Review

Unlocking the Sugar Code: Implications and Consequences of Glycosylation in Alzheimer's Disease and Other Tauopathies

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Review

Unlocking the Sugar Code: Implications and Consequences of Glycosylation in Alzheimer's Disease and Other Tauopathies

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Abstract

Alzheimer's disease (AD) is the most prevalent cause of dementia, characterized by progressive cognitive decline, amyloid-β (Aβ) plaques, and neurofibrillary tangles composed of hyperphosphorylated tau protein. Other tauopathies, including frontotemporal lobar degeneration (FTLD), progressive supranuclear palsy (PSP), and corticobasal degeneration (CBD), share pathological hallmarks centered on abnormal tau biology. Increasing evidence highlights the role of post-translational modifications in modulating these pathogenic processes. Among these, glycosylation, the enzymatic attachment of glycans to proteins or lipids, has emerged as a critical regulator of protein folding, trafficking, aggregation, and clearance. Both N-linked glycosylation (N-glycosylation) and O-linked glycosylation (O-glycosylation) influence tau stability, Aβ processing, receptor signaling, synaptic integrity, and neuroinflammation. Dysregulated glycosylation patterns have been documented in brains and cerebrospinal fluid (CSF) of AD patients, suggesting biomarker potential and novel therapeutic targets. Moreover, glycosyltransferases and glycosidases show altered expression in neurodegeneration, linking metabolic and inflammatory pathways to tauopathy progression. This review synthesizes current evidence on the implications and consequences of glycosylation in AD and other tauopathies, integrating mechanistic, pathological, and clinical findings. We also discuss advances in glycoproteomics, the interplay between glycosylation and phosphorylation, and the translational potential of targeting glycosylation pathways for diagnosis and therapy.

Keywords: Alzheimer's disease; tauopathies; glycosylation; N-glycosylation; O-glycosylation; amyloid-β; tau protein; neurodegeneration; post-translational modifications; glycoproteomics

1. Introduction

Alzheimer's disease (AD) is the leading cause of dementia, affecting over 50 million individuals worldwide, with prevalence projected to rise sharply as populations age [1]. Clinically, AD is defined by progressive cognitive decline, memory impairment, and eventual loss of autonomy. Neuropathologically, it is characterized by extracellular **amyloid-β (Aβ) plaques** and intracellular **neurofibrillary tangles (NFTs)** composed of hyperphosphorylated tau protein [2]. While these

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lesions form the cornerstone of the amyloid and tau hypotheses, AD is increasingly recognized as a multifactorial disorder, integrating immune, vascular, metabolic, and protein homeostasis pathways.

A crucial layer of regulation in these processes is **post-translational modification (PTM)**, which fine-tunes protein structure, stability, and localization. Among PTMs, tau phosphorylation has been extensively studied, but **glycosylation** has gained momentum as a determinant of disease progression [3]. Glycosylation refers to the enzymatic addition of glycans to proteins or lipids. Two major classes relevant to AD and tauopathies are: **N-glycosylation**, where glycans attach to asparagine residues and **O-glycosylation**, where glycans attach to serine or threonine residues [4].

Variants such as O-GlcNAcylation—the dynamic attachment of N-acetylglucosamine—play pivotal roles in regulating protein interactions and preventing aggregation [5]. Glycosylation influences folding, trafficking, degradation, and cell–cell signalling, processes that are fundamental to neuronal viability.

In tauopathies such as **frontotemporal lobar degeneration (FTLD)**, **progressive supranuclear palsy (PSP)**, and **corticobasal degeneration (CBD)**, glycosylation abnormalities intersect with tau phosphorylation, altering aggregation dynamics and neuronal toxicity. Similarly, the amyloid precursor protein (APP) processing and Aβ secretion are influenced by N-glycosylation, linking glycan biology to amyloid pathology [3] Moreover, glycosylation affects receptor signalling, immune activation, and synaptic function, positioning it as a central regulator of neurodegeneration.

Advances in **glycoproteomics** now enable precise mapping of glycosylation changes in AD brain tissue, cerebrospinal fluid (CSF), and serum, revealing disease-specific signatures with potential diagnostic and prognostic value [1]. Furthermore, enzymes such as **glycosyltransferases** and **glycosidases** emerge as candidate drug targets, while metabolic pathways regulating the hexosamine biosynthetic pathway link systemic glucose handling to neuronal glycosylation patterns [4].

This review synthesizes current knowledge on the **implications and consequences of glycosylation in AD and other tauopathies**, with focus on tau biology, amyloid processing, immune and synaptic modulation, and translational potential for biomarker discovery and therapy.

2. Tau Glycosylation in Alzheimer's and Related Tauopathies

Tau protein is a microtubule-associated protein essential for stabilizing cytoskeletal architecture and supporting axonal transport. In Alzheimer's disease (AD) and other tauopathies, tau undergoes extensive post-translational modifications that alter its biochemical and biophysical properties. While hyperphosphorylation has been studied extensively, evidence increasingly demonstrates that **glycosylation is a critical determinant of tau structure, aggregation, and toxicity** [6].

2.1. N-glycosylation of Tau

Early studies revealed that tau is aberrantly N-glycosylated in AD brains, whereas normal adult tau is typically not glycosylated [7]. The addition of N-linked glycans occurs at asparagine residues and alters tau's conformation, reducing its affinity for microtubules while increasing aggregation propensity [8]. N-glycosylated tau has been detected within paired helical filaments and neurofibrillary tangles, supporting a pathogenic role [4].

Importantly, aberrant N-glycosylation often precedes or facilitates hyperphosphorylation. Glycosylated tau shows increased susceptibility to kinases such as glycogen synthase kinase-3β (GSK3β), leading to pathogenic phosphorylation patterns [7]. This sequence highlights glycosylation as an upstream event in tauopathy pathogenesis.

2.2. O-GlcNAcylation of Tau

Another critical modification is O-GlcNAcylation, the addition of O-linked N-acetylglucosamine to serine or threonine residues. Unlike N-glycosylation, O-GlcNAcylation appears protective. Increased O-GlcNAcylation reduces tau phosphorylation and aggregation by competing with phosphorylation sites [8]. Animal studies show that enhancing O-GlcNAcylation stabilizes tau, improves neuronal survival, and ameliorates memory deficits [5].

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However, AD brains consistently show reduced O-GlcNAcylation, correlating with increased phosphorylation and tangle burden [9]. This reduction may result from impaired glucose metabolism and flux through the hexosamine biosynthesis pathway [3].

2.3. Glycosylation in Other Tauopathies

In frontotemporal lobar degeneration (FTLD), progressive supranuclear palsy (PSP), and corticobasal degeneration (CBD), tau aggregates share common modifications. Abnormal glycosylation of tau has been demonstrated across these conditions, although disease-specific differences exist in glycosylation site occupancy and glycan composition [10]. In PSP, tau shows increased high-mannose N-glycans, while in CBD, complex-type N-glycans are enriched, suggesting distinct enzymatic dysregulation [11].

Moreover, O-GlcNAcylation deficits are not restricted to AD but also appear in FTLD brain tissue, further linking impaired glucose metabolism to tau pathology across tauopathies [9].

2.4. Interplay Between Glycosylation and Phosphorylation

Perhaps the most critical insight is the interplay between glycosylation and phosphorylation. N-glycosylated tau is a better substrate for phosphorylation, while O-GlcNAcylation prevents phosphorylation at adjacent residues [12]. This creates a pathogenic imbalance: reduced O-GlcNAcylation and increased N-glycosylation synergistically drive tau hyperphosphorylation and aggregation [13].

This dynamic crosstalk suggests that therapies aimed at restoring O-GlcNAcylation or preventing aberrant N-glycosylation could rebalance tau homeostasis and slow disease progression. Indeed, small-molecule inhibitors of O-GlcNAcase (OGA), the enzyme removing O-GlcNAc, are under investigation as disease-modifying treatments [6].

3. Glycosylation and Amyloid-β Pathology

The amyloid cascade hypothesis proposes that abnormal processing of amyloid precursor protein (APP) initiates a series of pathogenic events culminating in Alzheimer's disease (AD). Glycosylation profoundly influences APP trafficking, secretase accessibility, and amyloid-β (Aβ) generation [5].

3.1. APP N-glycosylation and Trafficking

APP is a heavily N-glycosylated type I transmembrane protein. N-glycans at asparagine residues near its luminal domain regulate APP folding, trafficking through the secretory pathway, and stability at the cell surface [14]. Disruption of these N-glycans alters APP sorting, diverting it toward endosomal compartments enriched in β-secretase - β-site APP-cleaving enzyme 1 (BACE1), thereby increasing amyloidogenic cleavage [15].

Experimental studies confirm that loss of APP N-glycosylation enhances Aβ production, whereas stabilizing N-glycan structures reduces amyloidogenic processing [16]. These findings indicate that altered N-glycosylation in AD brains may bias APP processing toward Aβ generation.

3.2. O-glycosylation and Secretase Regulation

In addition to N-glycosylation, APP and its secretases undergo **O-glycosylation**, particularly O-GalNAc modification, which influences protein trafficking and enzymatic activity. O-glycosylation of APP modulates its endocytosis rate, thereby controlling access to β- and γ-secretases [5]. Reduced O-glycosylation correlates with increased amyloidogenic cleavage and elevated extracellular Aβ accumulation [8].

Secretases themselves are glycoproteins. BACE1 contains multiple N-glycans that regulate folding, transport, and stability. Inhibition of BACE1 glycosylation reduces its enzymatic activity and impairs Aβ generation [17]. Similarly, γ-secretase components such as nicastrin are highly

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glycosylated; glycan structures near the substrate-binding pocket determine APP cleavage patterns [18]. These modifications fine-tune Aβ species ratios, including the pathogenic Aβ42/40 balance.

3.3. Aberrant Glycosylation of Aβ Peptides

Emerging evidence suggests that Aβ peptides themselves can undergo glycosylation or interact with glycans. Modified Aβ shows altered aggregation kinetics and toxicity. Glycosylated Aβ peptides aggregate faster and form more neurotoxic oligomers compared to unmodified Aβ [6]. Additionally, glycans on neuronal membranes interact with Aβ, promoting deposition and impairing clearance [1].

Glycosylation also modulates Aβ clearance via **receptor-mediated endocytosis**. For instance, the receptor for advanced glycation end products (RAGE) binds both glycated proteins and Aβ, facilitating its transcytosis across the blood–brain barrier [2]. Enhanced RAGE glycosylation increases its affinity for Aβ, promoting deposition in the brain parenchyma [19].

The interplay between glycosylation and Aβ toxicity extends beyond processing and clearance. Aberrant glycosylation of synaptic proteins, receptors, and ion channels exacerbates Aβ-induced dysfunction. For example, **NMDA receptors** require N-glycosylation for proper surface expression; loss of this modification sensitizes neurons to Aβ-mediated excitotoxicity [20].Similarly, glycosylation of prion protein (PrP^C) modulates its interaction with Aβ oligomers, influencing synaptotoxic signalling cascades [17,21].

Furthermore, microglial and astrocytic receptors involved in Aβ clearance—such as TREM2 and CD33—are heavily glycosylated. Altered glycan structures modulate receptor affinity and downstream inflammatory responses [22]. This suggests that glycosylation contributes to the balance between protective clearance and harmful neuroinflammation.

3.5. Implications for Therapy

Given the centrality of glycosylation in APP metabolism and Aβ biology, **targeting glycosylation pathways** represents a promising therapeutic approach. Experimental strategies include inhibiting BACE1 glycosylation, enhancing protective O-glycosylation, and modulating glycosyltransferases that remodel glycans on APP and its processing enzymes [16,17]. Additionally, blocking RAGE glycosylation has been proposed to limit Aβ transport into the brain and reduce deposition [2,19,23–25].

4. Glycosylation, Synaptic Function, and Neuroinflammation

Synaptic dysfunction and chronic neuroinflammation are central drivers of neurodegeneration in Alzheimer's disease (AD) and tauopathies. Both processes are intimately modulated by glycosylation, which shapes receptor signaling, immune cell activation, and glial responses [22,26,27].

4.1. Glycosylation of Synaptic Receptors and Adhesion Molecules

Neuronal communication depends on the proper glycosylation of neurotransmitter receptors and cell adhesion proteins. N-methyl-D-aspartate (NMDA) receptors, critical for synaptic plasticity, require N-glycosylation for assembly, trafficking, and surface expression [20]. In AD models, aberrant glycosylation disrupts NMDA receptor localization, sensitizing neurons to amyloid-β (Aβ)-induced excitotoxicity.

Similarly, AMPA receptors rely on N-glycans for stability and gating properties; altered glycosylation reduces synaptic strength and long-term potentiation, processes essential for learning and memory [15].

Adhesion molecules such as neural cell adhesion molecule (NCAM) and L1CAM are highly glycosylated, and polysialylation of NCAM regulates neurite outgrowth and synaptic remodeling. Reduced polysialylation has been detected in AD hippocampus, correlating with impaired synaptic connectivity [28].

4.2. Immune Receptor Glycosylation and Microglial Activation

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Microglia, the brain's resident immune cells, rely on glycosylated receptors for recognition and clearance of pathological proteins. Triggering receptor expressed on myeloid cells 2 (TREM2) contains multiple N-glycosylation sites that regulate folding and surface expression. Mutations altering TREM2 glycosylation reduce receptor stability, impair microglial phagocytosis of Aβ, and increase AD risk [22,26,27].

Another example is CD33, a sialic acid-binding receptor implicated in AD genetic risk. CD33 glycosylation governs ligand binding and inhibitory signaling; aberrant glycosylation enhances its inhibitory effect, reducing Aβ clearance and exacerbating inflammation [12].

Astrocytes also display glycosylated receptors that influence neuroinflammation. For instance, GFAP-interacting proteins undergo glycan remodeling in reactive astrocytes, altering cytokine release and glial scar formation [5,29].

4.3. Cytokines, Chemokines, and Glycosylation

Inflammatory mediators in the central nervous system (CNS) are heavily glycosylated. Interleukin-6 (IL-6), a pro-inflammatory cytokine elevated in AD, requires N-glycosylation for secretion and receptor binding. Altered IL-6 glycosylation patterns modulate its bioactivity and half-life in the extracellular space [29–31]. Similarly, tumor necrosis factor-alpha (TNF-α) and interleukin-1β (IL-1β) undergo glycosylation changes in AD, influencing receptor affinity and downstream signaling [32–34].

Chemokine receptors such as CCR5 and CX3CR1 are also glycosylated, with changes in glycan branching modulating microglial migration and response to injury. In AD, aberrant glycosylation of these receptors contributes to chronic, non-resolving inflammation [11,28].

4.4. Glycosylation and the Complement System

The complement cascade, a major mediator of synaptic pruning and neuroinflammation, is highly influenced by glycosylation. C1q, the initiator of the classical pathway, carries sialylated glycans that regulate binding to immune complexes and synaptic elements. Loss of sialylation enhances complement activation and drives synapse elimination in AD models [9,35].

Other complement proteins, including C3 and factor H, show altered glycosylation in AD brain and cerebrospinal fluid, correlating with disease severity [5,8,14,23,26]. This suggests that glycosylation defects amplify maladaptive immune responses.

4.5. Neuroinflammation Beyond Amyloid and Tau

Glycosylation also extends its influence to pattern recognition receptors (PRRs) that detect damage-associated molecular patterns (DAMPs). RAGE (receptor for advanced glycation end products) is heavily glycosylated, and its modification enhances binding to glycated proteins and Aβ, facilitating inflammatory cascades [2,26]. Glycosylated RAGE amplifies NF-κB signaling, perpetuating neuroinflammation **[3]**.

In addition, toll-like receptors (TLRs) rely on N-glycans for stability and ligand recognition. Dysregulated TLR glycosylation biases microglia toward pro-inflammatory phenotypes, further fueling pathology [35–39].

4.6. Therapeutic Implications

Given its central role in receptor biology and inflammatory signaling, modulating glycosylation could rebalance immune responses. Potential strategies include glycoengineering of anti-inflammatory cytokines, inhibition of aberrant receptor glycosylation, or restoring protective glycosylation patterns on complement regulators [2,12,40].

5. Advances in Glycoproteomics and Biomarker Discovery

Biomarker discovery remains a critical frontier in Alzheimer's disease (AD) and tauopathies. While classical markers such as cerebrospinal fluid (CSF) amyloid-β42 (Aβ42), total tau (t-tau), and

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phosphorylated tau (p-tau) have clinical utility, their specificity and predictive power are limited **[32]**. Glycoproteomics, the large-scale study of glycosylated proteins, has emerged as a powerful approach to identify novel biomarkers by leveraging disease-specific glycosylation changes [34,41–43].

5.1. Glycoproteomic Alterations in Alzheimer's Disease

Proteomic studies demonstrate profound changes in glycosylation within AD brains. Comparative analyses of postmortem cortical tissue show altered N-glycan branching, sialylation, and fucosylation across multiple glycoproteins [1,44,45]. Specific glycosylation signatures distinguish AD from age-matched controls, implicating disrupted glycosyltransferase and glycosidase activity [3,33].

In CSF, glycoproteomics reveals increased bisected N-glycans and altered glycoforms of tau and amyloid precursor protein (APP) fragments, correlating with disease severity [46,47]. Serum analyses have also detected disease-specific glycosylation patterns, including reduced sialylation of acute-phase proteins and altered IgG Fc glycosylation, linking systemic inflammation to neurodegeneration [10,14,24,32,47,48].

5.2. Glycosylation as a Diagnostic and Prognostic Biomarker

The diagnostic potential of glycosylation is underscored by studies demonstrating that altered glycosylation of tau precedes overt phosphorylation changes [49]. Detection of glycosylated tau in CSF or plasma could thus provide early disease biomarkers. Likewise, **O-GlcNAcylation status of tau** correlates inversely with disease progression, suggesting its utility as a prognostic marker [46,50,51].

Moreover, glycan-based profiling has shown promise in differentiating AD from other dementias. For instance, patients with **frontotemporal lobar degeneration (FTLD)** and **progressive supranuclear palsy (PSP)** display distinct glycosylation patterns compared to AD, enabling differential diagnosis [16,20].

5.3. Mass Spectrometry and Glycoproteomic Technologies

Recent advances in mass spectrometry (MS) have revolutionized glycoproteomics. Methods such as electron-transfer dissociation (ETD) and higher-energy collisional dissociation (HCD) provide site-specific glycan characterization with high sensitivity. Enrichment strategies using lectins, hydrophilic interaction chromatography (HILIC), and nanoporous materials further enhance glycopeptide detection [5,12,52].

Novel probes and nanocomposites allow in situ visualization of glycosylation in brain tissue, bridging biochemical analyses with histopathology [53,54]. These tools have revealed regional differences in glycosylation within hippocampus, cortex, and subcortical structures, aligning with clinical phenotypes of memory loss, executive dysfunction, and motor impairment.

5.4. Immunoglobulin Glycosylation and Systemic Biomarkers

Beyond CNS proteins, peripheral immune system glycosylation offers insights into neurodegeneration. Altered **IgG Fc glycosylation** has been documented in AD, with reduced galactosylation and sialylation associated with pro-inflammatory phenotypes [20,47,55]. These changes may reflect systemic inflammation or feedback from neuroinflammatory cascades.

Additionally, plasma glycoproteomic profiling identifies altered glycosylation of acute-phase reactants such as haptoglobin and α1-acid glycoprotein, linking metabolic stress to disease progression [56–58].

5.5. Integration with Multimodal Biomarkers

Glycosylation-based biomarkers should not be considered in isolation but integrated with imaging, fluid, and genetic markers. Combining CSF tau glycosylation profiles with positron emission tomography (PET) amyloid imaging improves diagnostic accuracy over either modality

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alone [10,51]. Similarly, serum glycoproteomic signatures complement plasma phosphorylated tau (p-tau181, p-tau217) measurements, enhancing early detection potential [11,46].

5.6. Challenges and Opportunities

Despite major progress, glycoproteomics faces challenges: glycan heterogeneity complicates quantification, and standardized reference libraries are limited. Moreover, interindividual variability in glycosylation due to genetics, diet, and comorbidities complicates biomarker validation [1,59–61].

However, these same features offer opportunities. Disease-specific glycan "fingerprints" could yield highly specific biomarkers, and integration with machine learning approaches promises improved classification [3,62,63]. Longitudinal studies are beginning to reveal how glycosylation changes track disease trajectory, paving the way for prognostic applications.

6. Enzymatic Regulators of Glycosylation in Neurodegeneration

The balance of protein glycosylation is tightly regulated by glycosyltransferases and glycosidases, as well as by metabolic flux through the hexosamine biosynthetic pathway (HBP), which generates nucleotide sugars as glycosylation substrates. In Alzheimer's disease (AD) and other tauopathies, dysregulation of these enzymes and pathways alters glycosylation homeostasis, thereby influencing amyloid precursor protein (APP) metabolism, tau aggregation, receptor signaling, and neuroinflammation [1,50,57].

6.1. Glycosyltransferases in AD and Tauopathies

N-acetylglucosaminyltransferases (GnTs) regulate branching and extension of N-glycans. Upregulation of GnT-III increases bisected N-glycans on tau and APP, promoting pathological processing [16]. Similarly, elevated GnT-V activity has been detected in AD brains, producing β1,6-GlcNAc branching that alters synaptic receptor function [32,64,65].

Sialyltransferases, which attach sialic acid residues, are dysregulated in AD, leading to reduced sialylation of neuronal adhesion molecules such as NCAM and impaired synaptic remodeling [18]. Altered sialylation also contributes to immune dysfunction by modifying microglial receptor interactions with sialylated ligands [36,66].

In tauopathies beyond AD, such as progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD), distinct changes in glycosyltransferase expression drive unique glycosylation signatures. Comparative analyses reveal elevated fucosyltransferase activity in PSP, whereas CBD brains show increased sialyltransferase expression, contributing to disease-specific tau glycoforms [11,16,67].

6.2. Glycosidases and Tau Pathology

Glycosidases remove glycans from proteins and modulate glycan turnover. In AD, elevated β-N-acetylglucosaminidase (β-N-OGA) activity reduces protective O-GlcNAcylation of tau, facilitating hyperphosphorylation and aggregation [20,59,68]. Conversely, inhibition of β-N-OGA increases O-GlcNAcylation and reduces neurodegeneration in tauopathy mouse models [69,70].

Neuraminidases (sialidases) regulate the removal of sialic acids. Increased neuraminidase activity has been linked to loss of polysialylation on NCAM in AD hippocampus, impairing synaptic plasticity [18,32,71]. Additionally, altered lysosomal glycosidase activity disrupts degradation of glycoproteins, contributing to protein aggregation and lysosomal storage pathology observed in AD [3]. Abnormal N-glycosylation of tau promotes hyperphosphorylation and aggregation, while reduced O-GlcNAcylation removes a protective brake on phosphorylation. N- and O-glycosylation of APP and secretases regulate amyloid-β (Aβ) generation, with aberrant patterns favoring amyloidogenic processing. Synaptic receptors and adhesion molecules require proper glycosylation for stability and plasticity; their dysregulation contributes to synaptic failure. Immune receptors (TREM2, CD33, RAGE) and cytokines are glycosylated, shaping microglial and astrocytic activation, while complement protein glycosylation regulates synapse pruning. Finally, altered activity of

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glycosyltransferases, glycosidases, and the hexosamine biosynthetic pathway (HBP) underlies these shifts. Together, these processes highlight glycosylation as both a pathogenic mechanism and therapeutic target. A schematic overview of glycosylation is presented in Figure 1.

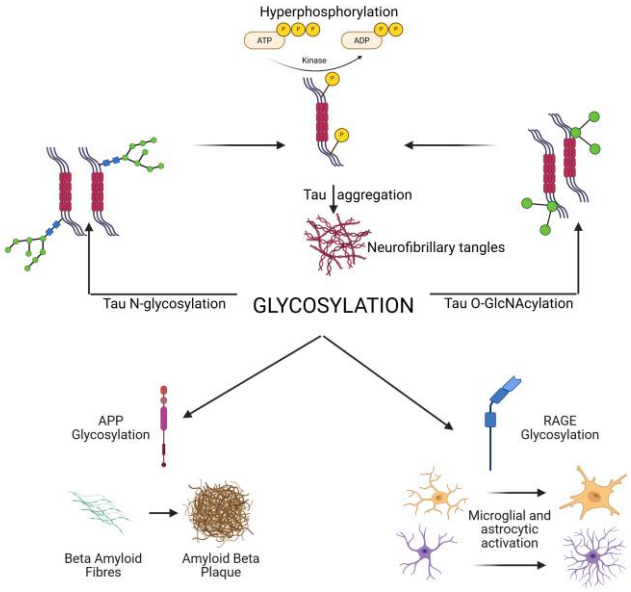

Figure 1. Schematic Overview of Glycosylation in Alzheimer's Disease and Tauopathies, illustrating how glycosylation affects tau, APP/Aβ, synaptic and immune receptors, and the enzymatic/metabolic regulators (HBP, OGT, OGA, GnTs). **Created with bioRender.** Acronyms in figure defined: APP (amyloid precursor protein), RAGE (receptor for advanced glycation end products).

6.3. Hexosamine Biosynthetic Pathway and Metabolic Regulation

The hexosamine biosynthetic pathway (HBP) provides UDP-N-acetylglucosamine (UDP-GlcNAc), the substrate for O-GlcNAcylation. Reduced glucose flux into the HBP, due to impaired brain glucose metabolism in AD, diminishes O-GlcNAcylation levels [60,72,73]. This metabolic defect links systemic insulin resistance and type 2 diabetes to enhanced risk of AD and tauopathies [74–76].

Experimental restoration of HBP flux via glucosamine supplementation increases O-GlcNAcylation and reduces tau phosphorylation in animal models, highlighting its therapeutic potential [68,77,78]. Similarly, caloric restriction and metabolic interventions that enhance glucose utilization may indirectly restore protective glycosylation patterns.

6.4. Crosstalk with Phosphorylation Pathways

The interplay between glycosylation and phosphorylation is tightly controlled by enzymes. Reduced O-GlcNAc transferase (OGT) activity decreases tau O-GlcNAcylation, thereby exposing phosphorylation sites for kinases such as glycogen synthase kinase-3β (GSK3β) [30,57,79,80]. Conversely, enhancing OGT activity shifts the balance toward protective O-GlcNAcylation [6,56].

This enzymatic tug-of-war suggests that targeting glycosylation enzymes may indirectly modulate tau phosphorylation, providing a dual mechanism for therapeutic intervention [34,68,81].

6.5. Enzymatic Dysregulation as Biomarkers

Aberrant expression of glycosylation enzymes is detectable in CSF and serum, offering biomarker potential. Elevated OGA and reduced OGT levels correlate with higher CSF tau and worse cognitive outcomes [3,29,82,83]. Similarly, altered glycosyltransferase expression patterns in peripheral blood mononuclear cells reflect disease stage and may serve as accessible biomarkers [39,76].

6.6. Therapeutic Implications

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Enzymes regulating glycosylation are increasingly viewed as druggable targets. OGA inhibitors, such as thiamet-G, are under preclinical investigation for enhancing tau O-GlcNAcylation [39,57,66,84]. Sialidase inhibitors, by preserving polysialylation, may protect synaptic plasticity. Small molecules targeting glycosyltransferases are less developed but hold potential for rebalancing glycosylation networks in neurodegeneration [8,81,85–87]. The glycosylation processes involved in Alzheimer's Disease and other tauopathies are summarized in Table 1.

Table 1. Summary of Glycosylation Processes in Alzheimer's Disease and Tauopathies.

Process / Target	Type of Glycosylation	Pathological Consequence	Biomarker / Therapeutic Relevance	Key References
Tau protein	N-glycosylation	Promotes hyperphosphorylation and aggregation	Detected in NFTs; biomarker potential	[12,82]
Tau protein	O-GlcNAcylation	Protective, reduces phosphorylation and aggregation	Reduced in AD brains; OGA inhibitors in trials	[20,59,68]
APP	N-glycosylation	Alters trafficking; increases amyloidogenic cleavage	Potential target for secretase regulation	[5,8,26]
BACE1 (β-secretase)	N-glycosylation	Stabilizes enzyme, promotes Aβ production	Inhibition reduces Aβ levels	[17,24,32,47,77,85]
Nicastrin (γ-secretase)	N-glycosylation	Modulates substrate binding and Aβ species ratio	Glycan-targeting therapies under exploration	[18,55,64,80]
Synaptic receptors (NMDA, AMPA)	N-glycosylation	Controls receptor trafficking and function	Aberrant glycosylation increases Aβ vulnerability	[38,61]
NCAM (adhesion)	Polysialylation	Regulates neurite outgrowth and synaptic plasticity	Reduced in AD hippocampus	[32,64,68]
Immune receptors (TREM2, CD33)	N-glycosylation	Controls stability and microglial response	Mutations affect AD risk	[27,59,67]
Cytokines (IL-6, TNF-α)	N-glycosylation	Regulates secretion and signaling	Altered profiles detected in CSF	[28,41]
Complement proteins (C1q, C3)	Sialylation	Regulates activation and synaptic pruning	Aberrant glycosylation enhances synapse loss	[9,12,54,60]
Enzymes (OGT, OGA)	Glycosylation enzymes	Balance O-GlcNAcylation/phosphorylation	Biomarker and therapeutic target	[83,88]

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Acronyms in table defined: APP (amyloid precursor protein), Aβ (amyloid-β), NFT (neurofibrillary tangle), NMDA (N-methyl-D-aspartate receptor), AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor), NCAM (neural cell adhesion molecule), TREM2 (triggering receptor expressed on myeloid cells 2), CD33 (cluster of differentiation 33), IL-6 (interleukin-6), TNF-α (tumor necrosis factor-alpha), CSF (cerebrospinal fluid), OGT (O-GlcNAc transferase), OGA (O-GlcNAcase).

7. Discussion

The accumulated evidence underscores glycosylation as a central, though historically underappreciated, driver of Alzheimer's disease (AD) and related tauopathies. Unlike phosphorylation, which has dominated the research landscape, glycosylation provides a multidimensional regulatory layer that influences protein stability, trafficking, aggregation, and clearance [1,19,89].

7.1. Glycosylation and the Hierarchy of Pathological Events

One of the persistent debates in AD research concerns the sequence of pathological events. Glycosylation research offers new perspectives. Evidence suggests that N-glycosylation of tau occurs early, priming the protein for hyperphosphorylation and aggregation [64,66,90]. In parallel, aberrant glycosylation of APP biases processing toward amyloidogenic cleavage [5,91]. Thus, glycosylation abnormalities may precede both amyloid and tau pathologies, positioning them as an upstream "common denominator."

7.2. Protective Versus Pathogenic Roles

Not all glycosylation is deleterious. O-GlcNAcylation of tau exemplifies a protective modification by competing with phosphorylation sites, it reduces aggregation and toxicity [16,77,92,93]. Conversely, reduced O-GlcNAcylation in AD brains correlates with worsened pathology [57,77,94]. Similarly, polysialylation of NCAM supports synaptic plasticity, but its reduction contributes to connectivity deficits [64,65,95,96]. The dualistic nature of glycosylation complicates therapeutic strategies, interventions must distinguish between protective and pathogenic glycosylation events [22,97].

7.3. Crosstalk with Metabolism and Phosphorylation

A recurring theme is the integration of glycosylation with broader cellular networks. Metabolic dysfunction, particularly impaired glucose utilization, reduces flux through the hexosamine biosynthetic pathway, limiting substrate availability for O-GlcNAcylation [3,98,99]. This explains why AD brains show reduced O-GlcNAc despite increased phosphorylation pressure. Moreover, enzymatic regulators such as OGT and OGA directly shape the phosphorylation landscape of tau by modulating glycosylation at competing sites [20,79,100].

7.4. Neuroinflammation as a Glycosylation-Driven Amplifier

Neuroinflammation is increasingly viewed not as a secondary phenomenon but as a core contributor to neurodegeneration. Glycosylation critically modulates immune receptor signaling. TREM2 requires N-glycosylation for stability; mutations impairing this modification reduce microglial Aβ clearance [27,101,102]. Conversely, aberrant glycosylation of CD33 enhances its inhibitory signaling, further dampening microglial phagocytosis [66,103]. Glycosylation of complement proteins amplifies maladaptive synaptic pruning [9,104]. Collectively, these findings highlight glycosylation as a molecular amplifier of neuroinflammatory cascades.

7.5. Biomarker Potential and Translational Challenges

Glycoproteomics offers promising avenues for biomarker discovery. Altered glycosylation of tau, APP, and inflammatory proteins has been consistently detected in CSF and serum [42,105–107]. These patterns not only differentiate AD from controls but may also discriminate between

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tauopathies such as PSP and CBD [67,108]. However, technical barriers remain: glycan heterogeneity complicates quantification, and interindividual variability poses validation challenges [1,109].

7.6. Therapeutic Perspectives

Therapeutic manipulation of glycosylation is a rapidly advancing field. OGA inhibitors that increase protective O-GlcNAcylation of tau are under active investigation [110]. Strategies targeting glycosyltransferases or glycosidases could theoretically rebalance glycosylation networks, though selectivity remains a major obstacle [5,16,111,112]. In addition, targeting glycosylation of immune receptors such as RAGE and TREM2 may offer immunomodulatory benefits [24,27,113].

7.7. Remaining Controversies

Despite major progress, several controversies remain. It is unclear whether glycosylation changes are primary drivers of pathology or secondary adaptations to cellular stress. Some argue that abnormal glycosylation results from metabolic and inflammatory dysfunction rather than initiating pathology [27,114]. Others suggest that glycosylation shifts act as compensatory mechanisms, initially protective but maladaptive when chronic [9,115]. Clarifying these temporal relationships will be essential for therapeutic translation.

Glycosylation has emerged as a pivotal post-translational modification in neurodegeneration, shaping the trajectory of pathology through its multifaceted impact on protein structure, stability, trafficking, and signaling. Across this review, several themes consistently emerge:

Tau regulation: Aberrant N-glycosylation primes tau for hyperphosphorylation and aggregation, while reduced O-GlcNAcylation removes a critical brake against pathogenic modifications [91,116].

Amyloid precursor protein (APP) and amyloid-β (Aβ): N- and O-glycosylation of APP and its processing enzymes profoundly influence amyloidogenic cleavage, with downstream effects on Aβ burden [5,117].

Synaptic and immune regulation: Glycosylation of receptors and adhesion molecules determines synaptic resilience, while glycosylation of immune receptors (TREM2, CD33, RAGE) amplifies maladaptive neuroinflammation [19,27,118].

Enzymatic control and metabolism: Enzymes such as OGT, OGA, and glycosyltransferases orchestrate glycosylation balance. Their dysregulation, often linked to impaired glucose metabolism and hexosamine biosynthetic pathway flux, couples systemic metabolic dysfunction to neurodegeneration [3,119].

Biomarker potential: Glycoproteomic studies reveal distinct glycosylation signatures in brain, CSF, and serum, offering diagnostic and prognostic markers and providing disease-specific fingerprints that differentiate AD from other tauopathies [11,34,120].

Collectively, glycosylation abnormalities are not epiphenomena but core contributors to disease mechanisms, interwoven with phosphorylation, inflammation, and metabolism [44,121,122].

8. Future Directions

While significant progress has been made, several research priorities and therapeutic opportunities remain:

Clarifying temporal dynamics: Longitudinal human studies are needed to determine whether glycosylation changes precede, accompany, or follow amyloid and tau pathology [9,123]. This temporal clarity will inform whether glycosylation can serve as a true early biomarker or therapeutic entry point.

Expanding glycoproteomic profiling: High-resolution glycoproteomics using advanced mass spectrometry, lectin arrays, and nanoparticle probes should be applied to large, well-characterized cohorts. Integration with imaging and fluid biomarkers will improve diagnostic specificity and enable personalized medicine [3,42,124].

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Targeted therapeutics: Clinical translation of OGA inhibitors and other glycosylation-modulating compounds should be pursued cautiously, with attention to the dualistic nature of glycosylation (protective vs. pathogenic). Parallel approaches may include sialidase inhibitors to preserve polysialylation, or small-molecule modulators of glycosyltransferases [5,24,125].

Systems biology approaches: Glycosylation does not act in isolation. Integrating glycosylation with phosphoproteomics, metabolomics, and transcriptomics will reveal multi-layered disease networks [1,126,127]. Such approaches can identify convergent pathways and potential drug targets.

Expanding to non-AD tauopathies: Comparative studies across PSP, CBD, and FTLD will refine understanding of disease-specific glycosylation signatures and highlight both shared and divergent mechanisms [11,128–130]. This comparative lens will sharpen differential diagnosis and inform tailored interventions.

Bridging bench to bedside: Translation will require standardization of glycoproteomic assays, establishment of reference databases, and validation in multicenter cohorts [13,131–133]. Importantly, therapeutic interventions targeting glycosylation must demonstrate CNS specificity while minimizing systemic off-target effects [16,17,19,134–142].

Taken together, these findings position glycosylation at the crossroads of molecular pathology, systemic metabolism, and neuroimmune signaling in Alzheimer's disease and related tauopathies. While the evidence underscores both pathogenic and protective aspects of glycosylation, it also highlights unresolved questions regarding timing, causality, and therapeutic feasibility [135,143]. The convergence of biochemical, glycoproteomic, and translational studies emphasizes that glycosylation is not a peripheral phenomenon but a central determinant of disease trajectory [133,144]. This integrative perspective sets the stage for the concluding remarks, which synthesize the mechanistic insights, biomarker potential, and therapeutic avenues into a broader framework for future research and clinical translation [11,105].

9. Conclusions

Glycosylation represents a critical but underappreciated frontier in neurodegeneration research. By modulating protein folding, phosphorylation, aggregation, immune activation, and synaptic function, it acts as both a pathogenic driver and protective modifier. Aberrant N-glycosylation of tau and APP promotes aggregation and amyloidogenic processing, while reduced O-GlcNAcylation and polysialylation remove protective mechanisms. In parallel, altered glycosylation of receptors and inflammatory mediators amplifies neuroinflammation and accelerates disease progression.

These insights highlight glycosylation as both a biomarker source and a therapeutic target at the convergence of technological advances. Progress in glycoproteomics now allows detection of disease-specific glycan signatures in cerebrospinal fluid and serum, supporting early diagnosis and differential classification among tauopathies. Therapeutic strategies aimed at rebalancing glycosylation, such as OGA inhibitors or glycosyltransferase modulators, are promising but require careful consideration of specificity and systemic effects.

Overall, by integrating glycosylation research with broader molecular and clinical frameworks of neurodegeneration, a new path can be opened toward tangible opportunities for biomarker development, earlier detection, improved prognostic tools, and innovative therapies.

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