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Circulating Inflammatory and Genetic Biomarkers in Glaucoma: Towards Personalized Neuroprotection Strategies.

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KEYWORDS

Glaucoma; Inflammatory biomarkers; Genetic biomarkers; Neuroprotection; Personalized medicine; Optic nerve; Disease progression.

ABSTRACT:

Glaucoma is a progressive neurodegenerative disease leading to optic nerve damage and irreversible visual impairment, and in spite of current treatments, trends suggest an ongoing rise in both disease prevalence and incidence, combined with violent forms of disease, such as acute glaucoma. Increasing evidence suggests that inflammation and genetic make-up play an important part in the disease pathogenesis and progression, and readouts from these systems that act as biomarkers will allow a more directed individual approach to the disease and its complications. Here we review current evidence on circulating inflammatory and genetic biomarkers in the disease, and their potential use in development of a personalized neuroprotection. Accordingly we have conducted a systematic review in accordance with PRISMA guidelines. We searched the electronic databases PubMed, Scopus, Web of Science and the Cochrane Library for articles on inflammatory and genetic biomarkers published between 1st January 2013 and 31st December 2025. Inflammatory mediators, genetic markers and their clinical significance in the glaucoma were included. We identified 1,368 records, of which 41 studies were eligible for inclusion.

1. Introduction

Glaucoma is a complex, multifactorial neurodegenerative disease that progresses with inexorable death of retinal ganglion cells (RGC death) and progressive structural and functional damage to the optic nerve. Management of these patients has relied heavily on the reduction of IOP as the only element of disease risk that can be modified. However, a sizeable proportion of patients continue to progress despite adequate IOP control, demonstrating the deficiencies of an IOP-centric paradigm. This might contribute to the more modern pivot toward a fundamental, biomarker directed, comprehensive view that might allow the targeting of the underlying pathology of neurodegeneration. In this context, the identification and deployment of molecular, cellular, and imaging biomarkers hold the promise of developing personalized neuroprotective strategies that can match pressure reduction for the prevention of disease. [1]

2. The Changing Paradigm: Glaucoma as a Neurodegenerative Disease

Beyond Intraocular Pressure: The Multifactorial Nature of Glaucoma

Though raised IOP is the most important and actionable modifiable risk factor for glaucoma, it is increasingly being recognized as only one piece of the underlying pathophysiologic puzzle. Epidemiologic and clinical experience suggest that despite optimal control of IOP, 30–50% of patients continue to show disease progression. Mechanisms that are considered common "IOP independent" contributors include vascular dysregulation, oxidative stress, mitochondrial dysfunction, chronic low grade inflammation, and glial activation. Other systemic and ocular risk factors,

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including advancing age, genetics, myopia, lower ocular perfusion pressure, systemic hypertension, and metabolic disease all contribute to an individuals' susceptibility to disease and/or the course of disease development and/or progression. Perhaps the most important and insightful of all of these features is the clear fact that most individuals with high concerns are simply never going to develop glaucomatous damage [2].

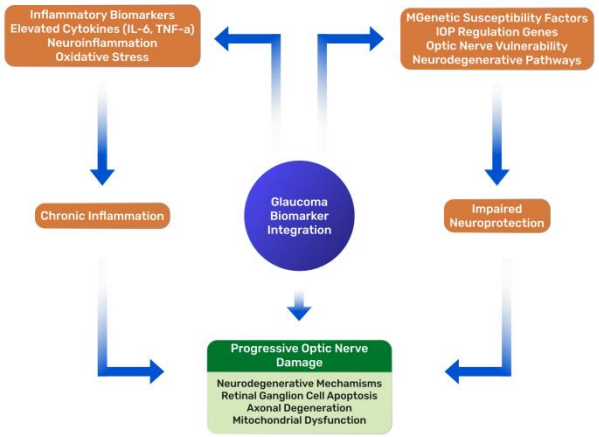

Figure 1. Integrated Inflammatory and Genetic Biomarker Network in Glaucoma Pathogenesis.

Comprehensive web diagram highlighting how circulating inflammatory and genetic biomarkers may feed into the disease of glaucoma at the node "Glaucoma Biomarker Integration" (deep blue). This node breaks off into three main areas inflammatory biomarkers (increased cytokines like IL-6, TNF-α, neuroinflammation and oxidative stress), genetic predisposition (genes which regulate IOP and vulnerability of the optic nerve, and neurodegeneration), and neurodegeneration (apoptosis of retinal ganglion cells, axonal degeneration and mitochondrial dysfunction). The three areas are then connected via the mechanistic pathways, as chronic inflammation, lack of neuroprotection, and optic nerve damage that leads to loss of the visual field and progression of glaucoma. [3]

The Neurodegenerative Continuum

Recent evidence positions Glaucoma not merely as an eye disease， but also as a neurodegenerative disease within a wide circle encompassing Alzheimer's disease and Parkinson's disease in the same category. The glaucomatous insult takes the form of progressive neurodegeneration of the RGCs and their axons， culminating in optic nerve head pallor and visual field deficits. Glaucoma has many similarities with the patterns of degeneration seen in central nervous system neurodegenerative diseases and includes defective axon transport ， mitochondrial dysfunction ， protein aggregation (e.g. amyloid-β and tau) and chronic neuroinflammation. There are bidirectional links documented between glaucoma and the neurodegenerative diseases in both directions with common mechanisms underpinning vulnerability of the neuron. [4].

The Unmet Need for Neuroprotection

The limitations of IOP-lowering therapies highlight the need for therapeutics that act upstream of RGC death. Neuroprotection, defined as the preservation of neuronal structure/function without concomitant lowering of IOP, is one of the critical unmet needs in glaucoma. Promising preclinical results with candidates like memantine, brimonidine, and citicoline have led to variable results in clinical trials that have failed to show drug-specific effects, in part due to heterogeneous nature of the disease and the lack of biomarker-driven patient selection. The concept of precision medicine aims to correct for this, allowing for the identification of different "flavors" of the disease (i.e., different pathogenic drivers, such as inflammation, vascular insufficiency, mitochondrial insufficiency), and targeting therapies accordingly. [5]

Biomarkers in Glaucoma: Definitions and Classifications

Biomarkers are critical for implementation of precision medicine, providing objective measures of disease presence, activity, and response to treatment. In glaucoma, they can be considered subdivided into risk biomarkers (identifying individuals at risk for developing disease), diagnostic biomarkers confirming disease presence, prognostic biomarkers that foretell disease progression, predictive biomarkers identify who will respond to what therapy, and pharmacodynamic biomarkers measure treatment effects. Circulating, imaging, and molecular biomarkers offer a multi-dimensional approach to personalised disease management. [6]

2. **Circulating Inflammatory Biomarkers**

The Role of Neuroinflammation in Glaucoma

Neuroinflammation is an overarching theme connected to glaucomatous neurodegeneration. The first activation of microglia occurs in the retina and optic nerve head and initiates the cascade of inflammatory signaling and chemistry. From here arises a sustained production of pro-inflammatory cytokines and toxic mediators that are believed to promote neurodegeneration through various mechanisms including astrocyte reactivity, gliosis, structural remodeling and axon damage. There is also the

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infiltration of autoreactive Tcells, suggesting an adaptive immune role and implicating heat shock protein immune responses in at least one form of this disease. Systemic inflammation may also have an enhancing role as glaucoma has been linked with cardiovascular and metabolic disease with overlapping inflammation. [7]

Cytokines and Chemokines

Interleukin-1β (IL-1β)

Interleukin-1β is a crucial pro-inflammatory cytokine involved in the activation of the NLRP3 inflammasome in microglia and retinal ganglion cells. Increased circulating levels of IL-1β have been observed in patients with glaucoma, with the levels correlating to the disease severity (greater visual field loss). IL-1β participates actively in neurodegeneration, with blockade leading to neuroprotection when using IL-1 inhibitors such as Anakinra. [8]

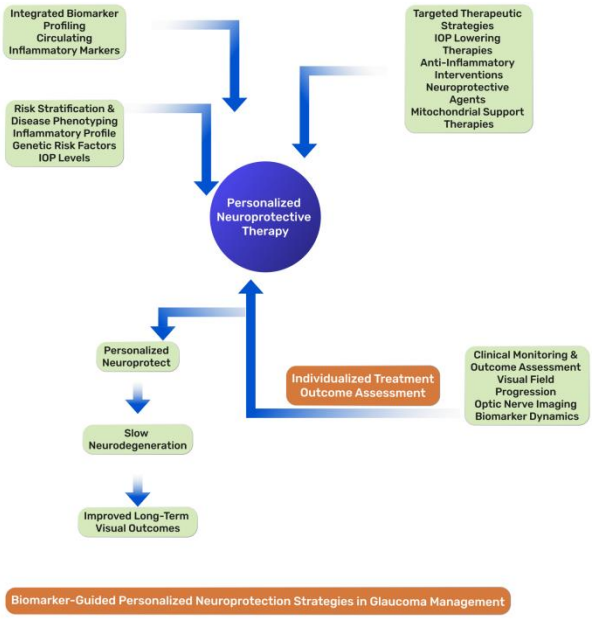

Figure 2. Biomarker-Guided Personalized Neuroprotection Strategies in Glaucoma Management.

Schematic overview of a personalized medicine framework for glaucoma, known as "Personalized Neuroprotective Therapy" (deep blue in colour). Offshoot from combined biomarker profiling (circulating inflammatory biomarkers and genetic risk signature information) leads to risk stratification, disease phenotyping, and drug choice (IOP lowering agents, antiinflammatories, neuroprotective drugs, mitochondria support therapies). Side modules emphasise delivery in terms of clinical monitoring and outcome evaluation (visual field, optic nerve imaging and biomarker). Arrow sequences emphasise that biomarker targeted treatment is personalized, neurodegeneration is slowed down and that this project enhances long-term visual outcomes. [9]

Tumor Necrosis Factor-α (TNF-α)

Tumor necrosis factor-α (TNF-α) is central to many inflammatory mediators and is implicated in microglial involvement and apoptosis which leads to RGC death. TNF-α has been reported to be elevated in both primary open-angle and normal-tension glaucoma, and with regards to the diurnal peaks of intraocular pressure. Targeting TNFα with biologic agents like etanercept and adalimumab may be the route of therapy. [10]

Interleukin-6 (IL-6)

Interleukin-6 IL-6 is a pleiotropic cytokine that can display both proinflammatory and antiinflammatory effects depending on the signaling context. Increased IL-6 levels have been detected in the circulation and ocular fluids of glaucoma patients and correlate with disease progression. Baseline IL-6 concentrations could predict the rate of visual field decline, supporting its place as a prognostic biomarker. With the pivotal role IL-6 plays in inflammatory signaling, receptor blockade could prove beneficial, although in this application it requires further investigation. [11]

Interleukin-10 (IL-10)

This anti-inflammatory cytokine balances inflammatory signalling and acts favouring cell survival. The finding of lower levels of IL-10 in those with glaucoma matches the association of that disease with a pro-inflammatory shift inducing neurodegeneration. The IL-6/IL-10 ratio may also be a useful biomarker - those with a worse prognosis have higher levels of it. That experimental work suggests attempting to signal IL-10 may have neuroprotective potential. [abf26]

Chemokines (CXCL10, CCL2, CX3CL1)

Chemokines are important in the recruitment and regulation of immune cells in the glaucomatous environment. CXCL10 promotes T-cell recruitment to the optic nerve, mediating the immune damage inflicted by these cells. CCL2 serves as a monocyte chemoattractant, correlating with disease severity, whilst CX3CL1 produced by neurons modulates microglial activation and is a major player in the neuron–glia crosstalk. [13]

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C-Reactive Protein (CRP)
C-reactive protein (CRP) and particularly the highsensitivity CRP (hs-CRP) is a systemic marker of inflammation associated with the severity and progression of glaucoma. Increased hs-CRP levels represent a body state that may be pro-inflammatory, leading to compromised vascular function, in particular disrupted ocular perfusion. The risk of disease progression has been shown to be significantly higher when hs-CRP levels are greater than 3 mg/L, highlighting a potential in prognostic biomarking. [14]

Heat Shock Proteins (HSPs)
Heat shock proteins are stress-inducible chaperones that can both promote cell protection and function as a target for autoimmunity. In glaucoma, they are a target for autoantibodies - anti-HSP60, anti-HSP70 and anti-HSP27 antibodies have all been reported and show some promise as auto-immune biomarkers with moderate sensitivity and specificity. However, HSP specific T cell responses have also been implicated in optic nerve damage. [15]

Other Inflammatory Markers
Additional biomarkers of inflammation—which point to aspects of immune and glial response—include neopterin, pentraxin-3, YKL-40 and S100B. Neopterin production is associated with macrophage activation. Pentraxin-3 is associated with innate immune responses and correlates with visual field loss. YKL-40 is released by activated microglia, whereas S100B is released by activated astrocytes. They are thought to reflect processes of active neuroinflammation in glaucoma. [16]

4. Genetic Biomarkers
Monogenic Forms of Glaucoma
Monogenic forms of glaucoma provide some of the clearest evidence that inherited molecular defects can directly drive retinal ganglion cell vulnerability, optic nerve degeneration and altered dynamics of aqueous humor.

While these monogenic forms account for a minority of all glaucoma cases, they are particularly informative at guiding specific pathogenic mechanisms that may also be present and contribute to the much more common and multi-factorial disease. In the clinical practice of identifying monogenic variants, juvenile-onset cases, familial clustering, severe normal-tension cases, and cases with unusually early progression may be particularly informative in terms of diagnosis and screening families for the genetically affected, while informing biomarker-driven personalization of surveillance and treatment. [17]

MYOC (Myocilin) Mutations
Mutations in MYOC are some of the best understood monogenic causes of primary open-angle glaucoma and juvenile open-angle glaucoma. Most pathogenic myocilin variants disrupt proper protein folding, resulting in retention in the endoplasmic reticulum of trabecular meshwork cells. The accumulation of mutant myocilin in the endoplasmic reticulum leads to endoplasmic reticulum stress, cellular dysfunction and impaired aqueous outflow, mediating the cascade that results in raised intraocular pressure and secondary retinal ganglion cell injury. MYOC-associated glaucoma is notable for its high penetrance (>90%), and, remarkably, its age-dependence, with many patients developing disease only in the third to fifth decades of life. MYOC testing is clinically relevant when evaluating for early onset or very strongly familial glaucoma, such that a result can guide aggressive surveillance or intervention. Because MYOC related disease remains substantially driven by pressure, conventional IOP lowering therapies tend to work well, although some mutation carriers can progress rapidly. [18]

OPTN (Optineurin) Mutations
OPTN mutations are rarer than MYOC pathogenic alterations, but are particularly prominent in normal-tension glaucoma where they provide a mechanistic link between glaucoma and neurodegenerative biology more broadly. Optineurin is involved in autophagy, vesicular trafficking, inflammatory signalling, and maintenance of axonal transport, all of which are implicated in the survival of retinal ganglion cells. Pathogenic variants interfere with these processes, rendering the neurons more vulnerable even prior to markedly increased intraocular pressure. The E50K mutation which is the most well-characterized pathogenic OPTN variant and leads to severe, often early-onset normal-tension glaucoma with rapid slope of visual relative structure function decline. From the perspective of translation, disease relating to OPTN alterations is most relevant in the context of neuroprotection insights, because of the way it pins down autophagy and NF-κB relative inflammatory pathways as attractive targets in this context. This has led to an interest in autophagy enhancers and inflammatory pathway modulators as prospect biomarker-directed therapies. [19]

TBK1 (TANK-Binding Kinase 1) Mutations
TBK1-associated glaucoma is most frequently caused by copy number variations ie duplications that increase TBK1 expression and activation of associated pathways. TBK1 is critical to innate immune signalling, autophagy, interferon-mediated inflammatory responses and is overactive in glaucoma, thought to drive chronic stress

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signalling within the optic nerve and retina. These changes are particularly prominent in familial normal-tension glaucoma and account for a small, but not trivial proportion of cases. TBK1 copy number variation may be a biomarker of great value since puts a mechanistic framework around the disease in which inflammation and defective homeostasis have leading roles rather than the currently recognised signature of increasing pressure as the only factor of importance. TBK1 is being investigated as a potential novel therapeutic target for preclinical development, making this biomarker of potential relevance therapeutically as well as diagnostically. [20]

Genome-Wide Association Studies (GWAS) Risk Loci

Genome-wide association studies have highlighted the polygenic nature of commonly-seen forms of the disease, and together with other lines of research provide compelling evidence that an important aspect of inherited risk relates to genetic variation in developmental pathways associated with optic nerve head biology and structure, extracellular matrix remodeling, regulation of vascular tone, lipid transport, growth and senescence, and neuronal susceptibility to potentially pathogenic damage. More than one hundred susceptibility loci have been identified so far for primary openangle glaucoma. One of the strongest associations with glaucoma risk is seen with CDKN2B-AS1, and this appears to influence aspects of cell cycle and/or cellular senescence processes in optic nerve tissues. Variants found in SIX1 and SIX6 provide links to aspects of eye development and optic disc biology, while ABCA1 implies a role for lipid handling and cellular membrane transport in the disease process. ATOH7 is involved in the development of retinal ganglion cells and regulates the size of the optic disc, and TMCO1 is also repeatedly found to be in strong statistical association, although its biologic mechanism is incompletely known. Together, the loci illustrate the rich biologic substrate of glaucoma and reinforce the notion that genetic markers for diseases can be useful not only for prediction, but also for mechanisms for classification. [21]

Single Nucleotide Polymorphisms (SNPs) and Disease Risk

Specific SNPs within glaucoma loci have also revealed interesting insights into the nature of disease risk and pathogenesis. For example, such variants within CDKN2B-AS1 (rs1063192, rs4977756) appear to be associated with altered risk and may affect senescence-related pathways that also target the resilience of the optic nerve. Variants within SIX1/SIX6 suggest a smaller optic disc area and a greater susceptibility to pressure-related injury suggesting that inheritance of optic nerve architecture may influence vulnerability when distribution of intraocular pressure elevation is not. Variants within the ABCA1 locus suggest a dysregulated lipid transport affecting optic nerve injury, and the suggestion that glaucoma may have links to the status of a wider metabolic milieu. One of the strongest examples of a subtype-specific genetic risk to date is seen within LOXL1 which shows very strong association with exfoliation glaucoma and confers a very high relative risk. SNPs will likely never be a standalone clinical test in most cases – but are valuable for polygenic profiling and biologically informative phenotyping. [22]

Polygenic Risk Scores (PRS) for Glaucoma

Polygenic risk scores exemplify one of the most exciting translational utilities for glaucoma genetics. These scores aggregate the cumulative action of many common risk alleles into a single quantitative indication of inherited risk. Models combining data from a plethora of GWAS loci can categorize individuals into scales of low, intermediate, and high risk, and may indicate that in the highest risk categories, individuals are about tenfold more likely to develop primary open-angle glaucoma than people in the lowest risk groups. Beyond predicting the likelihood of disease onset, high polygenic burden is associated with earlier onset and faster progression, even adjusting for intraocular pressure. Clinically, this renders genotype-dependent screening strategies, earlier surveillance of asymptomatic high-risk individuals, and more intensive monitoring of high-risk patients with established disease a possibility. They will require calibration in an ancestry-specific manner and clinical standardization, but PRS are a first step toward predictive precision ophthalmology.[23]

Pharmacogenomics of IOP-Lowering Therapy

Pharmacogenomics add an additional layer of complexity to the search for biomarkers in glaucoma, locating it in the interpersonal variation in treatment efficacy. Variants in prostaglandin receptor and transport genes such as PTGER and SLCO2A1, and metabolizing enzymes including CYP2C9 and CYP2C8 appear to affect responsiveness to prostaglandin analogs. Similarly, ADRB2 polymorphisms may contribute to sensitivity to betablockers such as timolol, revealing poor responders with persistently high intraocular pressure on therapy. Carbonic anhydrase-related gene variants may mediate efficiency of topical carbonic anhydrase inhibitors, and the pharmacogenomics of rho kinase inhibitors are a fledgling field of investigation. From the clinical standpoint, such biomarkers could one day guide treatment selection according to anticipated drug responsiveness as well as disease subtype, preserving the

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precious fruitfulness of the first-line effects already achieved by pragmatism, and adding delicious layers of_solver for its ripening, ensuring that meticulous sweeter pressure control benefits the maximum number of patients as possible.[24]

5. **Circulating Biomarkers of Vascular Dysregulation**
Endothelial Dysfunction Markers
Vascular dysregulation is increasingly noted as a significant non-IOP factor in glaucomatous optic neuropathy, in particular in normal-tension glaucoma, and in patients with progressive disease in the face of apparently adequate pressure control. Endothelial dysfunction biomarkers provide an important systemic view of this pathogenic nexus. Endothelin-1 is of particular interest because it is a potent vasoconstrictor that can reduce optic nerve head perfusion and lead to ischemic stress. Increased circulating endothelin-1 has been found in glaucoma and shown to correlate with loss of visual field, indicating both mechanistic and prognostic significance. Asymmetric dimethylarginine is an endogenous inhibitor of nitric oxide synthase reflecting impaired vasodilation capacity, and is elevated in glaucoma and may lead to a decreased autoregulation of ocular blood supply. Vascular endothelial growth factor and soluble vascular cell adhesion molecule-1 similarly reflect endothelial activation and remodeling, linking vascular dysfunction to an inflammatory response and tissue stress. Together these biomarkers suggest that glaucoma in at least a subset of patients is a vascular disease of the optic nerve. [25]

Ocular Perfusion Pressure and Vascular Reactivity
Ocular perfusion pressure is a functional best estimate of the interaction between systemic blood pressure and intraocular pressure, and is among the strongest clinical measures of vascular risk for glaucoma. Low perfusion pressures, at least those near or below 40 mmHg, correlate with faster progression, as expected if the optic nerve is not receiving adequate blood supply to sustain all its nerve fibers. However, both blood pressure and perfusion are static measures, and glaucoma affects vascular autoregulation as well, so ocular blood flow may not respond adequately to pressure variance and metabolic need. Laser speckle flowgraphy and colour Doppler imaging show changed vascular reactivity in glaucoma. There are also systemic variants, like low diastolic blood pressure, nocturnal hypotension, or blood pressure variability, that influence risk. Linking perfusion to biomarkers like endothelin-1, and ADMA in circulation may be helpful in identifying those patients for whom disease and visual field loss is less related to pressure load, and more to vascular insufficiency. [26]

Coagulation and Fibrinolysis Markers
Altered coagulation and fibrinolytic balance may be deleterious to glaucomatous optic nerve injury by exacerbating microvascular occlusion and endothelial dysfunction. Increased plasminogen activator inhibitor-1 indicates impaired fibrinolysis and a prothrombotic state that may affect tissue perfusion at the level of the optic nerve head, while elevated von Willebrand factor indicates endothelial injury or activation. Increased D-dimer, particularly in exfoliation glaucoma, indicates that ongoing fibrin turnover and microvascular instability may further affect the perfusion and integrity of the optic nerve tissue. Similarly, the detection of antiphospholipid antibodies in a subset of glaucoma may suggest that antibodies directed at tissues in these patients are responsible for vascular occlusive/injury mechanisms in the pathophysiology of the disease in some cases. All of these findings lend support to a model in which thromboregulatory abnormalities are combined with vascular dysregulation and inflammation to increase the susceptibility of the optic nerve to injury. [27].

Metabolic and Lipid Biomarkers
Metabolic dysfunction has emerged as an important component in glaucoma pathogenesis, related to aberrant vascular and inflammatory mechanisms. Unfavorable elements in the lipid profile, including low high-density lipoprotein cholesterol and increased low-density lipoprotein cholesterol have been associated with a greater risk for glaucoma with varying degree of strength depending on the population studied and the subtype of glaucoma investigated. Higher triglycerides and apolipoprotein B suggest a “more atherogenic” metabolic milieu which may impair micro-vascular function and perfusion of the optic nerve. Lipoprotein(a), associated notably with exfoliation glaucoma, may provide a pathogenic link between cardiovascular risk and glaucomatous damage. These biomarkers, therefore, not only are of interest because they may be able to detect the vascular-metabolic glaucoma phenotype, but also the target for systemic risk modification as part of a neuroprotective glaucoma strategy. [28]

6. **Circulating Biomarkers of Oxidative Stress and Mitochondrial Dysfunction**
Oxidative Stress Markers
A central feature in glaucomatous neurodegeneration is oxidative stress, arising when the reactive oxygen species overwhelm endogenous antioxidant defenses and damage macromolecules. One of the most-studied biomarker is 8-hydroxy-2'-deoxyguanosine, which reflects oxidative DNA damage and has been found to be elevated in serum, urine, and aqueous humor of glaucoma patients. Malondialdehyde is a marker of lipid

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peroxidation that is likewise elevated, with higher levels associated with greater evidence of visual field loss, suggesting a potential relationship between oxidative injury and functional damage. Advanced oxidation protein products reflect oxidative modification of proteins and reductions in total antioxidant capacity reflect global impairment of the antioxidant defence network. Taken together these biomarkers buttress the concept that glaucoma is associated not only with a localized ocular injury but also with some form of global oxidative disequilibrium that might conceivably govern its genesis and progression. [29]

Mitochondrial Dysfunction Markers

Mitochondrial dysfunction is emerging as a central pathogenic feature of glaucoma since retinal ganglion cells are very energy-consuming and intensely stressed by defects of oxidative phosphorylation and the energy supply to axons. Reduced copy number of mitochondrial DNA (mtDNA) may reflect a general impairment of mitochondrial biogenesis or a reduced mitochondrial 'reserve', and specific deletions and mutations in the mtDNA have been documented in glaucomatous tissues. Cell-free mtDNA released to circulation may be both an indicator of tissue injury and a pro-inflammatory signal that promotes amplification of inherent immune activation. A reduced NAD+/NADH ratio indicates a compromised mitochondrial metabolic state and redox imbalance. These biomarkers are particularly pertinent to the notion of personalised neuroprotection, since they may allow identification of those patient who are most likely to derive clinical benefit from therapies targeting mitochondrial energetics, redox homeostasis or metabolic resilience. [30]

Enzymatic Antioxidants

Antioxidant enzyme system Antioxidant enzymes are an important endogenously produced barrier to oxidative injury, and studies suggest dysfunction of both glutathione and superoxide dismutase systems exist in glaucoma. Decreased superoxide dismutase reduces detoxification of superoxide radicals, while reduced glutathione peroxidase and catalase activity impairs decomposition of hydrogen peroxide and related reactive species. Depletion of glutathione (one of the most important intracellular antioxidants) further weakens cellular defense capacity and may predispose retinal ganglion cells to chronic stress. It adds support to the view that the crippling of resilient and intrinsic protective systems is an important component that drives disease progression in glaucoma. These markers might help define an important subset of patients where the disease phenotype is more related to oxidative stress progression rather than increased insult. [31]

Nutritional Biomarkers

Nutritional aspects may alter antioxidant status, and mitochondrial performance, and may also influence vulnerability to and advancement of glaucoma. Less vitamin C, and vitamin E has been detected in those with glaucoma further demonstrating the negative connection of antioxidant nutrient accessibility to oxidative injury in eyecare. Vitamin D has been shown to reduce glaucoma risk partly attributable though immunomodulation, vascular, and neuroprotective pathways. The trace minerals zinc and selenium are critical co-factors for the reductionases, and deficiency of microminerals can render the retinal and optic nerve more sensitive to oxidative injury.. While not disease specific, they may be clinically relevant biomarkers in glycation readouts as part of a systems-biology initiative to investigate modifiable factors in neurodegeneration.[32]

7. **Multi-Omics Approaches and Emerging Biomarkers**

Metabolomics in Glaucoma

Metabolomics has extended the glaucoma biomarker beyond the ocular compartment, showing evidence of systemic biochemical networks indicative of excitotoxicity, mitochondrial stress, lipid remodelling and deviation of neuroimmune metabolism. Metabolomic studies of serum in glaucoma show consistent findings compared with controls, including an increase in glutamate/decrease in taurine, and changes in sphingolipids, ceramides and glycerophospholipids. The tryptophan–kynurenine axis has also received attention, with increased kynurenine levels and neurotoxic metabolites implicating the retinal ganglion cell injury in chronic neuroinflammation: evidence this disesase has a clear systemic metabolic phenotype rather than being a simply localised pressure mediated problem. (33)

Proteomics and Peptidomics

Proteomic profiling of glaucoma across aqueous humor and blood reveal a multitude of inflammatory, complement-associated and stress-response proteins detectable. Work in aqueous humor shows repeated evidence for enrichment of complement proteins including C3 and C5, apolipoproteins and other inflammatory mediators, while serum proteomic work suggests C3, clusterin, and haptoglobin may help in differentiating between glaucoma patients and normal controls. Peptidomic studies suggest a trend where neuroprotective peptides including PEDF- and NGF-like signals may be decreased, whereas pro-inflammatory peptide patterns are increased. High throughput mass spectrometry has been the engine behind most of these discoveries, and remains at the forefront in the search for new candidate biomarker panels. [34].

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MicroRNAs (miRNAs) as Circulating Biomarkers
Circulating microRNAs are also an attractive potential biomarker for glaucoma since they tend to be stable in biofluids often protected within exosomes for example, with some regulating the very pathways involved with extracellular matrix remodelling, apoptosis and inflammation and neuroprotection. Reviews in the field highlight a recurrent involvement of miR-29, miR-182, miR-204 and miR-146a in glaucoma-related biology. Multi-miRNA signatures have demonstrated encouraging diagnostic performance in published studies, while exosomal miRNA cargo will be especially informative as reported in some studies since it likely reflects more accurately the cellular state of the retina, trabecular meshwork and optic nerve environment. Right now the field is pre-standardisation, with large validation cohorts needed before moving to clinical routine. [35]

Long Non-Coding RNAs (lncRNAs)
Another transcriptomic layer relevant to glaucoma pathogenesis and biomarker discovery is that of long non-coding RNAs. There are experimental and translational studies implicating lncRs such as MALAT1, NEAT1 and TUG1 being dysregulated in glaucoma and contributing to apoptosis, oxidative stress, inflammatory signalling, and extracellular matrix remodelling. Initial reports show that circulating lncRs profiles can discriminate glaucoma from controls, and may associate with disease severity although the evidence base is much smaller compared to microRNAs. They may be appealing therapeutic targets as oligonucliotide strategies targeting these may modulate pathobiotic signalling. [36]

Epigenetic Biomarkers
Epigenetic biomarkers link the inherited likelihood with exogenous exposures and insults. In glaucoma, altered DNA methylation has been identified, both global hypomethylation and promoter hypermethylation of genes with neuroprotective and stress-related functions. Changes in histone acetylation have also been implicated, which is interesting since histone deacetylase inhibitors are neuroprotective in experimental models. Circulating cell-free DNA methylation is particularly appealing, as it may represent stable and tissue-informative classes of biomarkers that capture disease activity that genetic testing alone may not reflect. In all, epigenetic profiling in glaucoma is still in its infancy, but it is a good fit for the trend in mechanism-based endophenotyping.[37]

8.Integration of Biomarkers into Personalized Neuroprotection
Stratification of Glaucoma Patients by Endophenotypes
Biomarkers may also facilitate classifying patients into biologically meaningful endophenotypes rather than simply give clinical labels to cases based on arbitrary symptoms at presentation. For example, an inflammatory endophenotype would have elevated IL-1β, and TNF-α, IL-6, hs-CRP, but low IL-10, increased heat-shock protein autoimmunity etc, possibly corresponding to patients who seemingly progress faster despite controlled pressure. A vascular dysregulation endophenotype would have increased endothelin-1, ADMA but lower ocular perfusion pressure, nocturnal hypotension, vasoreactivity abnormalities, disc hemorrhages, migraine, Raynaud type phenomena. An oxidative stress, mtDNA dysfunction endophenotype would have elevated 8-OHdG, and MDA, lower total antioxidant capacity, compromised glutathione-related defenses, mitochondrial stress markers. There may be genetic endophenotypes based on pathogenic MYOC, optn, or tbk1 variants; high polygenic risks, or LOXL1-driven risk of exfoliation. In reality, I suspect most patients would fall into "mixed" categories which is why multimarker panels may turn out to be more powerful than single analytes. [38]

Biomarker-Guided Neuroprotective Trials
One of the key learnings from previous neuroprotection trials is that heterogeneous patient populations dilute signal and make potentially beneficial therapies appear to be ineffectual. Enrichment using biomarkers could counteract this by selecting patients whose predominant disease drivers are the same as the therapeutic mechanism being studied. For example, inflammatory agents are more likely to show benefit in patients with an inflammatory biomarker profile, whereas vascular or mitochondrial therapies may be more relevant in those with perfusion or oxidative stress signatures. Predictive biomarkers could identify likely responders ex-ante, while pharmacodynamic biomarkers could identify target engagement ex-post. This approach would also support adaptive trial designs in which changes in the biomarkers direct dose optimization or a reassignment of treatment. [39]

The Neuroprotective Pipeline
Our pipeline of neuroprotective agents encompasses anti-inflammatory, vascular, metabolic, neurotrophic and gene-based therapies. IL-1 blockade and the use of NLRP3 inflammasome inhibitors remain appealing because of strong preclinical rationale; TNF-α inhibitors have the support of mechanistic logic, but less glaucoma-speciic clinical data. Minocycline, another microglial modulator, has been studied with relevance to ophthalmic neurodegeneration, but its benefit awaits proof, particularly for biomarker-defined group effects.

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Vascular approaches, like calcium channel blockers and endothelin-receptor antagonists may be most relevant to normal-tension or vasospastic phenotype. Citicoline and coenzyme Q10 agents with neuroenergetic and mitochondrial support properties remain agents of note, with nicotinamide further under study, although large trials have not revealed benefit in the broader population. Neurotrophic-factor delivery, which may include BDNF-, CNTF- and NGF-based approaches to AAV-mediated neuroprotection, antisense strategies and gene-editing for mutations like MYOC or OPTN represents the most explicitly personalized arm of the pipeline. [40]

Developing a Personalized Neuroprotection Algorithm

A paradigm of personalized neuroprotection will start with conventional optic nerve imaging, IOP measurement, visual fields, and clinical risk factors and supplement it with a sharpshooter's panel of biomarkers focused on inflammatory, genetic, vascular, and oxidative pathways. Patients would then cluster according to dominant endophenotype, and adjunctive therapy would be chosen to match the most likely mechanism. Reassessing every three to six months will allow the clinician to judge both whether their targets are being hit and whether a clinical response is obtained. In this model, neuroprotection becomes adaptive and mechanism specific rather than empiric and uniform. That model does not yet represent standard care, but the biomarker evidence increasingly argues that it should be the place we rationally try to go. [41]

8. Challenges and Limitations

Biological Variability

The major roadblock to developing many of these blood biomarker systems is biological variability because circulating cytokines and vascular markers vary by circadian timing, exposure to systemic health status (e.g., chronic disease, etc., that have immuno-modulatory effects), medications, age, and sex; therefore, standardisation of sampling might be required. Glaucoma itself is highly heterogeneous so it currently is hard to see how a single blood biomarker can encompass all the different mechanisms and patterns of disease. Another limitation is that most of the circulating biomarkers reflect systemic physiology and do not directly report on something happening at the optic nerve head, retina or aqueous humor. This was recently demonstrated for a systemic assay in neurodegenerative diseases, and so on. [42]

Technical and Analytical Challenges

The technical obstacles are also considerable. There is still no harmonized framework for sample collection, assay execution, normalization, and reporting across studies, with respect to most candidate biomarkers no ideal diagnostic or prognostic cutoff have been worked out and in multiplex panels there are trade offs between depth, reproducibility, cost, and throughput. External quality assessment programs are also inadequate for many multi-omics platforms. As a result, results from discovery studies prove exceedingly hard to reproducibly obtain in independent cohorts.[43]

Clinical Implementation Barriers

Even when the biomarkers are biologically plausible, the road to biomarker use in glaucoma has real-world obstacles. Multi-omics profiling is expensive, reimbursement is sporadic, and many clinicians lack adequate training to interpret inflammatory, genetic, or omics biomarkers in a way that changes management. Even turnaround time becomes an issue, especially if a biomarker is to alter the timeliness of treatment adaptation rather than simply identifying risk retrospectively. For biomarker-guided glaucoma care to scale, practical and affordable assays with clear cut clinical decision thresholds will be necessary. [44]

Regulatory and Ethical Considerations

Regulatory and ethical issues will require increased consideration as testing for glaucoma biomarkers expands. Genetic testing relates results on identifiers not subject to glaucoma, leading to counselling and consent challenges. Multi-omics data also have privacy issues as they might contain identifiable genomic and health-risk information. Finally, access will not be evenly distributed: people already less well-served by glaucoma care will likely also be least access to advanced biomarker technologies. Any precision-medicine framework that ignores equity threatens to further widen the gap in preventing blindness. [45]

9. ctDNA Methylation and Epigenetic Resistance

ctDNA Methylation as a Biomarker

Circulating tumour DNA methylation represents a powerful epigenetic biomarker that augments genomic ctDNA analyses by capturing regulatory information about gene expression changes rather than mutation events. Changes in DNA methylation are more stable in circulation relative to genomic changes, preventing fragmentation/degradation while concomitantly serving as a surrogate tissue of origin for tumours. Platforms such as bisulfite sequencing, methylationspecific PCR, methylation panels, etc., achieve high resolution epimapping of the methylation landscape of various tumours. More importantly, levels of methylation burden, commonly called methylation fraction, is a quantifiable measure of tumour burden and correlate with disease

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activity for diagnostic and monitoring utility, making ctDNA methylation profiles useful in low mutation burden cancers and other uses. [46]

Epigenetic Drivers of Resistance

Epigenetic changes serve as an important mechanism of both innate and acquired resistance to anticancer treatment. Hypermethylation is an important means of silencing tumour supressor genes in terms of resistance to therapy; for example, MLH1 hypermethylation is associated with resistance to some cytotoxic drugs, while MGMT promoter methylation modulates sensitivity to alkylators like temozolomide. In the context of DNA repair pathways, BRCA1 methylation may create a homologous recombination deficient phenotype and sensitise tumours to PARP inhibition, with reversal of this methylation state conferring sensitivity on tumours through restoration of DNA repair. Epigenetic reprogramming is a necessary facet of lineage plasticity, allowing tumours to switch between phenotypic states (such as neuroendocrine transformation of prostate cancer), a phenomenon attested to by treatment resistance. The presence of epigenetic heterogeneity, which can refer to the absence of heterogeneous cells but also widely differing methylation patterns in tumour subclones contributes to resistance through providing a pool of dynamics. [47]

Monitoring Epigenetic Resistance

Serial analysis of ctDNA methylation allows clinicians to dynamically monitor how therapeutic stress alters methylation patterns over time, providing real-time insights into how resistance is evolving. For example, new promoter hypermethylation events might appear in the course of treatment indicating that the epigenetic silencing of pathways are being adapted as necessary "countermeasures. Promoter hypermethylation in the ctDNA context is also heavily associated with global hypomethylation signature of tumours and aggressive behaviour of the tumours. Cell-free methylated DNA immunoprecipitation (cfMeDIP) is a novel method to profile methylation landscape in a high-throughput, cost-effective, and bisulfite-free manner, allowing for scalable adoption towards clinical use. Methylation information is critical, as combining it with genomic mutation profiling provides a fuller picture of resistance, including epigenic drivers in cases where resistance arises from non-mutational means that would otherwise be missed. [48]

Epigenetic Therapies and ctDNA

Similarly, the combination of epigenetic therapy and ctDNA monitoring presents a tantalising opportunity for improving precision oncology. Hypomethylating agents like azacitidine and decitabine target the reversal of abnormal DNA methylation - reactivating silenced tumour suppressor genes and restoring drug sensitivity. ctDNA sampling allows real-time monitoring of demethylation events and response to these therapies. Histone deacetylase inhibitors like vorinostat and romidepsin further manipulate chromatin structure and gene expression and are typically used in combination. The concept of 'epigenetic priming' - when epigenetic therapies serve to realise/improve upon the immunity of the tumour and/or sensitise the tumour to chemotherapy/immunotherapy - may be discernable through altered patterns of ctDNA methylation. Following up and monitoring patients may enhance awareness of mutant epigenetic regulators 'Dnmt3a' / 'Tet2' through ctDNA. [49]

10. **Future Directions**

Multi-Omics Integration for Precision Phenotyping

The next leap in glaucoma biomarker science is likely to result from pulling genomics, proteomics, metabolomics, transcripomics, epigenomics together into single disease paradigms. Rather than thinking of glaucoma as a monolithic disease, multi-omics paradigms can determine biologically coherent sub-types based on geography (inflammatory activation, mitochondrial dysfunction, vascular dysregulation, extracellularmatrix remodeling) or mode of inheritance. Machine learning will be critical in this integration building clinical risk factors, patterns of IOP, oct and visual field indices, and certain aspects of molecular data into a clearer portrait of risk and therapy choice. A cross-cutting systems-biology based approach, sometimes called network medicine, may also clarify how molecules communicate with one another to lead to neurodegeneration in glaucoma, and uncover targets of interest for therapeutic intervention. At the finest resolution level of individual cells, single-cell omics are mapping disease-related changes in retinal ganglion cells, glia, and optical nerve, and leading towards neuroprotection at the cell level. [40]

Liquid Biopsy in Glaucoma

While liquid biopsy is better developed outside the eye than in, it is becoming increasingly relevant to glaucoma. The aqueous humor is helpful because it is very close to the disease site, and in addition to inflammatory signalling, oxidative stress, extracellular matrix remodelling and cell-to-cell cross talk, the microenvironment also serves as a transport means for “cargo” exosomes which may include disease-specific molecular cargo such as miRNAs, proteins and lipids, and which can be biomarkers but also vehicles for therapeutics. Cell free DNA and (differently) its patterns of methylation also appear to hold promise as an

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indicator of disease state and/or anatomy of origin, particularly within broader epigenetic biomarker programs designed for lenses of other tissue garnet matching studies. Looking ahead, do low-cost point-of-care technology solutions exist for rapid turnaround biomarker assessment at the point of contact and, paired with a specimen sampling to assay workflow pathways that lead to decentralizing ocular monitoring as in the case of glaucoma monitoring? [41]

Digital Biomarkers and Wearables

Digital biomarkers are likely to complement molecular testing in precision glaucoma care. Continuous or near-continuous intraocular pressure monitoring via contact lens sensors, home tonometry, and implantable systems may provide records of clinically relevant IOP fluctuations that office-based measurements overlook. Home visual field testing may advance through tablet- and web-based perimetry systems that enable frequent monitoring beyond clinic walls. Wearable devices may reveal systemic contributors such as sleep disruption, nocturnal hypotension, or activity-related vascular risk. Ultimately the value of these tools likely depends on their integration through AI-enabled models of digital, imaging, and molecular biomarkers into personalized risk profiles with adaptive management plans. [42-49]

Therapeutic Integration

The true clinical forte of biomarkers thereby rests with their incorporation into therapeutic decision making. Such biomarker-directed trial enrichment may refine the delivery of neuroprotective studies through selecting cohorts of patients most likely to derive benefit from anti-inflammatory, vascular, metabolic or gene-based approaches. Companion diagnostics have yet to be a routine phenomenon in glaucoma, but such is a conceivable resultant evolution of the biomarker if its predictive qualification ability resides in its indication of affinity for the therapeutic target of a discrete intervention. Theragnostic models are particularly alluring in the arena of neuroprotection in glaucoma; a biomarker inducing identification of a given pathway lends itself to analysis through serial measurements of confirmation of the intended target (engagement) in response to treatment. Epidemiological registry studies will be critical to enter in ascertainment of a potential improvement in patient outcomes through the offering of such biomarker-guided neuroprotection. [44]

11. Conclusions

Summary of Key Evidence

Current evidence positions glaucoma increasingly as a heterogeneous neurodegenerative disease, and not simply as a disease defined by elevated intraocular pressure. Inflammatory biomarkers such as IL-1β, TNF-α, IL-6, hs-CRP and decreased IL-10 support the idea that a proinflammatory endophenotype exists associated with faster progression. Genetic biomarkers with MYOC, OPTN and TBK1 mutations and also common polymorphisms added into polygenic risk scores aid risk prediction and mechanistic subclassification. Vascular biomarkers of endothelin-1, ADMA, and low ocular perfusion pressure supports a vascular dysregulation phenotype, whereas oxidative and mitochondrial markers of 8-OHdG, malondialdehyde, reduced antioxidant capacity and changed mitochondrial indices support a metabolically vulnerable subgroup. Emerging multi-omics signatures of metabolomic proteomic, miRNA, extracellular-vesicle, and epigenetic signatures also strengthens this notion of precision phenotyping.

Clinical Implications

The broader clinical impact is a move away from IOP-guided approaches to biomarker-directed personalized neuroprotection. Genetic testing and polygenic risk scores may aid targeting those in whom screening and monitoring are indicated earlier. Biomarker panels may help with endophenotype classification, targeting adjunctive therapy (particularly anti-inflammatory, vasomodulatory, antioxidant, or gene-directed ones). Repeated biomarker assessment may help adapt treatment over time rather than relying purely on structural and functional loss already evident when treatment is delivered. Meanwhile, biomarker-based trial enrichment may enable more efficient and interpretable studies of neuroprotection going forward.

Research Priorities

The next steps are prospective validation and standardization. Large multicenter cohorts will be critical to confirming which biomarker panels are truly useful for diagnosis, prognosis, and treatment response, and protocols for sample collection, analysis, quality control, and reporting, need to be agreed upon before cross-platform implementation will be reliable. Biomarker-enriched clinical trials with adaptive designs will be needed to test whether mechanism-matched neuroprotection improves outcomes in defined patient subsets. Lastly, implementation science will be required to determine how and for which patients biomarker testing can be incorporated into routine glaucoma care in a cost-effective and clinically usable way.

The Road Ahead

The future of glaucoma management will likely lie in the marriage of multi-omics, remote monitoring, wearable devices, and AI decision support. In that model, glaucoma care would progress to a true theragnostic

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model in which biomarkers define disease mechanism, guide customized neuroprotective therapy, and return real-time feedback on treatment effect. Such a vision must be equitable in access to populations and healthcare settings; if not, precision medicine may ultimately benefit only a handful of patients. The end goal is not a better ability to predict progression, but rather, one that allows intervention earlier in the serial course against the specific biological processes that are driving optic nerve degeneration in that individual patient.

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