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REVIEW

Glycosylation in T2 high and Th17 Asthma: A Narrative Review

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Abstract: Glycosylation, a fundamental biochemical process, entails the covalent attachment of sugar molecules to proteins, DNA, or RNA. Beginning with an overview of the pathophysiological features of asthma, this review proceeds to elucidate various facets of glycosylation in asthma pathology, specifically in T2 high asthma and Th17-mediated responses. We examined glycosylation's involvement in regulating airway inflammation, encompassing the modulation of pro-inflammatory cytokine release such as IL-4, IL-5, and IL-13, key components of T2 inflammation, as well as its significance in modulating immune cell functionality, notably T cells and dendritic cells. Moreover, we explored glycosylation's impact on airway remodeling processes, including its regulation of airway smooth muscle cell proliferation and migration. Addressing molecular mechanisms, this review delved into several glycosylation modifications of proteins and genes implicated in asthma pathogenesis, including IgE, IL-4 receptor, TGF-β, and the regulation of select glycosylation enzymes. Additionally, the review highlights the role of Th17 cells in T2 high asthma and their modulation through glycosylation. We underscored future research imperatives, including biomarker discovery, therapeutic realization, and the potential utility of glycosylation modifications in asthma prevention and management. In short, this review provides an in-depth analysis of the critical role of glycosylation in the pathogenesis of T2 high asthma and Th17 responses.

Keywords: glycosylation, asthma, airway inflammation, airway remodeling, immunity

Introduction

Asthma stands as a multifaceted respiratory disorder with a complex pathogenesis characterized by chronic airway inflammation, hyperresponsiveness, and remodeling.[1] Over the years, extensive research has shed light on various molecular mechanisms underlying its etiology and progression. Among these mechanisms, glycosylation emerges as a fundamental biochemical process that has garnered increasing attention for its significant implications in asthma pathophysiology.[2–4]

Glycosylation, the covalent attachment of sugar molecules to proteins, serves as a pivotal post-translational modification crucial for cellular signaling, recognition.[5] It is integral to numerous biological processes such as protein folding, stability, transport, molecular recognition, cell adhesion, ligand binding, and signal transduction.[6] Furthermore, it modulates protein interactions and influences the immunogenicity of protein. Glycosylation represents one of the most ancient and complex forms of post-translational modification, encompassing both N-linked and O-linked glycosylation, which collectively influence over 50% of characterized proteins.[7] N-glycosylation is conferred upon the side chain of asparagine (Asn) residues, whereas O-glycosylation occurs on serine (Ser), threonine (Thr), or tyrosine (Tyr) residues. (Figure 1)

The process of glycosylation involves the participation of several enzymes, including glycosyltransferases, glycosidases, and glycosylation modifying enzymes. Glycosyltransferases, such as β-1,4-galactosyltransferase (B4GALT) and α-1,3-galactosyltransferase (A3GALT2),[8,9] serve as pivotal regulatory factors responsible for transferring sugar moieties to recipient molecules. Glycosidases, exemplified by glucosidase (GLUC), are responsible for removing glycosylation

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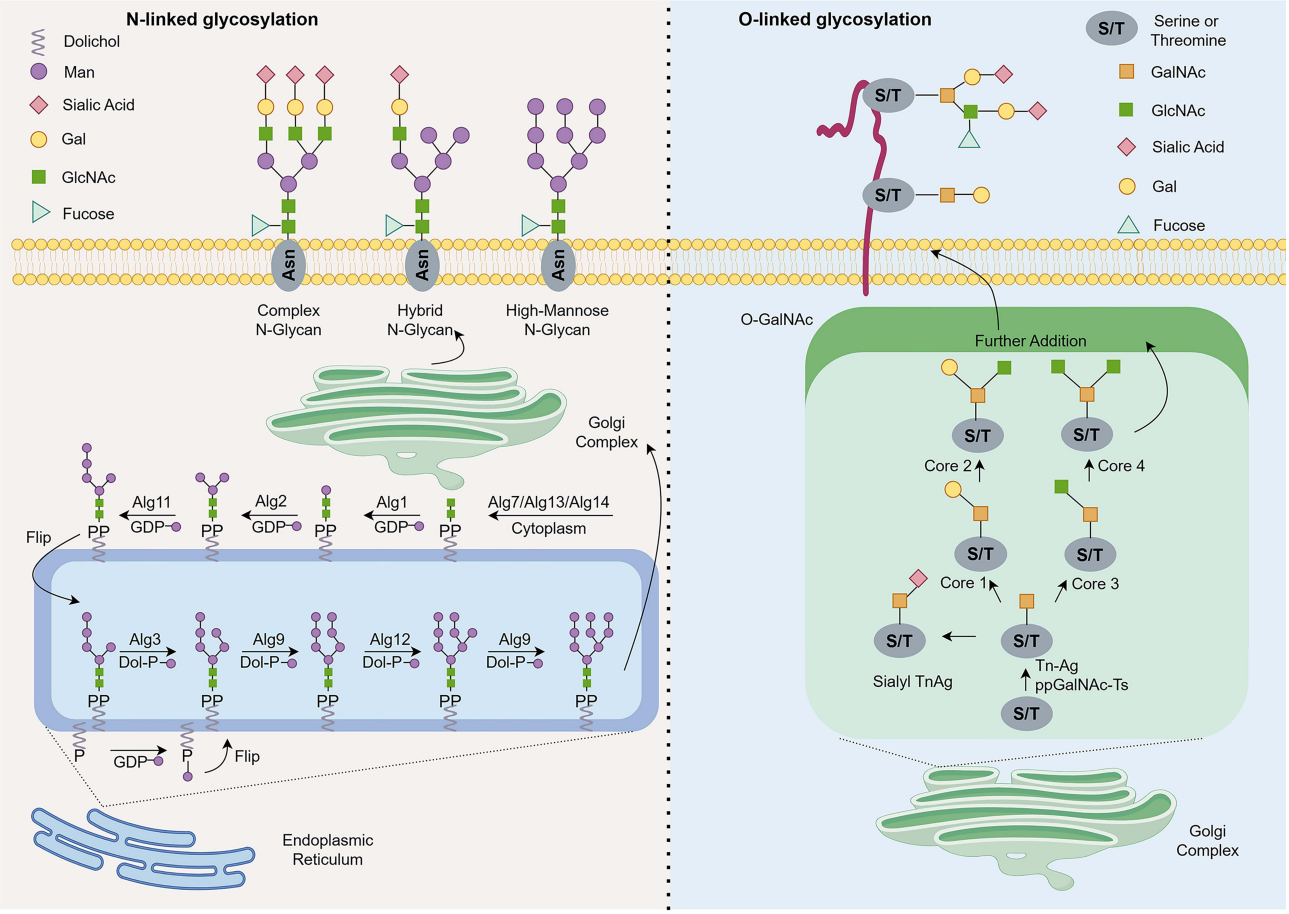

Figure 1 The mechanisms of N-linked glycosylation and O-linked glycosylation (By Figdraw). The process of N-linked glycosylation commences with the synthesis of a lipid-linked oligosaccharide, achieved by linking an oligosaccharide precursor from the cytoplasmic surface of the endoplasmic reticulum to a dolichol. One GlcNAc and five mannose residues are sequentially transferred from UDP-GlcNAc and GDP-mannose to the substrate through a multienzyme complex involving three mannosyltransferases, resulting in the formation of Man5GlcNAc2-P-Dol. Subsequently, under the action of invertase, these oligosaccharides are translocated across the endoplasmic reticulum membrane and undergo four rounds of mannosylation within the endoplasmic reticulum lumen to yield Man9GlcNAc2-P-Dol. The oligosaccharide moiety is then transferred to a newly synthesized protein containing an Asn-X-Ser/Thr sequence, catalyzed by oligosaccharyl transferase. N-glycosidic bonds are established between the terminal carbon atom of GlcNAc and the nitrogen atom on the asparagine side chain of this protein, thereby synthesizing N-glycosidic linkages. Furthermore, N-glycoproteins that undergo endoplasmic reticulum quality control exit from the endoplasmic reticulum, enter into Golgi apparatus for further modifications leading to complex N-glycoproteins destined for transport to cell membranes. O-linked glycosylation (referring to O-GalNAc glycosylation) is initiated by the enzymatic addition of GalNAc to polypeptides, a process catalyzed by N-acetylgalactosaminyltransferase. Under the influence of N-acetylgalactosaminyltransferase, GalNAc residues are transferred from uridine diphosphate GalNAc to serine and threonine side chains. A single GalNAc residue is linked to the α-hydroxyl group of serine or threonine via an α-O-glycosidic bond, resulting in the formation of the Tn antigen, which is subsequently extended by various glycosyltransferases into more complex O-glycan structures. Furthermore, Tn can be elaborated into four principal O-GalNAc cores as well as four rare variants: Core 1, Core 2, Core 3, and Core 4.

modifications by cleaving glucosidic bonds. Additionally, certain enzymes, like glycosyltransferases and glycosidases, modulate the structure and properties of glycosylation modifications.[10] Beyond enzymes directly implicated in glycosylation, genes encoding auxiliary factors, regulatory elements, and substrates pertinent to glycosylation exist.[11] Examples include Mannosyl (Alpha-1,3-)-Glycoprotein Beta-1,2-N-Acetylglucosaminyltransferase 1 (MGAT1)[12] and UDP-glucuronosyltransferase (UGT),[13] whose regulation also influences the process and outcome of glycosylation.

Recent studies have highlighted the intricate role of glycosylation in asthma development and progression, implicating it in key pathological processes underlying the disease.[14] This review embarks on a comprehensive exploration of the intricate interplay between glycosylation and asthma pathogenesis. It begins with an overview of the pathophysiological features characterizing asthma, laying the foundation for a detailed examination of glycosylation's multifaceted contributions to the disease process. Specifically, we delved into glycosylation's regulatory effects on airway inflammation, encompassing its modulation of pro-inflammatory cytokine release, such as interleukin-4 (IL-4), IL-5, and IL-13, as well as its influence on immune cell functionality, particularly T cells and macrophages. Additionally, the review elucidates

glycosylation's impact on airway remodeling processes, highlighting its role in regulating airway smooth muscle cell proliferation and migration. Addressing molecular mechanisms, it explores various glycosylation modifications of proteins and genes implicated in asthma pathogenesis, including transforming growth factor-beta (TGF-β), immunoglobulin E (IgE), and interleukins.

Main

TGF-β Glycosylation and Asthma

TGF-β plays a dual role in the pathogenesis of asthma. It serves a crucial role in regulating allergic inflammation by inhibiting the activation of Th2 cells and promoting the generation of regulatory T cells (Treg cells), thereby aiding in the alleviation of airway inflammation and allergic reactions. However, under conditions of prolonged exposure to allergens or stimuli, TGF-β may also contribute to structural changes in the airways, such as airway remodeling and fibrosis, exacerbating the clinical symptoms of asthma.[15]

TGF-β possesses multiple glycosylation sites.[16,17] In renal epithelial cells, core fucosylation, a form of glycosylation involving the addition of fucose to specific glycan structures on proteins, has been identified as essential for the proper functioning of both TGF-βRII and ALK5 (Receptors). Inhibition of core fucosylation using α1,6-fucosyltransferase (Fut8) small interfering RNA significantly decreased the phosphorylation of Smad2/3 proteins, leading to the inactivation of the TGF-β/Smad2/3 signaling pathway and resulting attenuation of epithelial-to-mesenchymal transition (EMT).[18] In a mouse model of renal interstitial fibrosis, knockdown of Fut8 results in loss of core fucosylation on TRβI and inhibition of the TGF-β_1/Smad2/3 pathway.[19] Furthermore, Fut8 knockout mice exhibit significant inhibition of TGF-β_1 receptor activation, whereas Fut8 knock-in can rescue the level of Smad2 phosphorylation, suggesting reactivation of the TGF-β signal.

Additionally, N-acetylglucosaminyltransferase-V (GnT-V) has been shown to influence TGF-β signal activation. Knockout of GnT-V reduces the polysaccharide branching of β-1,6-GlcNAc catalyzed by GnT-V on TGF-β receptors TβRI and TβRII, thereby inhibiting TGF-β_1/Smad3 signal transduction.[20] In lung cancer cells A549, GnT-V inhibits EMT of lung cancer cells by suppressing TGF-β_1/Smad signal transduction in a GnT-V activity-dependent manner.[21] The GalNAc-type O-glycosylation induced by peptide N-acetylgalactosaminyltransferases (ppGalNAc-Ts) can also regulate TGF-β signal transduction.[22] In breast cancer, ppGalNAc-T4 regulates TGF-β_1 signal transduction by catalyzing O-GalNAcylation of TβRII at the Ser31 site and TβRI, subsequently attenuating the dimerization of TβRI and TβRII, thus inhibiting the TGF-β_1 signal in human breast cancer cells.[23] Furthermore, in gastric cancer and glioma, it has been confirmed that ppGalNAc-Ts can inhibit the TGF-β signal.[24,25] The knockdown of α-2,3-sialyltransferase 1 (ST3Gal1) also has neem shown to inhibit the TGF-β_1 signal.[26] Given the crucial role of TGF-β in asthma, it is imperative to further validate whether the TGF-β glycosylation regulatory mechanisms observed in other disease models hold true in asthma models. Exploring whether these glycosylation-related genes can serve as therapeutic targets for asthma is necessary.

Glycosylation of Interleukin and Asthma

In addition to TGF-β, various interleukins play significant roles in the pathogenesis of asthma. For instance, IL-4 and IL-13 are pivotal regulatory factors in asthma inflammation, promoting the differentiation and activation of Th2 cells and participating in asthma regulation. Existing research indicates that several interleukins are also regulated by glycosylation. For example, in the vascular system of C57 mice, studies by Migurz et al suggest that O-GlcNAc modification appears to regulate the IL-10 signaling pathway, disrupting the physiological effects of IL-10.[27] Research by Jennifer et al suggests that MMP-9 effectively cleaves human IL-7 within the exposed loop between α helices C and D, and this process is delayed by glycosylation at the IL-7 N-terminus. Glycosylation and disulfide bonds, as two post-translational modifications, influence the bioavailability of IL-7 in the human species.[28] Furthermore, interleukins can also influence glycosylation. Hiroko et al discovered that IL-22-mediated host N-glycosylation may be impaired in patients with ulcerative colitis (UC), making UC-HMA mice more susceptible to CDI. This suggests that IL-22-mediated host glycosylation promotes the growth of commensal bacteria competing for nutritional niches with Clostridioides difficile.[29] Sina et al investigated the impact of glycosylation on the functionality of the IL-12 family and identified glycosylation sites within human IL-12 family subunits, which are modified upon secretion. Among the IL-12 family

cytokines, glycosylation only affects the secretion of the IL-35 cytokine.[30] Furthermore, glycosylation has varying effects on the functionality of IL-12 family cytokines, with IL-27 being the most significantly affected. In T cells, J. Mancilla et al reported the presence of receptors for IL-1. The extracellular portions of these receptors contain N-glycosylation chains, ie, glycosylation modifications. Researchers treated these T cells with four different plant lectins and glycosidases and found that some lectins could inhibit IL-1-induced proliferation of cells and block IL-1 binding, suggesting that glycosylation modifications may play an important role in the binding and function of IL-1 receptors.[31] Chitinase 3-like-1 (Chi3l1) and IL-13 are ligands for interleukin-13 receptor alpha 2 (IL-13Rα2). The binding of the former activates mitogen-activated protein kinase, AKT, and Wnt/β-catenin signaling pathways, playing important roles in innate and adaptive immunity, cell apoptosis, oxidative damage, allergic inflammation, tumor metastasis, wound healing, fibrosis, and repair in the lungs. Conversely, the binding of the latter primarily acts as a decoy, attenuating the effects of IL-13.[32] When N-glycosylation sites mutate, the binding of Chi3l1 to IL-13Rα2 increases, while reduced N-glycosylation enhances the binding and signaling of Chi3l1-IL-13Rα2. The binding of IL-13 to IL-13Rα2 depends on four N-glycosylation sites of IL-13Rα2, and reduced N-glycosylation of IL-13Rα2 decreases the IL-13-IL-13Rα2 binding. Chi3l1 inhibits N-glycosylation, while IL-13 stimulates N-glycosylation. These findings suggest that N-glycosylation is a crucial determinant of the binding of Chi3l1 and IL-13 to IL-13Rα2 and highlight the ability of Chi3l1 and IL-13 to modulate N-glycosylation machinery, thereby enhancing their respective bindings. This evidence indicates that glycosylation can directly regulate the structure and function of cytokines (release, binding ability to ligands, subsequent downstream signal intensity and can also regulate cytokine expression at the transcriptional level by influencing upstream signals (such as Wnt, AKT).

Glycosylation of IgE and Asthma

IgE plays a crucial role in asthma. IgE is generated by B cells under the influence of IL-4 and IL-13 secreted by Th2 cells, and binds to high-affinity IgE receptors (FcεRI) on the surface of mast cells and eosinophils.[33] Upon re-exposure to allergens, IgE binds to them, activating these cells and releasing inflammatory mediators such as histamine and leukotrienes, leading to bronchoconstriction, increased mucus secretion, airway inflammation, and airway remodeling, exacerbating asthma symptoms. IgE is a heavily glycosylated monomeric antibody with seven N-linked glycosylation sites distributed across the four constant domains of the heavy chain. N394 is a conserved glycosylation site with oligomannose glycans, while N383 is unoccupied, and the other five sites (N140, N168, N218, N265, N371) are occupied by complex biantennary glycans.[34,35] Preliminary studies suggest that glycosylation of IgE is crucial for FcεRI binding and effector function.[36] However, subsequent research has found that non-glycosylated IgE produced in Escherichia coli can also bind to FcεRI and trigger effector function, suggesting that glycosylation may not be essential.[37] Nevertheless, studies combining in vitro experiments, cell studies, and mouse models indicate that IgE glycosylation does indeed play a significant role. A point mutation N384Q in mouse IgE (mIgE), equivalent to human N383Q, abolished its binding to FcεRI in both ear mast cells and cell experiments, similar results were observed when using PNGaseF enzyme to remove all N-glycosylation from mIgE. These findings suggest that mIgE N384 glycosylation is necessary for initiating allergic reactions. Additionally, circular dichroism results show that removal of N-linked glycans alters the secondary structure of IgE, preventing its binding to FcεRI. These results highlight the role of glycosylation in binding to high-affinity receptors, similar to the role of IgG glycosylation in binding to FcγRI. This also suggests that IgE produced in Escherichia coli may adopt a conformation different from glycosylated IgE during folding, hence still able to bind to FcεRI. Specific IgE glycosylation patterns in allergic and atopic populations have been studied. Interestingly, despite both groups having similar levels of mannose, galactose, and bisecting GlcNAc in complex biantennary glycans, differences exist in terminal fucose and sialylation. Atopic IgE is enriched in terminal fucose, while sialylation increases in allergic IgE. Functional experiments demonstrate that degranulation of mast cells increases with peanut allergic IgE sensitization compared to atopic IgE. The importance of IgE sialylation is further confirmed by passive cutaneous anaphylaxis models, where sialylated IgE induces greater allergic reactions than non-sialylated IgE. These new findings underscore an intriguing contrast in antibody sialylation effects: while IgG sialylation is associated with anti-inflammatory activity, IgE sialylation appears to exacerbate allergic reactions.[38]

In addition, leukotrienes, prostaglandins, histamine, Toll-like receptors (TLRs), and endothelin-1 play crucial roles in the pathogenesis and exacerbation of asthma. These inflammatory mediators, released by mast cells, eosinophils, and other inflammatory cells, impact airway inflammation, bronchoconstriction, and mucus secretion through various pathways, exacerbating asthma symptoms.[39] The glycosylation status of these inflammatory mediators may influence their biological activity and modes of interaction. Glycosylation could modulate the binding affinity of these mediators to their receptors, affecting their distribution and clearance rates, thus impacting the extent of airway inflammation and bronchoconstriction.[40–42] Therefore, further research into the glycosylation status of these inflammatory mediators can enhance our understanding of their roles in asthma pathophysiology, providing new targets and strategies for asthma treatment. Table 1 Summarized key molecules regulated by glycosylation in asthma pathogenesis.

Glycosylation Regulates Asthma by Influencing Immune Cell Activation

The activation of immune cells plays a pivotal role in the pathophysiology of asthma. When asthma patients are exposed to triggering factors such as allergens or infections, immune cells such as T cells and eosinophils are activated and release inflammatory mediators such as IL-4, IL-5, and IL-13. These inflammatory mediators promote airway mucosal edema, excessive mucus secretion, and smooth muscle contraction, leading to airway narrowing and exacerbation of asthma symptoms. Glycosylation influences immune cell activation by regulating the structure and function of cell surface receptors. Glycosylation modifications affect the binding affinity of immune cell surface receptors to ligands, thereby modulating the activation of signaling pathways. Additionally, glycosylation can also affect the distribution and stability of receptors, influencing their availability on the cell surface. Taking T cells as an example, glycosylation influences the affinity between T cell receptor complexes and major histocompatibility complex (MHC), thereby regulating T cell activation and maturation.[43,44] Studies have shown that glycosylation of membrane receptors (for example, CD4, CD8, and T cell receptors) can modify the affinity for interactions with MHC.[45] Furthermore, sialylation located at α2-3 positions on CD8 coreceptor O-glycan reduces the affinity for MHC class I molecules, playing a crucial role in negative selection. Glycosylation also participates in the control of T cell differentiation Glycosylation reduction in CD25 has been shown to prevent T cell differentiation into Th1, Th2, and Treg-induced phenotypes, while promoting Th17 cell differentiation.[46] Sialylation affects certain protein interactions during Treg cell differentiation, such as the interaction between CD69 and the S100A8/S100A9 complex.[47] Removal of sialic acid by sialidase treatment in activated CD4 T cells inhibits the binding between these proteins and reduces Treg cell differentiation. Additionally, treatment with

Table 1 Glycosylation of Key Molecules in Asthma Pathogenesis

	Glycosylation Condition	Potential Roles in Inflammation and Asthma	Reference
TGF-β	Core fucosylation on TGF-βRII and ALK5 (Receptors)	TGF-β plays a crucial role in allergic inflammation by regulating Th2 cell activation and promoting regulatory T cell generation, aiding in alleviating airway inflammation and allergic reactions. Prolonged exposure to allergens or stimuli may lead to structural changes in the airways, such as airway remodeling and fibrosis, exacerbating asthma symptoms	[22–26]
IL-10	O-GlcNAc (O-linked N-acetylglucosamine) modification	O-GlcNAc modification regulates signaling, affecting the physiological effects of IL-10.	[27]
IL-7	N-terminal glycosylation	Glycosylation delays the cleavage of IL-7 by MMP-9, thereby influencing its biological activity.	[28]
IL-12	Multiple N-glycosylation sites on p35 and p40 subunits	Glycosylation affects the secretion and function of IL-12 family cytokines, particularly IL-35 and IL-27.	[30]
IL-1R	N-glycosylation	N-glycosylation modifications influence IL-1-induced T cell proliferation and receptor binding.	[31]
IgE	N-glycosylation at multiple sites (N140, N168, N218, N265, N371, N383, N394)	Multiple glycosylation sites on IgE influence its binding to FcεRI and effector function, constituting an integral part of allergic responses.	[34,35]

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glucosamine in mice reduces CD25 glycosylation, preventing differentiation into Th1 cells, increasing the survival rate of islet transplants in diabetic mice, and exacerbating the severity of experimental autoimmune encephalomyelitis.[46] Galectins in T cells also play a role in regulating processes such as activation, differentiation, and apoptosis. It has been reported that galectin-1 stimulates T cell apoptosis by recognizing CD43.[48] Another ligand for galectin-1 is glycoprotein CD45, which must express core 2 to trigger apoptosis signals.[49] These studies indicate that receptor glycosylation plays a pivotal role in modulating T cell function. Treg cells play important roles in the pathogenesis and development of asthma. The activation and secretion of cytokines by T cells, especially Th2 cells, directly contribute to the development of allergic inflammation in asthma, leading to airway mucosal inflammation and allergic reactions. In contrast, Treg cells act as regulatory immune cells that normally suppress allergic inflammatory responses, alleviate airway inflammation and allergic reactions, and exert a protective effect. However, in asthma patients, the number and function of Treg cells are abnormal, leading to immune imbalance, uncontrolled allergic inflammatory responses, and exacerbation of asthma. Therefore, receptor expression on cell membranes is likely to influence asthma progression by affecting T cell activation functions and Treg cell differentiation.

Macrophages also play a crucial role in asthma. They participate in regulating airway inflammation, antigen presentation, airway remodeling, immune response modulation, and pathogen clearance. Macrophages directly influence the pathogenesis and progression of asthma through the release of inflammatory mediators, modulation of T cell function, and pathogen clearance. Moreover, the two forms of macrophages (M1 and M2) play critical roles in immune polarization.[50] Upon activation, macrophages experience metabolic shifts that drive their differentiation into either an inflammatory or fibrotic phenotype, orchestrated by the mammalian target of rapamycin-hypoxia-inducible factor 1α (mTOR-Hif1α) pathway.[51] In the M1-like pro-inflammatory state, activation of the mTOR-Hif1α axis results in upregulated GLUT1 expression, enhanced glucose uptake, increased glycolysis, and the stimulation of synthetic metabolic pathways like the pentose phosphate pathway, all of which support sustained inflammation.[52] In contrast, in the M2 state, these pathways are suppressed, with mitochondrial metabolism taking precedence through oxidative phosphorylation and fatty acid oxidation.[53] Crucially, these metabolic alterations also influence the glycosylation process, which functions both as an effector and regulator of immune metabolic changes in macrophages. The interplay between metabolism and glycosylation is especially apparent in protein O-GlcNAcylation. In this process, O-GlcNAc, derived from the hexosamine biosynthetic pathway (HBP), is attached to serine or threonine residues on cellular proteins. Such modification exhibits significant dynamism, being facilitated by the OGT enzyme and reversed by the OGA enzyme.[54] The function of O-GlcNAcylation in macrophage polarization is intricate and occasionally paradoxical. Certain investigations propose that O-GlcNAcylation bolsters the M1-like phenotype by altering and activating crucial pro-inflammatory transcription factors. Conversely, additional studies suggest diminished HBP activity and protein O-GlcNAcylation in macrophages treated with LPS.[55] In the same study, the immune response and necroptosis are enhanced by inhibiting protein O-GlcNAcylation through OGT enzyme deficiency. This is accomplished by reducing O-GlcNAcylation of RIPK3 and inhibiting its interaction with RIPK1.[55] Consistent with this, OGT enzyme deficiency drives macrophages towards the M1-like phenotype.[56] Of note, heightened levels of O-GlcNAcylation are detected in macrophages exhibiting an M2-like phenotype.[57] This can be attributed to increased availability of HBP substrates, including acetyl-CoA and glutamine, which enhance through enhanced glutamine breakdown and increased glutamine uptake in M2-like macrophages.

Additionally, the glycosylation processes within airway epithelial cells involve several key molecules, whose glycosylation states directly influence the pathophysiological mechanisms of the disease.[58] Mucins such as MUC5AC and MUC5B are major secretory mucins present in airway epithelial cells.[59,60] Glycosylation of these mucins increases their viscosity and elasticity, leading to excessive mucus secretion and airway obstruction in asthma patients.[2,61] The expression and glycosylation levels of MUC5AC and MUC5B are significantly elevated in the airway epithelial cells of asthma patients.[60] This excessive mucus secretion can trap and accumulate more allergens and pathogens, further exacerbating airway inflammation and narrowing. E-cadherin is crucial for tight junctions between airway epithelial cells, and its glycosylation affects cell adhesion and barrier function.[62] Normally, E-cadherin helps maintain the integrity of the epithelial barrier, preventing the invasion of external pathogens and allergens.[63] However, in asthma, abnormal glycosylation of E-cadherin can compromise barrier function, allowing more pathogenic factors to penetrate the epithelial

barrier, triggering, and worsening inflammatory responses.[64,65] Toll-like receptor 4 (TLR4) is expressed in airway epithelial cells and recognizes pathogen-associated molecular patterns (PAMPs).[66] The glycosylation of TLR4 is critical for receptor stability and signal transduction.[67] In asthma, the glycosylation state of TLR4 regulates the response of airway epithelial cells to environmental allergens and pathogens.[68] Excessive TLR4 activation can lead to overproduction of inflammatory mediators, exacerbating airway inflammation and remodeling. MUC1 is a transmembrane mucin on the surface of airway epithelial cells, and its glycosylation status affects its ability to protect epithelial cells from pathogen invasion.[69] Altered glycosylation of MUC1 may play a role in the pathogenesis of asthma, influencing inflammation and immune responses.[3] Glycosylation of MUC1 can modulate its interactions with pathogens and its clearance efficiency.[70] In asthma patients, MUC1 may be less effective at clearing pathogens, leading to persistent inflammation and allergic reactions. Integrins are transmembrane receptors involved in cell-cell and cell-matrix adhesion. Glycosylation of integrins in airway epithelial cells can influence cell adhesion and migration functions.[71] In the inflammatory response of asthma, abnormal glycosylation of integrins can enhance interactions between airway epithelial cells and inflammatory cells such as eosinophils and mast cells, promoting the accumulation and activation of these inflammatory cells in the airways, thereby exacerbating inflammation and tissue damage. Additionally, N-acetylglucosaminyltransferases (GnTs) are key enzymes in the glycosylation process, involved in the synthesis and modification of N-glycans.[72] In airway epithelial cells, abnormal expression, and activity of GnTs can affect the structure and function of glycoproteins, impacting the pathophysiology of asthma.[73] Changes in GnT activity can alter the glycosylation states of various membrane and secreted proteins, affecting their function and stability. For instance, overactivity of GnTs may lead to hyperglycosylation of mucins,[74,75] increasing mucus secretion and the risk of airway obstruction. Table 2 presented a summary of the impact of glycosylation on immune cells and epithelial cells in the pathophysiology of asthma. Figure 2

Table 2 Glycosylation Influence on Immune Cells in Asthma Pathophysiology

Cell Types	Glycosylation Sites	Potential Roles in Inflammation and Asthma	Reference
T cells	CD4, CD8, T cell receptors	- Glycosylation influences the affinity between T cell receptor complexes and major histocompatibility complex (MHC), regulating T cell activation and maturation. - Sialylation at α2-3 positions on CD8 coreceptor O-glycan reduces the affinity for MHC class I molecules, crucial in negative selection.	[45,48]
	CD25	- Glycosylation reduction in CD25 prevents T cell differentiation into Th1, Th2, and Treg-induced phenotypes while promoting Th17 cell differentiation.	[46]
	CD69, S100A8/S100A9 complex	- Sialylation affects protein interactions during Treg cell differentiation, such as the interaction between CD69 and the S100A8/S100A9 complex.	[47]
	Galectin-1, CD43, CD45	- Galectin-1 stimulates T cell apoptosis by recognizing CD43. - Glycoprotein CD45 must express core 2 to trigger apoptosis signals.	[49]
Macrophages	GLUT1	- Inflammatory macrophages upregulate GLUT1 expression, enhancing glucose uptake and glycolysis, supporting sustained inflammation.	[52]
	O-GlcNAcylation	- O-GlcNAcylation influences macrophage polarization, with potential roles in both the M1-like and M2-like phenotypes. - Enhanced O-GlcNAcylation may bolster the M1-like phenotype by activating pro-inflammatory transcription factors.	[54]

(*Continued*)

Table 2 (Continued).

Cell Types	Glycosylation Sites	Potential Roles in Inflammation and Asthma	Reference
Airway Epithelial Cells	MUC5AC/MUC5B (Mucins)	Increase in viscosity and elasticity of mucus secretion, leading to airway obstruction; Elevated expression and glycosylation levels in asthma patients.	[60]
	E-cadherin	Abnormal glycosylation compromises barrier function, allowing penetration of allergens and pathogens, exacerbating inflammation.	[63]
	MUC1	Altered glycosylation may influence inflammation and immune responses; Reduced efficiency in pathogen clearance, leading to persistent inflammation and allergic reactions.	[64,65]
	Toll-like Receptor 4 (TLR4)	Regulates response to environmental allergens and pathogens; Excessive activation exacerbates inflammation and remodeling.	[68]
	Integrins	Abnormal glycosylation enhances interactions with inflammatory cells, promoting accumulation and activation, exacerbating inflammation and tissue damage.	[72]
	N-Acetylglucosaminyltransferases (GnTs)	Altered expression/activity affects glycoprotein structure/function, impacting asthma pathophysiology; Overactivity may lead to hyperglycosylation, increasing mucus secretion and airway obstruction.	[72]

Discussion

Here, we emphasize the critical role of glycosylation of various molecules, including cytokines, interleukins, and interferons, in the onset and progression of asthma. Asthma is a heterogeneous disease, encompassing multiple phenotypes, such as T2 high asthma, obesity-related asthma, and other less understood subtypes. In addition to immune modulation, epithelial injury plays a pivotal role in asthma pathogenesis. The airway epithelium, a pseudo-stratified columnar structure, resists external stimuli through structural integrity, mucosal cilia clearance and innate immune barriers. Serving as both a physical and immunological barrier, damage to the airway epithelium increases permeability, facilitating allergen entry and immune activation. Compromised epithelial integrity enhances the release of pro-inflammatory cytokines such as TSLP, IL-25, and IL-33, which further promote Th2-driven inflammation.

Viral, allergic, and environmental factors play significant roles in disrupting the airway epithelial barrier, contributing to the pathogenesis and exacerbation of asthma.[76–78] Viral infections, particularly with rhinovirus, respiratory syncytial virus, influenza virus, parainfluenza virus, adenovirus, and coronavirus, bind to specific receptors on airway epithelial cells, leading to internalization, replication, and activation of innate immune responses.[79] In asthma, impaired interferon responses and compromised barrier function result in increased viral replication and pro-inflammatory cytokine release, further disrupting epithelial cell-cell contacts. For instance, rhinovirus disrupts tight junction (TJ) integrity by causing the loss of ZO-1, with more pronounced effects in asthmatic-derived epithelial cultures.[80] Additionally, the immune response induced by virus may amplify the overall inflammatory load in the upper and subcutaneous tissues, and the resulting deep tissue inflammation further destroys the epithelial barrier.[81] Allergens such as the main house dust mite (HDM) allergen Der P1, which contains proteolytic activity, can directly destroy TJ or indirectly destroy them by activating protease activated receptor 2 (PAR-2).[82] Environmental factors, including ozone, cigarette smoke, and particulate matter, further impair epithelial integrity. Smoking disrupts epithelial junctions directly and indirectly through Th17-mediated inflammation and IL-17 secretion.[83] Pollutants like particulate matter and ozone degrade TJ proteins and reduce epithelial resistance, while household cleaning products, including laundry detergents, disrupt TJ, contributing to asthma development and worsening.[84,85]

Glycosylation influences epithelial repair mechanisms, and aberrant glycosylation of mucins and adhesion molecules may exacerbate airway damage and remodeling. [86] TGF-β plays a dual role in asthma, exerting both positive effects on regulating allergic inflammation and negative effects on airway structural changes.[87,88] Notably, the glycosylation status of TGF-β may modulate this process, raising the question: does the glycosylation of TGF-β change at different stages of

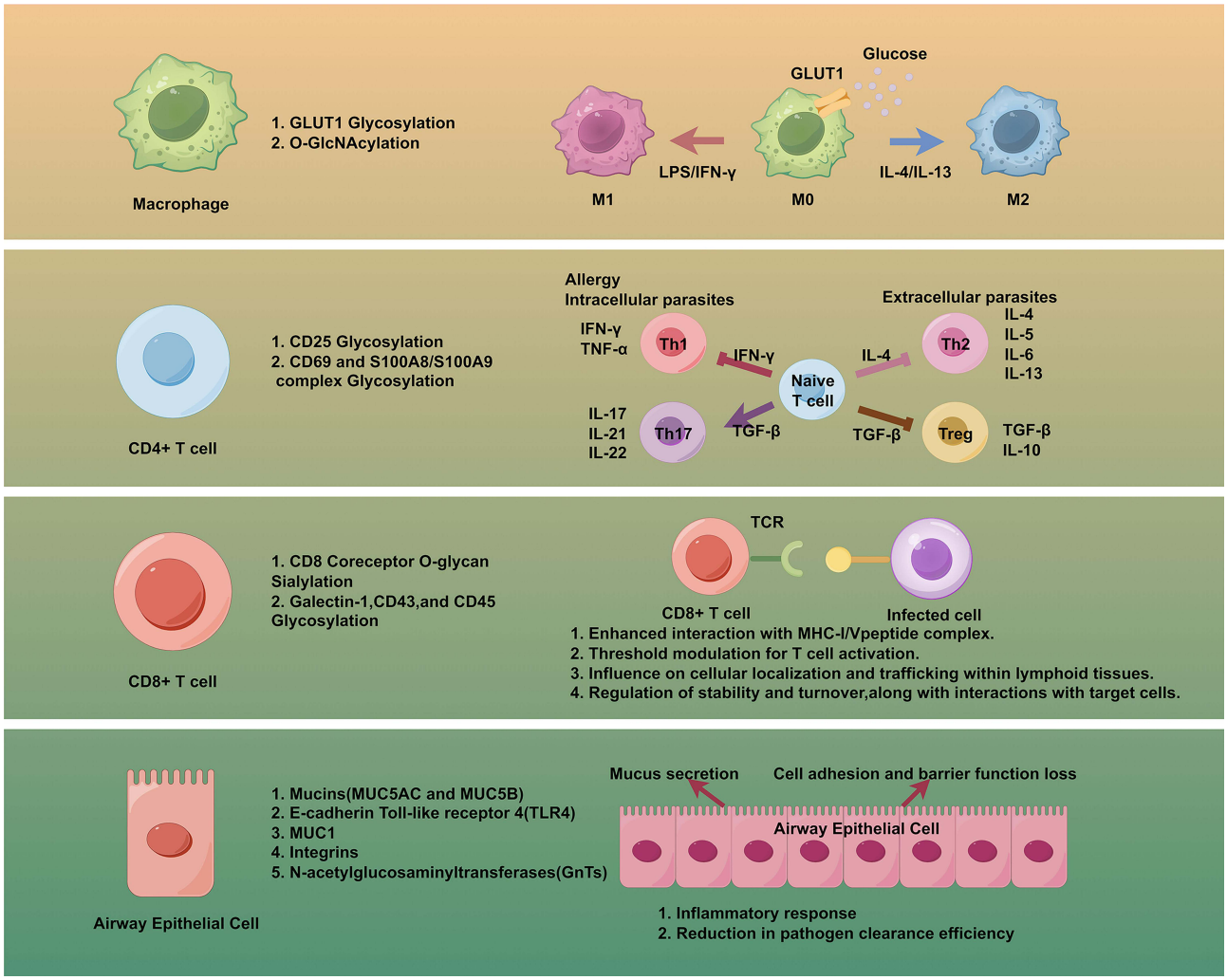

Figure 2 Glycosylation regulates asthma by influencing immune cell activation (By Figdraw). Glycosylation plays a crucial role in modulating the functionality of immune cells, influencing their roles in immune responses and inflammation processes. In macrophages, glycosylation of GLUT1 likely regulates glucose uptake, thereby impacting cellular metabolic status and activity. Additionally, O-GlcNAcylation participates in the regulation of pivotal signaling pathways such as NF-κB and Akt, affecting the production and secretion of cytokines, consequently influencing the polarization state and functions of macrophages. Moreover, glycosylation also exerts significant effects on the functionality of $CD4^+$ and $CD8^+$ T cells. For $CD4^+$ T cells, glycosylation modifications may influence the binding of CD25 to its ligand IL-2, thereby modulating signal transduction and T cell activation. Simultaneously, modulation of the stability and function of CD69 and the S100A8/S100A9 complex by glycosylation can impact T cell activation and pro-inflammatory responses. These glycosylation modifications have critical implications for the activation, proliferation, and function of $CD4^+$ T cells and naïve T cells, consequently influencing their roles in immune responses. In regulating the antigen recognition and activation processes of $CD8^+$ T cells, glycosylation also plays a pivotal role. For instance, glycosylation of the $CD8^+$ co-receptor may regulate its binding efficiency and specificity to MHC-I/peptide complexes. Furthermore, glycosylation modifications of Galectin-1, CD43, and CD45 may affect cell-cell interactions and signal transduction, consequently influencing the activation and effector functions of $CD8^+$ T cells. Additionally, regarding airway epithelial cells, glycosylation of mucins (such as MUC5AC and MUC5B) and E-cadherin contributes to protecting the airway surface from external stimuli and facilitating mucus clearance. Glycosylation mediated by integrins regulates the interaction between the extracellular matrix and intracellular structures, influencing cell migration and adhesion. These glycosylation modifications significantly impact the functionality of airway epithelial cells and contribute to the pathogenesis of asthma, offering novel avenues for asthma research and potential therapeutic targets.

asthma, and how does this alteration affect its regulatory role in airway inflammation and structure? Furthermore, the article also mentions the roles of other interleukins such as IL-10, IL-7, and their potential regulation by glycosylation in asthma. These discussions provide new insights into understanding the pathogenesis of asthma.

Chronic inflammation serves as the fundamental link between obesity and asthma.[89] With the increasing prevalence of obesity, obesity-related asthma has emerged as a significant and increasingly common phenotype of the disease. Unlike traditional asthma, obesity-related asthma typically presents with a non-T2 phenotype characterized by chronic low-grade systemic inflammation, insulin resistance and altered metabolic pathways.[90] Patients with this subtype often have a more severe disease course and a reduced response to conventional asthma therapies compared to their non-obese counterparts.[91] While the precise inflammatory mechanisms underlying obesity-related asthma remain incompletely

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understood, the association between weight loss and improved asthma control is well established.[92] Although research in this area is limited, glycosylation modification - known to play a critical role in inflammatory responses and metabolic dysfunction - may significantly influence the progression of this subtype of asthma. Glycosylation of various immune mediators and airway proteins could potentially contribute to disease pathogenesis. Further investigation is warranted to elucidate how glycosylation mechanisms interact with obesity-induced inflammation to modulate asthma outcomes. Such research could provide valuable insights into targeted therapeutic strategies for the treatment of obesity-related asthma.

Another focus is on the critical role of IgE in asthma and the impact of its glycosylation on binding to receptors and effector functions. While past studies suggest that non-glycosylated IgE can bind to receptors and trigger effector functions, recent research indicates that glycosylation remains necessary for this process.[93] This raises an intriguing question: does the glycosylation status of IgE change with the development of asthma, and how does this alteration affect its affinity for binding to receptors and effector functions? Exploring these questions can enhance our understanding of the role of IgE in the pathogenesis of asthma. Glycosylation modifications can affect the binding affinity of immune cell surface receptors to ligands, thereby modulating the activation of signaling pathways, which is crucial for the activation and maturation of immune cells such as T cells. Additionally, we need to consider not only the glycosylation of IgE but also the impact of glycosylation of other inflammatory mediators on the onset and exacerbation of asthma. Inflammatory mediators play essential roles in the pathophysiology of asthma, including leukotrienes, prostaglandins, histamine, TLRs, and endothelin-1, directly affecting the severity of asthma by regulating airway inflammation, bronchoconstriction, and mucus secretion.

Glycosylation modifications also participate in the regulation of T cell differentiation, affecting the generation and function of Th1, Th2, and Treg cells.[94] Of note is the role of glycosylation in Treg cells. Treg cells can suppress allergic inflammatory responses under normal circumstances, thereby alleviating airway inflammation and allergic reactions, exerting a protective effect against asthma. However, in asthma patients, abnormal numbers, and functions of Treg cells lead to immune imbalance, uncontrolled allergic inflammatory responses, and worsened asthma conditions.[95] Therefore, changes in glycosylation status may result in abnormal Treg cell function, thereby influencing the development and progression of asthma. Glycosylation plays a critical role in the activation of macrophages, directly influencing the onset and progression of asthma. Macrophages are pivotal in asthma's pathophysiology, with their activation status crucial for regulating airway inflammation, antigen presentation, airway remodeling, immune response modulation, and pathogen clearance. Glycosylation impacts macrophage function and activation through various mechanisms. It modulates the binding affinity of macrophage surface receptors to ligands, affecting signaling pathway activation levels.[96] Glycosylation also influences intracellular signaling pathway activation and participates in regulating macrophage metabolism, impacting cellular energy and immune metabolism balance.

In addition to asthma, glycosylation processes also play a significant role in other immune-related diseases, such as allergic rhinitis. The molecular interplay in allergic rhinitis could be similarly influenced by glycosylation modifications, affecting key immune cells and mediators involved in the disease. Recent studies, including Berghi O et al's work on the relationship between Chemokine Ligand 3 (CCL3) and allergic rhinitis,[97] highlight how altered glycosylation may impact immune responses, contributing to the pathophysiology of this condition. Understanding these processes in the context of allergic rhinitis offers exciting possibilities for developing new therapeutic strategies aimed at modulating glycosylation pathways to manage both asthma and allergic rhinitis more effectively.

In summary, glycosylation plays a multifaceted role in the onset and progression of asthma, influencing various molecules such as cytokines, interleukins, interferons, and IgE. The glycosylation status of molecules like TGF-β and IgE can modulate their functions and interactions, affecting airway inflammation and structural changes in asthma. Additionally, glycosylation modifications impact immune cell surface receptors' binding affinity to ligands, thus regulating signaling pathways crucial for immune cell activation and maturation, including T cells and macrophages. Moreover, glycosylation affects T cell differentiation, particularly in Treg cells, which play a vital role in immune balance and allergic inflammation suppression. Understanding the complex interplay between glycosylation and immune responses, including macrophage activation, provides valuable insights into asthma pathogenesis and offers potential therapeutic targets for managing asthma effectively. Finally, understanding the role of glycosylation in obesity-related asthma and other non-T2 phenotypes provides a more comprehensive understanding of asthma's pathophysiology, offering potential therapeutic targets for more personalized asthma treatments.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors have declared that no competing interest exists.

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