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Review: Transcriptomic profiling of the optic nerve head and optic nerve proper in healthy and glaucomatous eyes: A scoping review

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Glaucoma, a progressive optic neuropathy characterized by progressive degeneration of retinal ganglion cells and their axons, is a leading cause of blindness worldwide. Early injury is thought to occur at the optic nerve head (ONH), though the entirety of the optic nerve is eventually affected. This scoping review synthesizes transcriptomic studies of the ONH and optic nerve proper (ONP) in healthy and glaucomatous eyes. Our search identified 15 studies using RNA sequencing approaches across human, nonhuman primate (NHP), and other animal models. Across studies, several consistent molecular themes emerged. Glial activation, particularly involving astrocytes and microglia, was a dominant feature, with upregulation of inflammatory, cytoskeletal, and extracellular matrix–related genes. Mechanosensitive signaling pathways were also prominently altered, reflecting the sensitivity of the ONH to intraocular pressure–induced stress. Temporal analyses suggested an early phase of glial and inflammatory responses, followed by later transcriptional signatures of axonal dysfunction within the ONP. Emerging evidence also highlights spatial and cell-type–specific heterogeneity within the ONH. Overall, the data support a model in which glaucomatous injury begins at the ONH and progresses to axonal degeneration within the ONP. However, the literature remains limited by methodological heterogeneity, limited studies in humans and NHPs, and reliance on bulk sequencing rather than more advanced transcriptomic techniques. Future studies using spatially resolved and/or single-cell approaches, particularly in human tissue, are needed to refine our mechanistic understanding and identify therapeutic targets.

Glaucoma is the leading cause of irreversible blindness worldwide and is characterized by progressive degeneration of retinal ganglion cells and their axons, resulting in optic nerve damage and visual field loss [1]. Although elevated intraocular pressure (IOP) is the most significant modifiable risk factor, the pathogenesis of glaucoma is complex and multifactorial. A growing body of evidence suggests that the initial site of injury is the optic nerve head (ONH), where retinal ganglion cell axons exit the eye and are exposed to biomechanical and metabolic stress [2-4]. The optic nerve proper (ONP), which contains the myelinated portions of these axons, is believed to subsequently undergo degenerative changes that reflect both primary injury at the ONH and secondary propagation of disease processes.

The ONH is a structurally and biologically complex region composed of astrocytes, microglia, vascular elements, and extracellular matrix (ECM) components that together maintain its biomechanical integrity. In response to elevated IOP and other stressors, this microenvironment undergoes significant structural and molecular remodeling. Astrocytes adopt reactive phenotypes characterized by cytoskeletal reorganization and altered gene expression, while microglia exhibit activation patterns consistent with neuroinflammatory signaling [5,6]. Concurrently, ECM remodeling—including changes in collagen composition and matrix metalloproteinase activity—alters the mechanical properties of the ONH and may further exacerbate axonal stress [3,7]. These findings highlight the close interplay between biomechanical and molecular mechanisms in glaucomatous injury.

Advances in transcriptomic technologies have enabled increasingly detailed characterization of these molecular changes. Early studies employing gene expression profiling identified broad alterations in pathways related to inflammation, stress response, and ECM remodeling, while more recent RNA sequencing approaches have provided higher-resolution insights into cell-type–specific responses and cellular heterogeneity within the ONH and ONP [2,6]. These studies have revealed dynamic transcriptional processes involving glial activation, immune signaling, and disruption of axonal homeostasis. However, the literature remains heterogeneous, with variability in experimental models, tissue

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sources, and analytical platforms complicating synthesis and interpretation.

While most prior research in glaucoma transcriptomics has been focused on the retina [8-11], there is an expanding body of literature focused on the transcriptomic profile of the ONH and ONP in glaucomatous eyes. Given how critical these sites are to the pathophysiology of glaucoma, a thorough review of these ONH- and ONP-focused studies is warranted. Accordingly, the purpose of this scoping review is to thoroughly evaluate and integrate the existing literature on ONH and ONP transcriptomics in healthy and glaucomatous eyes, with the goals of identifying consistent molecular pathways and cellular responses, characterizing regional and cell-type–specific heterogeneity, and highlighting key gaps to guide future research.

METHODS

The protocol for this review was preregistered on Open Science Framework. Three databases (PubMed, Web of Science, and Embase) were searched using search strings customized for the syntax of each platform. The full search strings used for each database are available in Appendix 1. Briefly, each search string was broken into three sections: the first specifying the anatomic regions of interest (ONH and ONP), the second detailing the analytical methods of interest (bulk RNA sequencing, single-cell RNA sequencing, single-nucleus RNA sequencing, and spatial transcriptomics), and the third stipulating the disease states of interest (healthy eyes, glaucomatous eyes, and/or eyes with ocular hypertension). Of note, analytical methods that did not involve direct RNA sequencing but rather relied on other, indirect methods of quantifying gene expression (i.e., microarray) were not included in this review.

Query of each database occurred on November 14, 2025. Duplicate articles were removed after downloading search results from all databases. Subsequently, a title and abstract screening process was conducted by authors JL and SP. Articles were screened according to a preset list of criteria reported in Appendix 2, with requirements stipulating that articles passing this phase of review present novel, primary research (i.e., not be a reanalysis of previously reported datasets, a methods paper, or a review paper), be written in English or have an English translation available, and include direct RNA sequencing of the ONH and/or ONP (not simply the retinal ganglion cell bodies, which reside in the retina). Disagreements between reviewers were settled by discussion. All passing articles were then advanced to full-text review, in which the same criteria were applied to the body of each paper. If a paper passed full-text review, it was deemed suitable for inclusion in this review. The reference sections of all papers deemed suitable for inclusion were scrutinized for additional articles that may meet inclusion criteria but were not uncovered in the authors' initial database search.

RESULTS

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses for scoping reviews flow diagram shown in Figure 1 illustrates the process by which the original 312 database search results were winnowed to the 15 manuscripts ultimately qualifying for inclusion in this review. A study characteristics table (Appendix 3) has been compiled to summarize the relevant components of each included manuscript.

Across the 15 studies included in this review, a combination of bulk RNA sequencing (n = 13) [2,6,12-22], single-nucleus RNA sequencing (n = 1) [23], and spatial transcriptomics (n = 1) [24] were employed. No included papers used single-cell RNA sequencing. Two papers [23,24] were conducted in human eyes, one in a nonhuman primate model [15], one in a feline model [12], two in rats [14,19], and nine in mice [2,6,13,16-18,20-22]. Sample size ranged from 2 [15] to 60 eyes [14], with several studies not explicitly stating the number of eyes from which their tissues or cell cultures were derived. Ten studies reported solely on the ONH, one solely on the ONP, and four on both regions. Six studies reported only on the transcriptomic profiles of ONH or ONP astrocytes [2,13,17,18,21,24], one on only monocytes, one on only microglia [6], and six on a mixture of two or more cell types [12,14,15,19,20,22,23].

DISCUSSION

Methodological approaches and experimental models: While the variegated technical approaches employed by the studies included in this review have enabled interrogation of the ONH and ONP transcriptome across different anatomic scales and disease stages, they have also complicated direct cross-study comparisons. Additionally, the paucity of nonbulk RNA sequencing analyses reported in the literature suggests the need for more localized investigation of transcriptional responses to glaucoma in the future.

The transcriptomic profiling of the ONH and ONP in both healthy and glaucomatous states has been investigated across a diverse array of experimental systems, including human donor tissue, nonhuman primates, and rodent models of ocular hypertension. Animal models, particularly murine and primate systems, have been instrumental in enabling controlled investigation of IOP-induced injury and temporal

transcriptional dynamics [6,14,16]. However, the fact that most included studies (11 of 15) were performed in rodents, which are known to lack a collagenous lamina cribrosa [25], calls into question the applicability of these results to human disease. In contrast, human studies, while fewer in number, provide critical validation of disease-relevant pathways in native tissue, albeit often limited to advanced glaucomatous stages [23,24]. Importantly, technical challenges—including variability in tissue dissection and the difficulty of isolating pure ONH samples without retinal or scleral contamination—remain pervasive limitations across studies [23]. Despite these challenges, the convergence of findings across platforms and species supports the robustness of several key biological themes.

Glial activation and neuroinflammatory signatures: A central and highly reproducible finding across studies is

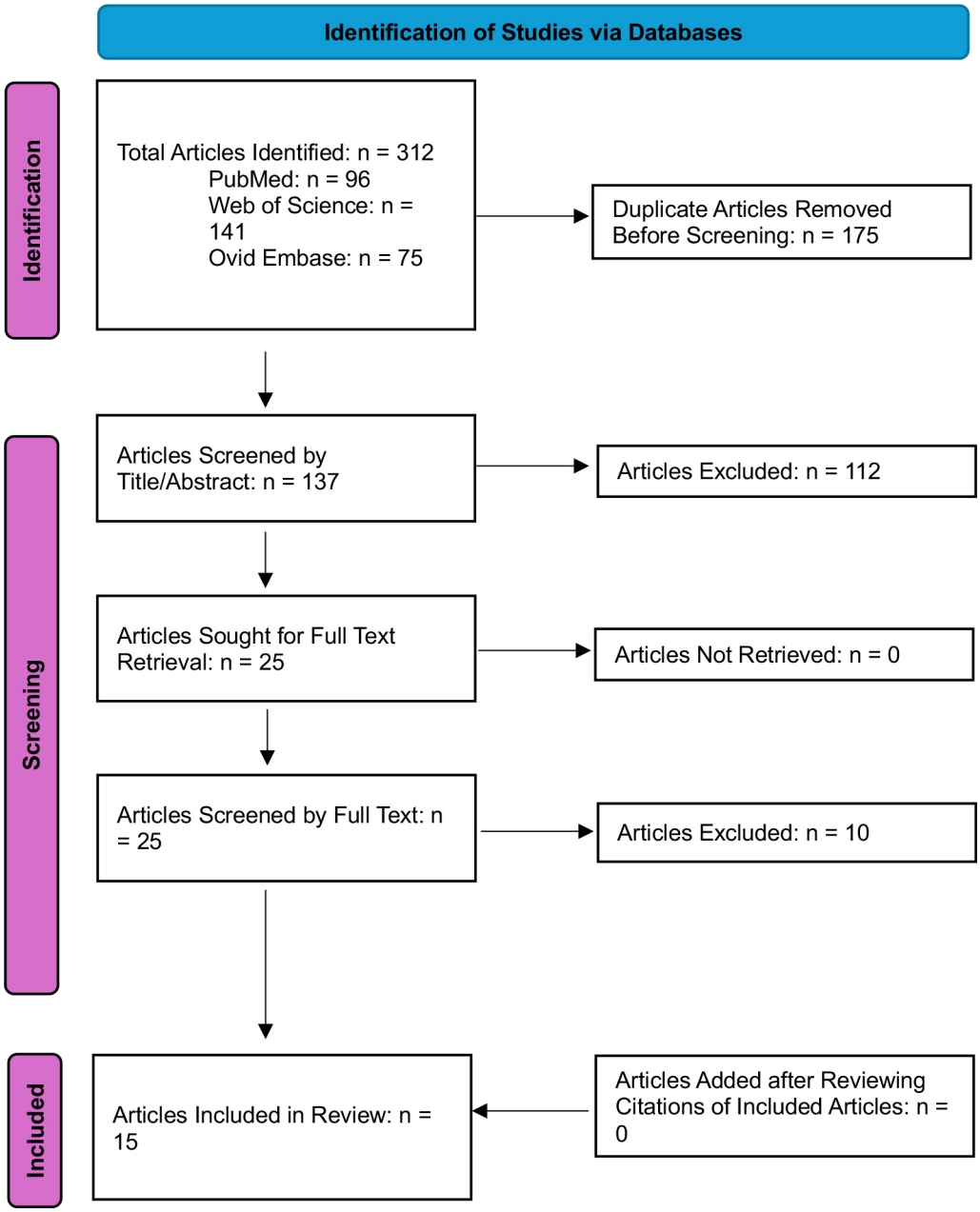


Figure 1. PRISMA-ScR flow diagram depicting the article review process. Preferred reporting items for systematic reviews and meta-analyses for scoping reviews diagram depicting article review process.

the dominant role of glial cells—particularly astrocytes and microglia—in mediating the ONH response to glaucomatous stress. Astrocytes exhibit robust transcriptional reprogramming characterized by upregulation of cytoskeletal components, ECM-associated genes, and calcium-binding proteins such as members of the S100 family [12,13,17]. These changes are consistent with a reactive phenotype reflecting both structural remodeling and mechanosensitivity. Notably, astrocytic responses are spatially heterogeneous, with distinct transcriptional profiles observed across prelaminar, laminar, and retrolaminar regions of the ONH [12,21], suggesting that local biomechanical environments shape glial behavior.

Microglial activation represents a complementary and equally consistent feature of the glaucomatous transcriptome. Multiple studies report upregulation of genes associated with innate immune signaling, including proinflammatory cytokines and complement cascade components [15,16,20]. Importantly, microglial activation is frequently observed at early time points following IOP elevation, in some cases preceding overt axonal degeneration [6,16], suggesting a potential role in initiating or amplifying injury cascades. However, the functional role of microglia appears to be context-dependent, with evidence supporting both neuroprotective and neurotoxic effects, depending on disease stage and activation state [15].

Together, these findings support a model in which glial cells are not merely passive responders but active participants in the early pathogenesis of glaucoma, integrating mechanical stress signals and orchestrating downstream inflammatory and structural responses.

Extracellular matrix remodeling and mechanotransduction: Extracellular matrix remodeling is a prominent and unifying feature of the ONH transcriptomic response to elevated IOP. Multiple studies demonstrate increased expression of collagen isoforms, matrix metalloproteinases, and tissue inhibitors of metalloproteinases, along with activation of transforming growth factor β signaling pathways [14,19,20]. These transcriptional changes are suggestive of a fibrotic remodeling process that alters the structural and biomechanical properties of the ONH.

The interplay between ECM remodeling and mechanotransduction is particularly noteworthy. The ONH is a biomechanically sensitive structure, and transcriptional responses to IOP elevation appear to reflect both the direct effects of mechanical strain and secondary alterations in tissue stiffness and architecture [18,19]. Astrocytes in particular are thought to play a central role in sensing and responding to these mechanical cues [12,18], further linking glial activation to ECM dynamics. This convergence of structural and molecular changes supports the conceptualization of glaucoma as a disease in which mechanical and biologic processes are tightly coupled.

Axonal degeneration, temporal dynamics, and spatial heterogeneity: While early transcriptomic changes in glaucoma are dominated by glial activation and ECM remodeling, later stages of disease are characterized by transcriptional signatures indicative of axonal dysfunction and degeneration within the optic nerve. Studies examining optic nerve tissue report downregulation of genes involved in axonal transport, cytoskeletal organization, and mitochondrial function, as well as alterations in oligodendrocyte-associated transcripts [6,22]. These findings support a model in which axonal injury is a downstream consequence of earlier ONH pathology, mediated in part by disrupted axon–glia interactions and metabolic support.

Temporal analyses further refine this framework by delineating a sequence of molecular events following IOP elevation. Acute models demonstrate rapid induction of stress response pathways, followed by sustained glial activation and ECM remodeling [6,14]. In some cases, early transcriptional changes are partially reversible upon normalization of IOP [24], suggesting the presence of a therapeutic window during which intervention may prevent irreversible damage. In contrast, chronic models exhibit persistent inflammatory signaling and widespread dysregulation of neuronal maintenance pathways [22,23].

An important insight emerging from recent studies is the extent of spatial heterogeneity within the ONH. Regional analyses have identified distinct transcriptional profiles along the anterior–posterior axis, including the prelaminar, laminar, and retrolaminar compartments [12]. However, more granular spatial mapping—such as quadrant- or clock-hour–based analyses—remains largely unexplored and represents an important direction for future research.

Limitations: The heavy skewing of the available literature (n = 15) toward mouse-based studies (n = 9), rather than studies employing other animal models, limits the generalizability of the trends reported in this scoping review in nonmurine contexts. Likewise, the high interstudy variability in sample size, the unbalanced numbers of studies examining the ONH versus the ONP, the tendency of studies to focus on astrocytes at the expense of other cell types, and the heavy preponderance of studies relying on bulk sequencing (n = 13) as opposed to other, higher-resolution RNA sequencing techniques all weaken the strength and scope of the conclusions able to be drawn from the aggregate data.

Conclusion: Taken together, the available transcriptomic evidence supports a model in which glaucomatous injury

is initiated at the level of the ONH through mechanically induced astrocyte activation and ECM remodeling, followed by recruitment of microglia and activation of inflammatory pathways, ultimately culminating in axonal degeneration within the ONP. However, it must be noted that this proposed temporal sequence is based on the synthesis of data from multiple studies and thus remains hypothetical, with further research being warranted to clarify the exact timeline of events in the injured optic nerve. Regardless, this integrated framework highlights the ONH as the primary site of early molecular dysfunction and underscores the importance of glial and mechanotransductive pathways in disease pathogenesis. Additionally, it underscores the utility of detecting glaucoma as early as possible, when transcriptomic alterations may be reversible [24].

Despite significant advances, key limitations remain, including small sample sizes, variability in tissue processing, sparse analysis of the ONP and nonastrocyte cell types, and limited localized transcriptomic analyses by ONH and ONP subregion. Furthermore, while animal models have provided critical mechanistic insights, continued validation in human tissue is essential to ensure translational relevance, as most of the animal findings reported in the literature have not yet been replicated in human tissues. Future studies leveraging larger cohorts, single-cell and/or spatial transcriptomics, and integrative multiomics approaches—particularly those that target diverse populations of cells within both the ONP and the ONH—will be essential for refining our understanding of glaucomatous neurodegeneration and identifying novel therapeutic targets.

APPENDIX 1. DATABASE SEARCH TERMS.

To access the data, click or select the words "Appendix 1."

APPENDIX 2. REVIEW PROTOCOL.

To access the data, click or select the words "Appendix 2."

APPENDIX 3. TABLE CONTAINING RELEVANT CHARACTERISTICS OF INCLUDED STUDIES.

To access the data, click or select the words "Appendix 3."

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