• Review Article •

# Enzymatic glycosylation as a potential molecular link between Alzheimer's disease and glaucoma

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## Abstract

● Alzheimer's disease (AD) and glaucoma are prevalent age-related neurodegenerative disorders affecting the brain and the eye, respectively. Despite their distinct clinical manifestations, both conditions share convergent pathological features, including neuronal loss, neuroinflammation, and metabolic stress, suggesting common upstream regulatory mechanisms. Protein glycosylation, a fundamental post-translational modification, has emerged as a key modulator of neuronal survival, protein aggregation, and inflammatory signaling in neurodegenerative diseases. In this review, we summarize recent advances in enzymatic glycosylation that are mechanistically relevant to both AD and glaucoma, with particular emphasis on N-linked glycosylation (N-glycosylation) and O-linked β-N-acetylglucosaminylation (O-GlcNAcylation). We focus on key enzymes, including O-GlcNAc transferase (OGT), O-GlcNAcase (OGA), and N-acetylglucosaminyltransferase III (GnT-III), and describe their roles in regulating neuronal viability, microglial activation, trabecular meshwork function, and retinal ganglion cell (RGC) survival. Integrating evidence from cerebral and ocular systems, we propose two glycosylation-dependent regulatory axes: the OGT/OGA–O-GlcNAc axis as an upstream metabolic and stress sensor, and the GnT-III–bisecting GlcNAc–intercellular adhesion molecule-1 (ICAM-1) axis as a downstream modulator of neuroinflammatory cell–cell interactions. We discuss the potential of glycosylation signatures as biomarkers in cerebrospinal fluid, plasma, and aqueous humor, and the feasibility of enzyme-targeted modulation as a therapeutic strategy. Collectively, this enzyme-centered framework provides a conceptual and regulatory perspective on potential links between AD and glaucoma, highlighting opportunities for translational research while acknowledging current evidence gaps that warrant further investigation.

● **KEYWORDS:** Alzheimer's disease; glaucoma; neuroinflammation; glycosylation; glycosyltransferase
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## INTRODUCTION

Alzheimer's disease (AD) and glaucoma are widely acknowledged as the most prevalent age-associated neurodegenerative disorders that affect millions of people worldwide[1]. In 2003, glaucoma has been described as ocular AD by McKinnon[2], emphasizing that both conditions share pathological features such as neuronal apoptosis, inflammation, and metabolic imbalance. Clinical evidence supports this connection: patients with glaucoma have a higher risk of developing AD[3-4] while individuals with AD show an increased prevalence of glaucoma[5-6]. Despite their distinct clinical manifestations, both diseases are characterized by progressive and irreversible neuronal degeneration. These convergent pathological features suggest the involvement of shared upstream regulatory mechanisms driving neurodegeneration in both the brain and the eye[7]. However, the molecular mechanisms underlying this clinical and pathological association remain poorly defined.

Protein glycosylation is a fundamental post-translational modification that critically regulates protein stability, trafficking, and signaling pathways implicated in neurodegeneration[8]. This process is tightly controlled by specific glycosylation enzymes whose dysregulation can profoundly alter cellular homeostasis[9-10]. Among these modifications, N-linked glycosylation (N-glycosylation) and O-linked β-N-acetylglucosaminylation (O-GlcNAcylation) have emerged as key regulators of neuronal survival, protein aggregation, and inflammatory signaling[11].

Aberrant glycosylation has been increasingly implicated in the pathogenesis of both AD and glaucoma, influencing multiple disease-relevant cellular processes. In AD, aberrant glycosylation enhances microglial inflammation, accelerates amyloid-β (Aβ) aggregation, and promotes neuronal injury[12]. In glaucoma, transcriptomic studies have revealed extensive dysregulation of glycogens in ocular tissues, particularly within the trabecular meshwork (TM), suggesting that glycosylation-related pathways are perturbed early in the disease[13]. While these alterations have traditionally been linked to aqueous humor outflow and intraocular pressure regulation, emerging evidence indicates that glycosylation-dependent regulation of the extracellular matrix (ECM) remodeling, neurotrophic signaling, and local immune responses may also shape a pro-degenerative retinal microenvironment relevant to retinal ganglion cell (RGC) vulnerability and neuroinflammation[14-15]. In this review, we summarize recent advances in enzymatic glycosylation that are mechanistically relevant to both AD and glaucoma, with particular emphasis on N-glycosylation and O-GlcNAcylation. We focus on key enzymes, including O-GlcNAc transferase (OGT), O-GlcNAcase (OGA), and N-acetylglucosaminyltransferase III (GnT-III), and their roles in regulating neuronal survival, microglial activation, and RGC degeneration. Integrating evidence from cerebral and ocular systems, we propose two glycosylation-dependent regulatory axes as shared regulatory frameworks that may contribute to overlapping pathogenic processes in AD and glaucoma, as summarized in Figure 1.

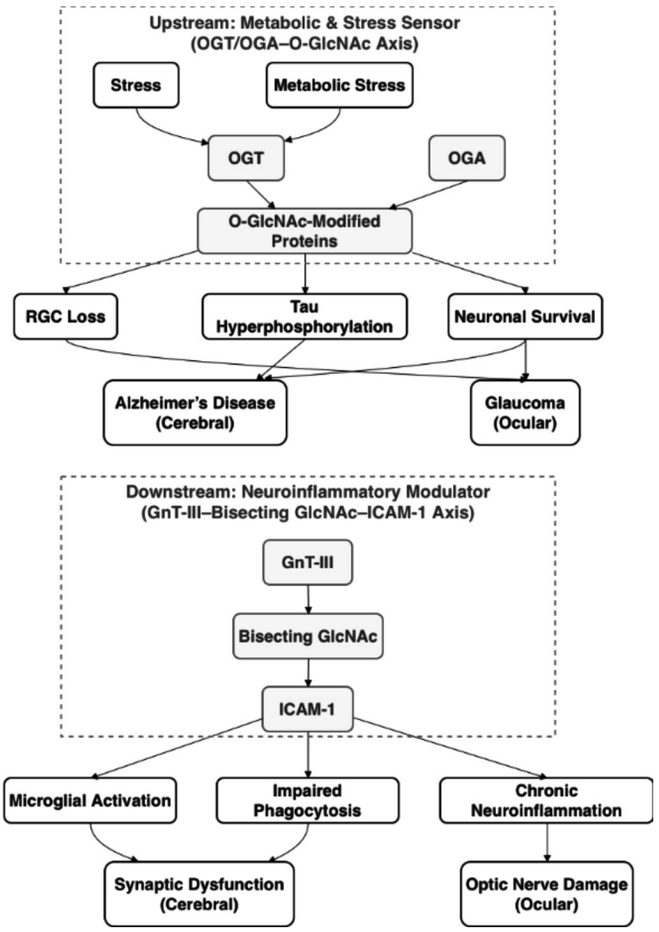


**Figure 1 Glycosylation-dependent regulatory axes: a molecular bridge in neurodegeneration** GlcNAc: N-acetylglucosamine; GnT-III: N-acetylglucosaminyltransferase III; ICAM-1: Intercellular Adhesion Molecule-1; OGA: O-GlcNAcase; OGT: O-GlcNAc transferase; RGC: Retinal ganglion cell.

## OVERVIEW OF ENZYMATIC GLYCOSYLATION

Glycosylation is a fundamental post-translational modification that affects almost all proteins and lipids in eukaryotic cells[16]. By modulating protein folding, receptor-ligand interactions, and immune recognition, glycosylation acts as an upstream regulator of cellular signaling pathways implicated in neurodegenerative diseases[17]. Within the central and peripheral nervous systems, glycan moieties sculpt neurite outgrowth, synaptic plasticity, and action-potential propagation[18]. The process is tightly controlled by enzymes located in the endoplasmic reticulum (ER) and Golgi apparatus whose dysregulation can profoundly alter neuronal and glial cell function[19].

**Major Types of Protein Glycosylation** Among the diverse forms of protein glycosylation, N-glycosylation and O-linked glycosylation are particularly relevant to neurodegenerative processes in both AD and glaucoma[20]. N-glycosylation begins in the ER, where a preassembled oligosaccharide is transferred to the asparagine residue of a nascent protein[21]. Subsequent remodeling in the Golgi apparatus by glycosyltransferases, including N-acetylglucosaminyltransferases (GnTs), generates complex N-glycan structures that modulate protein-protein interactions and inflammatory signaling[22]. Classical O-glycosylation occurs mainly in the Golgi apparatus and modifies serine or threonine residues, thereby influencing protein stability and extracellular interactions[23]. The polypeptide N-acetylgalactosaminyltransferase (GALNT) family of enzymes initiates this process, while elongation and modification generate diverse O-glycan structures[24]. Distinct from classical O-glycosylation, O-GlcNAcylation represents a dynamic intracellular modification critically involved in neurodegenerative disease mechanisms[25]. This reversible modification, mediated by OGT and OGA, functions as

a cellular nutrient and stress sensor that directly regulates neuronal resilience and survival[26].

**Biological Roles Across Tissues and Systems** Glycosylation exerts pleiotropic effects across tissues by regulating protein stability and intercellular communication[16]. It influences protein stability and secretion[27], modulates receptor trafficking[28], and affects the assembly of ECM[29]. In immune and vascular cells, surface glycans regulate recognition and activation, while in vascular endothelium they maintain barrier integrity and control leukocyte adhesion[30], thereby shaping neuroinflammatory and vascular responses shared by AD and glaucoma. In the central nervous system (CNS), specific glycan patterns are essential for neural development and repair[31]. Such abnormal glycosylation patterns are increasingly linked to the pathogenesis of both AD and glaucoma[32-33].

**Advances in Glycomics and Glycoproteomics Analysis** Recent advances in glycomics and glycoproteomics have enabled deeper analysis of these processes[34]. Technologies such as mass spectrometry and lectin microarrays now permit large-scale profiling of glycan structures and glycosylation enzyme activity in neurodegenerative disease contexts[35]. These approaches provide critical insights into how enzymatic glycosylation modulates cell signaling, inflammation, and neuronal degeneration in both the brain and the eye[16]. Understanding these glycosylation pathways therefore offers a mechanistic foundation for identifying cross-disease biomarkers and therapeutic targets linking AD and glaucoma.

## MECHANISTIC ROLES OF GLYCOSYLATION IN AD

Aberrant enzymatic glycosylation is increasingly recognized as an upstream regulator of AD pathogenesis rather than a secondary consequence of neurodegeneration[36]. Disease-associated alterations in glycan structure directly affect protein folding, intracellular trafficking, and receptor signaling, thereby modulating amyloid precursor protein processing, tau post-translational modification, microglial activation, and synaptic integrity[37]. In AD, these glycosylation-driven processes are primarily mediated through two regulatory axes: the OGT/OGA–O-GlcNAc axis and GnT-III–dependent inflammatory modulation.

**Regulation of Amyloid-β Metabolism and Aggregation** Enzymatic glycosylation directly regulates Aβ metabolism by controlling the processing efficiency and subcellular localization of amyloidogenic enzymes, including the heavily N-glycosylated β-site amyloid precursor protein-cleaving enzyme 1 (BACE1) and nicastrin[38]. Alterations in their N-glycan composition modulate protein stability, endosomal trafficking, and enzymatic activity, resulting in enhanced amyloidogenic amyloid precursor protein cleavage and increased Aβ production[39]. Additional studies have documented that aberrant glycosylation of molecular chaperones and transport receptors impairs Aβ clearance and accelerates extracellular plaque assembly[37,40-41].

**Control of Tau Protein Phosphorylation** O-GlcNAcylation serves as a critical enzymatic regulator of tau phosphorylation status and aggregation propensity[42]. O-GlcNAc and phosphorylation often compete for the same serine or threonine residues on tau protein[43]. Reduced O-GlcNAcylation disrupts this balance, facilitates tau hyperphosphorylation, and accelerates neurofibrillary tangle formation[44]. Increasing O-GlcNAc levels through OGA inhibition decreases tau aggregation and improves neuronal survival in experimental models[45]. Such evidence supports that maintaining O-GlcNAc balance may prevent abnormal tau-driven neurotoxicity.

**Microglial Inflammatory Responses and Neurodegeneration** Microglia, the resident innate immune cells of CNS, undergo glycosylation-dependent functional reprogramming during AD progression, linking aberrant glycan processing to chronic neuroinflammation[46]. Glycosylation modulates both the inflammatory repertoire and the phagocytic/migratory capacity of microglia[20]. Dysregulated expression of GnT-III induces aberrant bisecting GlcNAc modification of intercellular adhesion molecule-1 (ICAM-1), impairing microglial phagocytosis and motility and accelerating AD pathology[39,47].

Notably, these glycosylation-dependent mechanisms directly affect neuronal viability and immune-neuronal interactions, providing a mechanistic framework that conceptually links glycosylation-dependent neuronal and inflammatory regulation in AD to RGC vulnerability in glaucoma.

## MECHANISTIC ROLES OF GLYCOSYLATION IN GLAUCOMA

In contrast to AD, where glycosylation-dependent mechanisms have been characterized primarily at the level of neuronal proteins, glaucoma research has focused largely on ocular tissues and the retinal microenvironment. However, accumulating evidence indicates that glaucoma-related metabolic and mechanical stressors may converge on the same glycosylation-dependent regulatory axes—namely, O-GlcNAc–mediated stress sensing and GnT-III–regulated inflammatory adhesion—thereby indirectly governing RGC vulnerability. Notably, while these pathways are well characterized in other neurodegenerative contexts, direct experimental interrogation of OGT/OGA-mediated O-GlcNAc signaling specifically within RGCs under glaucomatous conditions remains limited, highlighting an important gap for future investigation.

**Glycosylation-Dependent Trabecular Meshwork Dysfunction and ECM Remodeling** Diskin *et al*[13] reported that dysregulated glycogen expression in TM represents an early molecular event in glaucoma with effects beyond

intraocular pressure (IOP). Altered glycosyltransferase and glycosidase activity modifies TM protein glycosylation, disrupting ECM organization, cell adhesion, and mechanotransduction[48]. These changes increase outflow resistance and promote chronic stress, inflammation, and vascular dysfunction[49], which may secondarily impair RGC homeostasis by altering neurotrophic support and amplifying inflammatory and ischemic signaling. Such chronic metabolic and inflammatory stressors represent plausible upstream inputs capable of perturbing O-GlcNAc–mediated stress sensing and downstream glycosylation-dependent inflammatory signaling in retinal and glial cells.

**Glycosylation-Associated Retinal Ganglion Cell Neurodegeneration** Although direct evidence for glycosylation changes within RGCs remains limited, glycosylation-associated pathways appear to critically influence RGC vulnerability and degeneration. Glycosylated neuronal proteins, including L1 and Nell2, are essential for axonal guidance and survival, while extracellular glycoproteins such as osteopontin modulate supportive glial cells, contributing to age-related RGC loss[50-52]. Altered glycosylation also affects neurotrophic and survival signaling, with wingless-type MMTV integration site family (WNT) and insulin-like growth factor 1 receptor (IGF1R) pathways implicated in glaucomatous neurodegeneration[53-54]. Beyond enzymatic glycosylation, metabolic stress and non-enzymatic glycation, particularly in diabetes, further exacerbate RGC loss[55]. Collectively, these findings highlight that RGCs are highly sensitive to disruptions in glycosylation-related processes, primarily *via* effects on neuroprotective signaling and the retinal microenvironment rather than direct cell-autonomous mechanisms. Although these mechanisms differ from the tau- and amyloid-centered pathways in AD, glycosylation-dependent modulation of neurotrophic and survival signaling in RGCs represents a functional parallel at the level of neuronal vulnerability.

**Glycosylation-Controlled Neuroinflammation and Complement Activation** In glaucoma, altered glycosylation in TM and surrounding retinal tissue shapes a pro-inflammatory microenvironment that indirectly compromises RGC survival[56]. Dysregulated glycosylation modulates microglial activation and immune signaling, promoting excessive synaptic pruning and inflammatory damage[57]. In parallel, glycosylation of complement components, such as C1q, can enhance complement activation, further exacerbating RGC injury[58]. Together, these glycosylation-driven immune and complement alterations highlight an indirect, microenvironment-mediated mechanism linking local molecular changes to glaucomatous neurodegeneration[56]. Importantly, these inflammatory processes involve adhesion molecules and complement components whose function is known to be tightly regulated by glycosylation, supporting a potential role for the GnT-III-bisecting GlcNAc–ICAM-1 axis in shaping immune-retinal interactions in glaucoma, analogous to its role in AD.

**Convergence of Glycosylation-Mediated Pathways: Bridging Glaucomatous Neurodegeneration and AD** Collectively, glaucoma-related changes in TM and retinal microenvironment induce chronic metabolic and inflammatory stress, which may converge on glycosylation-dependent regulatory pathways shared with AD. Perturbation of the OGT/OGA–O-GlcNAc axis is likely to affect stress-responsive inflammatory signaling. Meanwhile, downstream modulation of adhesion molecules and immune interactions *via* GnT-III-mediated bisecting GlcNAc modifications could amplify neuroinflammation, indirectly impairing the survival of RGCs.

## SHARED MECHANISMS: HOW GLYCOSYLATION CAN BRIDGE AD AND GLAUCOMA

**Clinical and Epidemiological Evidence** AD and glaucoma, while traditionally considered distinct neurodegenerative disorders affecting the brain and eye, exhibit significant clinical and pathological overlap[59-60]. Epidemiological studies show that glaucoma patients have a higher risk of developing AD[3], while AD cohorts display increased glaucoma prevalence[61-62]. Neuroimaging and biochemical analyses reveal neuronal loss, neuroinflammation, and atrophy in both diseases, indicating common molecular mechanisms involving glycosylation abnormalities[63]. Together, these observations provide a strong clinical rationale for exploring shared upstream molecular mechanisms, among which dysregulated glycosylation has emerged as a compelling candidate.

**OGT/OGA–O-GlcNAc Axis as a Shared Metabolic and Stress-Sensing Regulator** Across both CNS and the retina, the OGT/OGA–O-GlcNAc axis is increasingly recognized as a conserved metabolic and stress-responsive regulatory axis that links cellular energy status to inflammatory and survival signaling[64]. In AD, reduced O-GlcNAcylation directly enhances tau hyperphosphorylation and disrupts neuronal stress resilience, while also modulating microglial inflammatory activation[64-65]. In glaucoma, although direct manipulation of O-GlcNAcylation in RGCs has been less extensively characterized, chronic mechanical, metabolic, and oxidative stress within TM and retinal microenvironment represents a plausible upstream stress context that may converge on O-GlcNAc-dependent signaling pathways in retinal neurons and glia[66-67]. Thus, dysregulation of the OGT/OGA–O-GlcNAc axis suggests a unifying conceptual framework through which systemic and local stressors may promote neurodegeneration in both the brain and the eye[64,66].

**GnT-III–bisecting GlcNAc–ICAM-1 Axis as a Shared Inflammatory Effector Pathway** Beyond metabolic sensing, glycosylation also governs inflammatory cell–cell interactions through specific N-glycan modifications. In AD, dysregulated expression of GnT-III promotes aberrant bisecting GlcNAc modification of ICAM-1, impairing microglial migration and phagocytic function and thereby amplifying chronic neuroinflammation[47]. In glaucoma, immune activation within TM and retina similarly depends on adhesion molecules, complement components, and glial-immune interactions whose activity is tightly regulated by glycosylation[56,58]. Although direct evidence for GnT-III–ICAM-1 dysregulation in glaucoma remains limited, the shared dependence of neuroinflammatory signaling on glycosylation-sensitive adhesion pathways supports this axis as a common downstream effector linking immune-mediated neuronal injury in both diseases[56].

**Shared Mechanisms of Neuronal and Retinal Ganglion Cell Degeneration** In AD, dysregulated O-GlcNAc cycling mediated by OGT and OGA directly modulates tau phosphorylation, mitochondrial stress responses, and neuronal apoptotic vulnerability[68-69], while aberrant N-glycan branching by enzymes such as GnT-III alters adhesion molecules including ICAM-1, impairing microglial migration and phagocytic clearance and thereby sustaining chronic neuroinflammation[47]. Although direct interrogation of these glycosylation pathways in RGC remains limited[70], the convergence of metabolic stress, mitochondrial dysfunction, and immune activation in glaucoma supports the existence of analogous glycosylation-sensitive mechanisms governing RGC vulnerability[71-72], positioning glycosylation-regulated signaling nodes as a plausible mechanistic bridge between neuronal degeneration in AD and RGC loss in glaucoma. Based on the current evidence, the major glycosylation-related enzymes/modifications, their pathological roles, biomarker sources, therapeutic strategies, and levels of evidence in AD and glaucoma are summarized in Table 1.

## TRANSLATIONAL PROSPECTS OF GLYCOSYLATION RESEARCH

If glycosylation-dependent signaling axes indeed represent a shared mechanistic bridge between AD and glaucoma, an important next question is whether these pathways can be leveraged for translational applications, including biomarker development and targeted intervention.

**Biomarker Potential: Glycosylation Signatures in Blood, Cerebrospinal Fluid, and Aqueous Humor** Recent advances in glycomics and metabolomics have increasingly drawn attention to glycosylation as a potential biomarker for neurodegenerative diseases[73]. Abnormal glycosylation patterns have been reported in the brain tissue and cerebrospinal

**Table 1 Summary of glycosylation-related enzymes/modifications, pathological mechanisms, biomarker potential, and therapeutic strategies in Alzheimer's disease and glaucoma**

| Glycosylation enzyme/modification | Disease | Primary cell type/tissue | Key pathological role | Biomarker source | Therapeutic strategy | Evidence level | References |
|---|---|---|---|---|---|---|---|
| OGT/OGA (O-GlcNAcylation) | AD | Neurons; microglia | Tau hyperphosphorylation, neuronal stress vulnerability, neuroinflammation | Brain tissue; CSF | Modulation of O-GlcNAc balance | Strong | [42–45, 64–65, 68–69, 73–75] |
| GnT-III (bisecting GlcNAc N-glycosylation) | AD | Microglia; neurons | ICAM-1–mediated microglial dysfunction, amyloid accumulation | Brain tissue; CSF | GnT-III inhibition | Moderate–strong | [39, 47, 74–75, 82] |
| OGT/OGA (O-GlcNAcylation) | Glaucoma | RGCs (putative); glia; TM | Stress-responsive signaling, RGC vulnerability | Aqueous humor (potential) | Targeting metabolic stress pathways | Limited/emerging | [64, 66–67, 77–78] |
| GnT-III–regulated N-glycosylation | Glaucoma | TM; retinal immune cells | ECM remodeling, immune adhesion, indirect RGC injury | Plasma N-glycans; aqueous humor (potential) | Enzyme-targeted normalization | Emerging | [13, 48, 56, 58, 76–77] |
| Glycosylated neurotrophic and axonal proteins | Glaucoma | RGCs; supporting glia | Impaired neurotrophic signaling and axonal maintenance | Retinal tissue (experimental) | Restoration of glycosylation-dependent support | Limited | [50–54] |
| Enzyme-targeted glycosylation modulation | AD&Glaucoma | Neurons; microglia; TM; RGCs | Multi-level neuroprotection *via* reduced inflammation and stress | CSF; plasma; aqueous humor | Small-molecule or siRNA-based modulation | Moderate (AD)/emerging (glaucoma) | [47–48, 79–84] |

AD: Alzheimer's disease; CSF: Cerebrospinal fluid; ECM: Extracellular matrix; GnT-III: N-acetylglucosaminyltransferase III; ICAM-1: Intercellular adhesion molecule-1; OGT: O-GlcNAc transferase; OGA: O-GlcNAcase; O-GlcNAcylation: O-linked β-N-acetylglucosaminylation; RGC: Retinal ganglion cell; siRNA: Small interfering RNA; TM: Trabecular meshwork.

fluid (CSF) of AD patients and are correlated with cognitive decline[74-75]. Notably, these changes are mechanistically linked to dysregulated activity of key glycosylation enzymes, including OGT, OGA, and GnT-III, supporting glycan signatures as downstream molecular readouts of the OGT/OGA–O-GlcNAc and GnT-III–dependent regulatory axes proposed in this review.

In glaucoma, although evidence for systemic or ocular glycosylation signatures remains limited, emerging data support their relevance. Ng *et al*[76] employed fluorescence-assisted capillary gel electrophoresis to profile plasma desialylated N-glycans in glaucoma and cataract cohorts and identified three of 21 major desialylated N-glycan peaks exhibited significant, sex-specific differences between glaucoma and cataract cohorts. While retinal or TM tissues were not directly examined, the altered N-glycan structures are consistent with changes in N-glycan branching and terminal modification regulated by Golgi-localized glycosyltransferases such as GnT-III. However, glycosylation studies in glaucoma remain limited, and systematic data on glycan profiles in aqueous humor are lacking[77], representing a critical gap given that aqueous humor directly reflects TM metabolism, local inflammatory signaling, and retinal neuronal stress. Because O-GlcNAcylation functions as a conserved intracellular nutrient- and stress-sensing modification mediated by the OGT/OGA axis, quantification of O-GlcNAc–related metabolites or glycosylation-sensitive protein modifications in aqueous humor, particularly those linked to stress-responsive signaling and inflammatory pathways, may provide biologically grounded biomarkers biologically grounded biomarkers of early metabolic and inflammatory perturbations in glaucomatous eyes[78].

**Enzyme-Targeted Modulation of Glycosylation as a Shared Therapeutic Strategy** Current studies are exploring small-molecule inhibitors and siRNA-based approaches to reduce excessive glycosylation, aiming to alleviate neuroinflammation and protein aggregation[79-81]. In AD models, inhibiting the expression or activity of GnT-III reduces abnormal glycosylation, decreases amyloid plaque accumulation and inflammation, and improves memory and cognition, supporting a causal role for GnT-III–dependent N-glycan remodeling in AD pathogenesis and indicate that enzyme-level intervention can simultaneously correct aberrant glycosylation patterns and modify disease-relevant outcomes[47,82]. In glaucoma, adjusting the activity of glycosyltransferases or glycosidases to restore normal TM cell glycosylation may improve aqueous humor outflow and lower intraocular pressure[48]. Importantly, the therapeutic implications of glycosylation normalization may extend beyond pressure regulation. Restoring glycosylation homeostasis has been associated with improved vascular function, attenuation of inflammatory signaling, and stabilization of glycosylation-sensitive neurotrophic factor receptors, collectively supporting neuronal integrity and promoting RGC survival[83-84].

Together, these observations suggest that enzyme-targeted modulation of glycosylation can exert multi-level protective effects across distinct tissues in AD and glaucoma, despite differences in anatomical context and primary disease triggers. Notably, the same enzyme-centered pathways that give rise to disease-associated glycosylation signatures may also serve as actionable therapeutic nodes, reinforcing the conceptual integration of biomarker development and targeted intervention. Future studies will need to further refine enzyme specificity, optimize tissue-selective delivery, and rigorously evaluate the long-term safety of glycosylation-targeted therapies before clinical translation.

## DISCUSSION

This review proposes enzymatic glycosylation as a conceptual and mechanistic link between AD and glaucoma, two age-related neurodegenerative disorders traditionally studied in isolation. By focusing on enzyme-centered regulatory nodes rather than disease-specific downstream manifestations, we aim to integrate heterogeneous findings from cerebral and ocular systems into a coherent framework. Specifically, we highlight two interconnected glycosylation-dependent axes: the OGT/OGA–O-GlcNAc axis as an upstream metabolic and stress sensor, and the GnT-III–bisecting GlcNAc–ICAM-1 axis as a downstream modulator of neuroinflammatory cell–cell interactions.

**Enzyme-Centered Glycosylation as a Shared Regulatory Framework** A major challenge in cross-disease comparison lies in the apparent asymmetry of mechanistic evidence. In AD, glycosylation has been directly linked to core neuropathological hallmarks, including Aβ accumulation, tau hyperphosphorylation, synaptic dysfunction, and microglial activation[37-38,40-46,64-65,85]. In contrast, glycosylation studies in glaucoma have largely focused on TM remodeling and intraocular pressure regulation, with fewer data directly addressing RGC degeneration[13,48,56,58,70-72]. This discrepancy reflects differences in research maturity rather than a fundamental divergence in underlying biology.

By shifting attention from tissue-specific outcomes to conserved enzymatic regulators, glycosylation emerges as a plausible shared mechanism. While enzymatic glycosylation is a well-established driver in systemic metabolic complications, such as corneal nerve degeneration in diabetes[86], its role in the intrinsic pathogenesis of glaucoma remains relatively overlooked in favor of conventional mechanical or genetic paradigms. Our review highlights a critical knowledge gap: the OGT/OGA-controlled O-GlcNAcylation system

functions as a rapid and reversible intracellular modification that integrates nutrient availability, oxidative stress, and inflammatory signaling[25-26,64,66-67]. Dysregulation of this axis has been shown to sensitize neurons to metabolic stress in AD models[42-45,64,68-69], and based on emerging evidence, may similarly influence RGC vulnerability under glaucomatous stress conditions[66-67,77-78]. Although direct experimental validation in RGCs remains limited, the conserved stress-sensing role of O-GlcNAcylation across neuronal populations supports its relevance to both diseases.

**GnT-III–Dependent N-Glycosylation and Neuroinflammatory Convergence** GnT-III–mediated bisecting GlcNAc modification represents a second key point of convergence. In AD, GnT-III–dependent N-glycan remodeling has been implicated in altered ICAM-1 glycosylation, dysregulated microglial adhesion and migration, and amplification of neuroinflammatory responses that exacerbate amyloid pathology[39,47]. These findings support a causal role for enzyme-driven N-glycan remodeling in shaping inflammatory microenvironments.

In glaucoma, GnT-III has primarily been studied in the context of TM ECM organization and aqueous humor outflow[13,48,56,58,76-77]. However, TM dysfunction is increasingly recognized as more than a purely mechanical contributor to disease; it also influences local inflammatory signaling and metabolic stress within the ocular environment. Given that ICAM-1 and related adhesion molecules are expressed in ocular tissues and participate in immune cell recruitment, it is biologically plausible that similar GnT-III–dependent glycosylation mechanisms operate in glaucomatous eyes, indirectly affecting RGC survival through sustained inflammatory and vascular stress. While current evidence in glaucoma is largely indirect, this conceptual continuity provides a testable hypothesis rather than a speculative association.

**Addressing Redundancy and Evidence Gaps** One limitation of the current literature, reflected in earlier versions of this manuscript, is the tendency to repeatedly describe TM-related glycosylation changes without integrating them into a broader neurodegenerative context. In the revised framework, TM alterations are repositioned as part of a glycosylation-sensitive microenvironment that modulates downstream neuronal stress rather than as isolated pathological events. This perspective reduces redundancy and strengthens the argument that glycosylation acts across multiple cellular compartments to influence disease progression.

Importantly, not all proposed links are supported by equivalent levels of evidence. Glycosylation-mediated mechanisms in AD are supported by extensive molecular and *in vivo* studies, whereas glaucoma-related data remain fragmented. Acknowledging this imbalance is essential. Rather than weakening the proposed model, explicitly defining these evidence gaps underscores key priorities for future research, including direct assessment of O-GlcNAcylation and N-glycan remodeling in RGCs and comprehensive glycomic profiling of aqueous humor.

**Implications for Biomarker Development and Therapeutic Targeting** An enzyme-centered view of glycosylation has practical translational implications. Because enzymatic activity integrates multiple upstream signals, glycosylation patterns may serve as sensitive molecular readouts of early disease-related stress. In AD, altered glycan signatures in CSF and brain tissue already correlate with disease severity[73-75]. In glaucoma, preliminary plasma N-glycan data and the accessibility of aqueous humor suggest opportunities for developing localized biomarkers that reflect both TM metabolism and retinal stress[76-78].

Therapeutically, targeting glycosylation enzymes offers the possibility of modulating multiple downstream pathways simultaneously. In AD models, inhibition of GnT-III or modulation of OGT/OGA activity has been shown to attenuate neuroinflammation and protein aggregation[47,79-82]. Although comparable interventional studies in glaucoma are sparse, normalization of glycosylation homeostasis may provide benefits beyond IOP reduction, including improved inflammatory balance, vascular function, and neurotrophic signaling relevant to RGC survival.

**Conceptual Significance and Future Directions** Taken together, this review does not claim that identical glycosylation pathways have been fully delineated in AD and glaucoma. Rather, it proposes that conserved enzymatic regulators of glycosylation constitute a unifying molecular layer through which diverse stressors converge to drive neurodegeneration. By framing glycosylation as an active regulatory system rather than a passive modification, this perspective encourages cross-disciplinary investigation and facilitates the translation of mechanistic insights between central and ocular neurodegenerative diseases.

Future studies should prioritize enzyme-specific, cell-type-resolved analyses and longitudinal designs to clarify causality and therapeutic windows. Such efforts will be essential to determine whether glycosylation-targeted strategies can be safely and effectively leveraged in clinical settings.

## CONCLUSION

Collectively, emerging evidence now positions aberrant enzymatic glycosylation as a unifying molecular pathway that underpins the pathogenesis of both AD and glaucoma. By regulating protein folding, inflammatory signaling, and neuronal survival, glycosylation proposes a biochemical bridge connecting ocular and cerebral neurodegeneration. Ongoing

advances in glycomic and glycoproteomics technologies have created unprecedented opportunities to discover cross-disease glycan biomarkers in blood, CSF, and aqueous humor. Moreover, targeting key glycosylation enzymes such as OGT and GnT-III may provide innovative therapeutic strategies to restore cellular homeostasis, reduce protein aggregation, and improve neuronal resilience. Notwithstanding these promising advances, substantial translational barriers persist, most notably the paucity of large-cohort validation for glycosylation-based biomarkers and the urgent need for safer, more selective enzyme modulators. Future research should emphasize interdisciplinary collaboration among neuroscientists, ophthalmologists, and glycobiologists to clarify the temporal dynamics of glycosylation changes, develop sensitive clinical assays, and evaluate the therapeutic potential of glycosylation-targeted interventions. Through such integrated efforts, glycosylation research may transform our understanding of neurodegenerative diseases and offer new opportunities for early diagnosis and treatment.

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