR-29 family, including **hsa-miR-29a**, **hsa-miR-29b**, and **hsa-miR-29c**. In a study by Luna et al., the transfection of TM cells with **miR-29b** mimic caused the downregulation of various ECM genes, including collagens and fibronectin, as well as the targeting of genes involved in ECM remodeling (SPARC/osteonectin). Interestingly, persistent oxidative stress induced by incubation at 40% oxygen led to a critical downregulation of miR-29b in trabecular meshwork (TM) cell lines that were related to an increased expression of several ECM genes [42]. Strategies to elevate miR-29 expression in TM cells may be advantageous to limit ECM deposition, avert cell loss, and maintain normal levels of AH outflow facility. However, this family has not been studied in targeting TM function in XFG eyes, nor has its role in XFS and XFG eyes been identified in any study. Further, the regulation of miRNA biogenesis and the TGF-β pathway in exfoliation remains unexplored. A detailed study in this direction may give insights into how TGF-β-regulated processes are modulated differentially in disease progression or in different ethnic populations.

2. Autophagy and Mitochondrial Dysfunction and Protein Aggregate Clearance

It was recently demonstrated a decreased UPR clearance in XFG compared to earlier forms of the disease associated with increased TGF levels in all disease stages, which suggest the potential regulation of the autophagy pathway and TGF–autophagy cross-talk involved in cell repair and aggregate clearance [43]. Autophagy is an intracellular trafficking system that conveys cytosolic constituents to the lysosome for ensuing degradation, which is crucial for misfolded protein clearance, cell homeostasis by ubiquitin–proteasomal degradation, and cell repair [44][45][46][47][48]. Immunohistochemical and mass spectrometry investigations have uncovered that exfoliative material is a profoundly glycosylated proteinaceous complex that is very impervious to degradation, both inside the body and under experimental conditions [44]. Given the significance of the autophagic clearance of protein aggregates, autophagy-related genes (ATG genes) might be involved in XFG pathology beyond primary glaucoma [46]. Studies have also shown the association of neurodegeneration with mitochondrial dysfunction and abnormal mitophagy [49][50][51]. Impaired mitophagy causes the accumulation of damaged mitochondria that may have a severe impact on acell's ability to manage oxidative insult and/or ability to clear misfolded proteins, which may be impaired in XFG eyes. A decreased autophagic flux (an indicator of autophagic activity) caused by oxidative stress may be one of the factors that lead to the progressive failure of cellular TM function with age [52][53][54][55][56]. Autophagy genes were abruptly upregulated in severe POAG and primary angle-closure glaucoma (PACG) compared to moderate glaucoma, suggesting the role of autophagy in disease progression [46].

In summary, research related to mitochondrial dysfunction and impaired mitophagy in XFG has been less extensive to date, with very few studies evaluating the role of the environment in triggering the dysregulation of these processes in XFG. There is a compelling need to supplement the existing literature on XFG pathogenesis with functional studies analyzing various populations and different environmental influences on mitochondrial function in XFS/XFG.

3. The Blood–Aqueous Barrier in Eyes with Exfoliation Syndrome

The eye, similar to the brain, is an organ endowed with immune privilege, an attribute conferred by complex ocular barrier systems. Two kinds of barriers have been distinguished inside the eye, each described by its unique tissue restriction, immunologic properties, and physiological capacities, namely, the blood–aqueous barrier (BAB) and the blood–retina barrier (BRB) [57][58]. Eyes with XFS frequently show clinical signs of impairment of the BAB [59]. The breakdown of the BAB is confirmed by an elevation in AH proteins. Mice without the *LOXL1* gene, a significant genetic risk factor for XFS and XFG, displayed an increased dispersion of fluorescein at the BAB, indicating the interruption of the ciliary epithelial barrier [60]. Kuchle et al. studied the alteration in the BAB in XFS patients by the histochemical staining of endogenous

albumin and reported the impairment of the BAB in XFS that was confined to the iris and, to a lesser extent, may involve the ciliary body [61]. Elevated levels of AH clusterin in XFS, POAG, and XFG cases compared to controls has been reported by several studies [62][63]. Zenkel et al. [64] reasoned that this was due to the disintegration of the BAB and leakage of systemic clusterin into the AH. On the other hand, Doudevski et al. [63] contended that this increase could not be explained by the breakdown of the BAB alone and that local synthesis might therefore play a significant role. Yildirim et al. found that serum interleukine 6 (IL-6) levels were altogether higher in XFS when contrasted with controls, suggesting higher levels of subclinical inflammation and BAB in XFS patients [65]. Kondkar et al. observed that higher plasma tumor necrosis factor alpha (TNF-α) levels might be a marker for the progression of XFS to XFG [66]. What triggers the disruption of BAB in XFS patients is unclear, though some risk factors such as oxidative stress, raised homocysteine, AH nitric oxide (NO), and vascular endothelial growth factor (VEGF) are presumed to play a role. Eraslan et al. revealed high acylated ghrelin/ghrelin proportions in XFG cases and suggested that acylated ghrelin may adversely trigger prostaglandin and NO release in XFG, causing progressive damage [67]. Bleich et al. observed that significantly elevated (twofold) homocysteine levels in the AH and the plasma of XFG patients with aqueous homocysteine was significantly correlated with corresponding plasma levels [68]. VEGF is also known to increase vascular permeability, contributing to disrupted BABs in XFS [69][70]. This may also explain the frequent ischemic systemic associations in XFS patients, including cardiovascular disease, transient ischemic attacks, and vascular occlusive disease. The mean AH and plasma VEGF concentrations and the mean AH NO concentrations were significantly higher in patients with XFG than in controls [69][70][71]. Studies have reported marginally higher mean AH and plasma levels of NO and VEGF in XFG than in patients with XFS, but the differences were not statistically significant. These studies imply a need for further studies on how these factors cause BAB breakdown and precipitate a cascade of protein complex aggregate accumulation over different ocular structures in XFS. It may be worthwhile exploring the role of ambient light and continued TGF-β exposure in the key downstream pathways such as autophagy, the disruption of the BAB, mitochondrial dysfunction, and oxidative stress in the TM cells causing functional damage. Understanding these processes in animal or invitro models would be crucial to identify mechanisms to reverse or dissolve these aggregates and prevent tissue dysfunction in XFG.

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