# O-GlcNAcylation: The crosstalk between infection immunity and autophagy in sepsis (Review)

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Received March 7, 2025; Accepted July 15, 2025

DOI: 10.3892/mmr.2025.13646

**Abstract.** Sepsis is a life-threatening condition triggered by dysregulated host immune responses, involving complex interactions among immune cell dysfunction, metabolic reprogramming and impaired autophagy. As a dynamic post-translational modification of serine/threonine residues, the attachment of N-acetylglucosamine (GlcNAc) via an oxygen linkage (O-GlcNAcylation) serves as a central hub in the pathogenesis of sepsis by integrating immunometabolic adaptation and autophagy regulation. This modification, dynamically controlled by O-GlcNAc transferase and O-GlcNAcase, modulates immune cell activation, inflammatory signaling and pathogen clearance. In sepsis, aberrant O-GlcNAcylation exacerbates organ damage by promoting pro-inflammatory cytokine release and suppressing protective autophagy. Studies have highlighted its dual role: Enhancing O-GlcNAcylation can bolster antiviral immunity, while targeted inhibition could mitigate bacteria-induced hyperinflammation. Furthermore, O-GlcNAcylation regulates the initiation, elongation and lysosomal fusion stages of autophagy by modifying key proteins, including beclin1, unc-51-like kinase 1 and synaptosome-associated protein 29, thereby influencing immune cell function. The present review also explores the mechanisms by which O-GlcNAcylation modulates immune responses across diverse pathogens, namely bacteria, fungi, viruses and parasites, via signaling pathways such as NF-κB and STAT, emphasizing the importance of site-specific interventions and biomarker development. In conclusion, targeting O-GlcNAcylation offers a potential novel direction for sepsis treatment. However, further exploration of its dynamic equilibrium in the precise regulation of the immune-autophagy network is necessary.

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*Key words:* O-GlcNAcylation, autophagy, pathogen infection, immune cells, sepsis

**Contents**



## 1. Introduction

Sepsis, resulting from a dysregulated host immune response to infection and characterized by the excessive release of inflammatory mediators and abnormal immune cell activation, remains a major challenge in global healthcare (1). In 2017, ~11.0 million sepsis-related mortalities were reported worldwide, representing 19.7% of all global mortalities. Despite a 52.8% decline in the age-standardized sepsis mortality from 1990 to 2017, sepsis remains a leading cause of death, prompting researchers to explore new treatment strategies (2).

The attachment of N-acetylglucosamine (GlcNAc) via an oxygen linkage (O-GlcNAcylation) is a post-translational modification (PTM) of the serine (Ser) and threonine (Thr) residues in proteins. This PTM can regulate the activation, proliferation and apoptosis of immune cells, as well as the production of inflammatory mediators, by influencing various metabolic pathways and cellular processes (3,4). The regulatory role of O-GlcNAcylation is particularly important in the context of sepsis (5), as it not only regulates the immune response to infection but also controls autophagy, the main mechanism by which cells clear pathogens and damaged organelles. Therefore, O-GlcNAcylation may play a critical role in the development of sepsis by affecting immune cell function and the efficiency of autophagy. The present review aims to investigate the underlying mechanisms of O-GlcNAcylation as a bridge between infection immunity and autophagy in sepsis, and to assess its potential as a therapeutic target.

## 2. Infection immunity in sepsis

Sepsis is a life-threatening condition characterized by organ dysfunction resulting from dysregulation of the host response to infection (6), and affected ~48.9 million individuals

worldwide in 2017, posing a great threat to health (2). The pathogens responsible for sepsis include bacteria, fungi, viruses and parasites.

Immune cells play a key role in the pathogenesis of sepsis. Immunological studies have shown that the host immune response in sepsis involves several sequential or concurrent processes that lead to excessive inflammation and immune suppression. This immune dysfunction results in impaired innate and adaptive immune responses (7).

During the initial phase of sepsis, the body mounts a robust inflammatory response to infection. Immune cells such as macrophages, dendritic cells, neutrophils and lymphocytes are activated following the recognition of pathogen-associated and damage-associated molecular patterns, which triggers the inflammatory response (8). As sepsis progresses, patients often develop immunosuppression, characterized by diminished immune cell function, particularly decreased activity of T cells and B cells, and increased activity of regulatory T (Treg) cells. This immunosuppressive state increases susceptibility to secondary infections and may lead to clinical deterioration and even death (Fig. 1) (8,9).

In sepsis, autophagy plays a vital role in cytoplasmic quality control, cellular metabolism, and innate and adaptive immune responses. It involves a variety of immune cells, including neutrophils, macrophages, T cells and B cells (10,11). In neutrophils, autophagy facilitates the clearance of pathogenic microorganisms, supports cellular function and prevents cell death. Studies have shown that the autophagic activity of neutrophils increases during sepsis, which may help to maintain their survival and function. However, the hyperactivation or inhibition of autophagy can impair the function of neutrophils, thereby affecting the progression of sepsis (12,13). In macrophages, autophagy not only facilitates the clearance of pathogens but also regulates the inflammatory response. During sepsis, the autophagic activity of macrophages may be suppressed, leading to the excessive release of inflammatory mediators and amplification of the inflammatory response. Conversely, the activation of autophagy can attenuate macrophage-mediated inflammation, offering protection against sepsis (14). Autophagy is also essential for the survival and function of T cells. In sepsis, the autophagic activity of T cells is weakened, which results in increased T-cell apoptosis and immunosuppression. In a murine model of sepsis, mice deficient in a T-cell-specific autophagy gene known as autophagy related 7 exhibited a higher mortality rate and greater immunosuppression than was observed in wild-type mice, suggesting a protective role for T-cell autophagy in the regulation of T-cell apoptosis and immunosuppression (10,15). The role of B cells in sepsis has not been fully elucidated; however, autophagy has been indicated to affect the immune response in sepsis by regulating B cell maturation and antibody production, with the activation of autophagy being suggested to contribute to the maintenance of B cell function and prevent immunosuppression (10). In summary, the effect of autophagy on immune cells in sepsis is multifaceted, involving various immune cells, such as neutrophils, macrophages, T cells and B cells. Activation or inhibition of autophagy may have an important effect on the pathogenesis of sepsis, and the regulation of autophagy may be a novel therapeutic strategy for sepsis.

## 3. Basic biological functions of protein O-GlcNAc modification

O-GlcNAcylation is a crucial PTM in which GlcNAc molecules attach to Ser or Thr residues in proteins. O-GlcNAc modifications differ from other types of glycosylation in several important aspects (3,16-18): i) They involve the addition of a monosaccharide, unlike other types where complex sugar chains are involved; ii) they primarily occur in the cytoplasm and nucleus, rather than via the Golgi or endoplasmic reticulum pathways; iii) the modification process is dynamic, reversible and regulated by O-GlcNAc transferase (OGT) and O-GlcNAcase (OGA); iv) they interact with other PTMs, such as phosphorylation, methylation and ubiquitination, to regulate protein activity and function; and v) they play a role in the regulation of key cellular biological functions. Due to these characteristics, O-GlcNAcylation makes a multifaceted contribution to cell biology and disease development.

*Impact of the interaction between O-GlcNAcylation and phosphorylation in terms of sepsis.* O-GlcNAcylation and phosphorylation are two key protein PTMs that regulate a variety of physiological and pathological processes through dynamic competition or synergy. O-GlcNAcylation involves the addition of a single GlcNAc group to Ser or Thr residues, whereas phosphorylation involves the addition of phosphate groups, often at the same or adjacent sites, resulting in a competitive or cooperative regulatory relationship between the two mechanisms (19). For example, in metabolic regulation, O-GlcNAcylation inhibits the Ser9 phosphorylation of glycogen synthase kinase-3β, thereby reducing the hyperphosphorylation of Tau protein, which may protect against neurodegenerative diseases such as Alzheimer's disease (20,21). Similarly, the Ser40 phosphorylation of tyrosine hydroxylase (TH) promotes dopamine synthesis, whereas O-GlcNAcylation reduces TH activity by inhibiting phosphorylation at this site, thereby affecting L-DOPA levels (22). In addition, O-GlcNAcylation can increase the activity of glycogen phosphorylase, suggesting that synergistic effects may exist between these two PTMs in certain contexts (23).

In the pathological process of sepsis, the balance between O-GlcNAcylation and phosphorylation markedly influences the regulation of inflammatory responses and cell death. Recent studies have shown that O-GlcNAcylation can inhibit phosphorylation-driven pro-inflammatory signaling by targeting key inflammation-related proteins. For example, the O-GlcNAcylation of gasdermin D (GSDMD) inhibits its phosphorylation-dependent activation, thereby attenuating lipopolysaccharide (LPS)-induced pyroptosis, a mechanism that may protect against vascular endothelial injury in sepsis (24). Similarly, homeodomain-interacting protein kinase 2 (HIPK2) inhibits hyperinflammation by promoting the acetylation of NF-κB via the phosphorylation of histone deacetylase 3 (HDAC3), while O-GlcNAcylation may affect this pathway indirectly by regulating the activity or stability of HIPK2 (25). The NF-κB acetylation promoted by the HIPK2-mediated phosphorylation of HDAC3 has been shown to ameliorate colitis-associated colorectal cancer and sepsis in mice. In another study, Toll-like receptor 4 (TLR4) was shown to activate ERK1/2 phosphorylation, leading to the

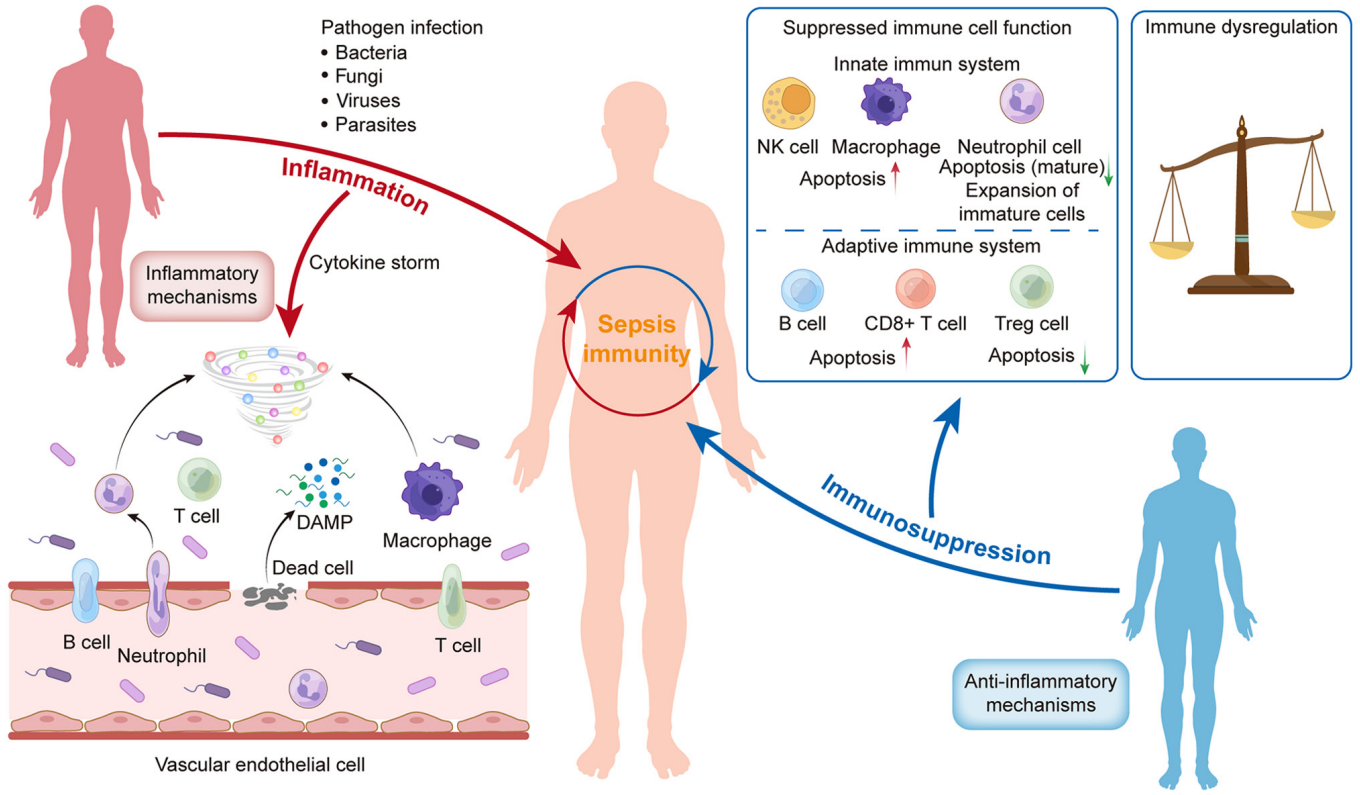


Figure 1. Pathophysiologic course of sepsis. During the development of sepsis, the balance of the immune system is disrupted. DAMP, damage-associated molecular pattern; NK, natural killer; Treg, regulatory T.

downregulation of Kruppel-like factor 4, thereby exacerbating the inflammatory response in sepsis (26).

In sepsis, phosphorylation is often associated with the amplification of pro-inflammatory and cell death signals. For example, peptidylprolyl cis/trans isomerase, NIMA-interacting 1 exacerbates the inflammatory response in septic shock by promoting the phosphorylation of p38 MAPK, which increases the activation of the NLR family pyrin domain containing 3 (NLRP3) inflammasome. O-GlcNAcylation can counteract this effect by competitively modifying the same or adjacent sites of p38 MAPK, thereby preventing its phosphorylation and blocking downstream inflammatory signaling (27,28). Notably, O-GlcNAcylation and phosphorylation may act synergistically in certain contexts. For example, O-GlcNAc modification has been shown to increase glycogenolysis by promoting the phosphorylation of glycogen phosphorylase L during energy stress (23). In summary, the dynamic interplay between O-GlcNAcylation and phosphorylation in sepsis reflects a precisely regulated balance that controls inflammatory intensity, cell death patterns and metabolic adaptation. Targeting this interaction may offer novel strategies for the treatment of sepsis.

*Impact of the interaction between O-GlcNAcylation and ubiquitination in terms of sepsis*. There is a complex, cross-regulatory relationship between O-GlcNAcylation and ubiquitination, both of which are involved in cellular stress responses, metabolic regulation and disease progression. O-GlcNAc modification affects the stability, activity and interactions of proteins by the dynamic addition or removal of GlcNAc groups, thereby influencing the ubiquitination process (29). For example, O-GlcNAcylation can increase the stability of key proteins by inhibiting their ubiquitination; the O-GlcNAcylation of the circadian regulators brain and muscle ARNT-like 1 and circadian locomotor output cycles kaput prevents their ubiquitin-mediated degradation, thereby maintaining the normal functioning of the biological clock (30). In addition, the synergistic or antagonistic effects of O-GlcNAcylation and ubiquitination play critical roles in processes such as DNA damage repair and cancer metabolism (31,32). The activity of certain E3 ubiquitin ligases, such as members of the cullin-RING ligase (CRL) family, can be regulated by O-GlcNAc modifications, thereby affecting the ubiquitination levels of their substrate proteins (33). The ubiquitin-proteosome system itself is highly complex, with various ubiquitin chain types, including lysine (Lys)48- and Lys63-linked chains, and dynamic modification patterns. These features form a multi-level interaction network with O-GlcNAcylation to coordinate cellular responses to stresses such as oxidative stress and nutrient deprivation (29,34).

The cross-regulation between O-GlcNAcylation and ubiquitination plays a key role in modulating the intensity of the inflammatory response and maintaining cellular homeostasis. Studies have shown that O-GlcNAc modification can dynamically modulate pro-inflammatory signaling pathways by targeting key components of the ubiquitination system. For example, in macrophages, O-GlcNAc-modified NOD-like receptor X1 (NLRX1) downregulates IL-1β expression by interacting with inhibitor of κB kinase α (IKK-α) and inhibiting its ubiquitination-dependent activation, thereby

potentially limiting tissue damage due to excessive inflammatory responses in sepsis (35). In addition, the E3 ubiquitin ligase tripartite motif containing 27 (TRIM27) exacerbates sepsis-related oxidative stress and endothelial dysfunction by promoting the ubiquitin-mediated degradation of peroxisome proliferator-activated receptor γ (PPARγ), and O-GlcNAc modification may counteract the pro-inflammatory effects of TRIM27 by stabilizing PPARγ protein levels (30,36). Notably, the diversity of ubiquitination systems, including different chain linkages such as Lys48- and Lys63-linked chain types, contributes to the dual regulatory features observed in sepsis: Lys48-linked ubiquitination typically targets proteins for proteosomal degradation, helping to clear damaged proteins, whereas Lys63-linked ubiquitination amplifies inflammation by activating pathways such as the NF-κB pathway (29,37). O-GlcNAc modification may balance the inflammatory phenotype of macrophages by selectively regulating the activity of specific E3 ligases, such as E3 ubiquitin-protein ligase COP1, and affecting the ubiquitination status of transcription factors such as CCAAT/enhancer binding protein β (38).

Ubiquitination often serves as a central node for pro-inflammatory and cell death signaling in sepsis, while O-GlcNAc modification may exert a protective effect through multi-level regulatory mechanisms. For example, microbial infection-induced endothelial cell dysfunction is associated with the aberrant ubiquitination of a variety of proteins, such as NADPH oxidase 4 (NOX4), whose stability is regulated by ubiquitination, and its overexpression exacerbates oxidative stress (36,37). O-GlcNAc modification may reduce the production of reactive oxygen species (ROS) by directly modifying NOX4 or regulating the activity of its E3 ligases, such as TRIM27, analogous to its modulatory role in the CRL family ubiquitin ligases involved in DNA damage repair (33). Small-molecule drugs targeting the ubiquitination system, such as deubiquitinase inhibitors, have been shown to modulate the inflammatory cascade in sepsis (39). Similarly, the development of OGT inhibitors or activators may provide new therapeutic strategies by modulating the O-GlcNAc-ubiquitination axis. Notably, there may be synergistic effects between these pathways: For example, O-GlcNAcylation may enhance the stability of NLRX1, promoting its binding to IKK-α and thereby indirectly inhibiting the ubiquitin-dependent activation of the IKK complex; this regulatory homeostasis may exhibit distinct regulatory characteristics at different stages of sepsis (35). In conclusion, the interplay between O-GlcNAcylation and ubiquitination constitutes a complex regulatory network in sepsis. Further elucidation of the underlying mechanism may lay a foundation for the development of targeted interventions to prevent inflammatory imbalance and organ injury.

*Impact of the interaction between O-GlcNAcylation and methylation in terms of sepsis*. There is extensive cross-regulation between O-GlcNAc modification and both DNA and histone methylation, which together contribute to the maintenance of epigenetic homeostasis and the regulation of gene expression. Studies have shown that OGT directly modifies DNA methyltransferase 1 through glucose-dependent O-GlcNAcylation, thereby inhibiting its activity, reducing the overall level of genomic methylation and affecting transposon silencing (40,41). At the histone level, OGT is recruited to specific chromatin regions by disruptor of telomeric silencing 1-like, a histone methyltransferase, where it catalyzes the O-GlcNAcylation of histone H2B, which works synergistically with histone H3 Lys79 (H3K79) methylation to regulate gene transcriptional activation (31). In addition, metabolic signals, such as glucose availability, are integrated into the epigenetic regulatory network via O-GlcNAc modification. For example, the c-Myc oncoprotein modulates mitochondrial metabolism and O-GlcNAc cycling, influencing the activity and subcellular localization of DNA and RNA demethylases, thereby linking cellular metabolic state to epigenetic reprogramming (42).

The crosstalk between O-GlcNAcylation and methylation regulates epigenetic reprogramming and metabolic adaptation, which affects the inflammatory response and organ injury. Dysregulation of this epigenetic modification is particularly prominent in monocytes from patients with sepsis and is strongly associated with the aberrant expression of pro-inflammatory cytokines such as TNF-α and IL-6, as well as organ dysfunction (43). In addition, the synergistic interaction of histone methylation with O-GlcNAcylation has a dual role in sepsis: During the endotoxin tolerance stage, G9a-mediated H3K9 methylation and DNA methylation contribute to silencing of the TNF-α gene (44), while O-GlcNAc modification dynamically regulates the expression of pro- and anti-inflammatory genes by regulating DOT1-like histone Lys methyltransferase-dependent H3K79 methylation (31). This multilevel epigenetic-metabolic-ubiquitination regulatory network provides a new paradigm for targeting immunometabolic imbalances in sepsis.

In conclusion, O-GlcNAcylation forms a multi-dimensional regulatory network with other PTMs, including phosphorylation, ubiquitination and methylation, that supports a shift in sepsis treatment from a single anti-inflammatory mode to a systematic regulation based on the dynamic integration of the PTM network. This integrated perspective could provide enable the reversal of immunometabolic imbalances in sepsis.

## 4. O-GlcNAcylation and autophagy

The PTM of proteins plays a key role in autophagy, either by directly regulating the expression of autophagy-related genes or by modulating key components of the autophagy signaling pathway (45-47). Among these PTMS, O-GlcNAcylation has been shown to be closely associated with the regulation of autophagy; it regulates autophagy by modifying key autophagy-related proteins, thereby affecting their activity, stability and subcellular localization (18). Several proteins with different roles in the autophagy pathway have been identified as potential targets of O-GlcNAcylation (Fig. 2 and Table I) (28,48-60).

The activation of unc-51 like autophagy activating kinase 1 (ULK1) by stressors such as nutrient deprivation (for example, amino acid starvation) and energy stress (for example, ATP depletion/AMP elevation) triggers the autophagic process. ULK1 and ULK2 form protein complexes with various mitosome-associated proteins, including 200 kDa FAK family kinase-interacting protein, autophagy related (ATG)13 and ATG101, which jointly regulate the initiation phase of autophagy (61). These ULK protein complexes play a key regulatory role in the

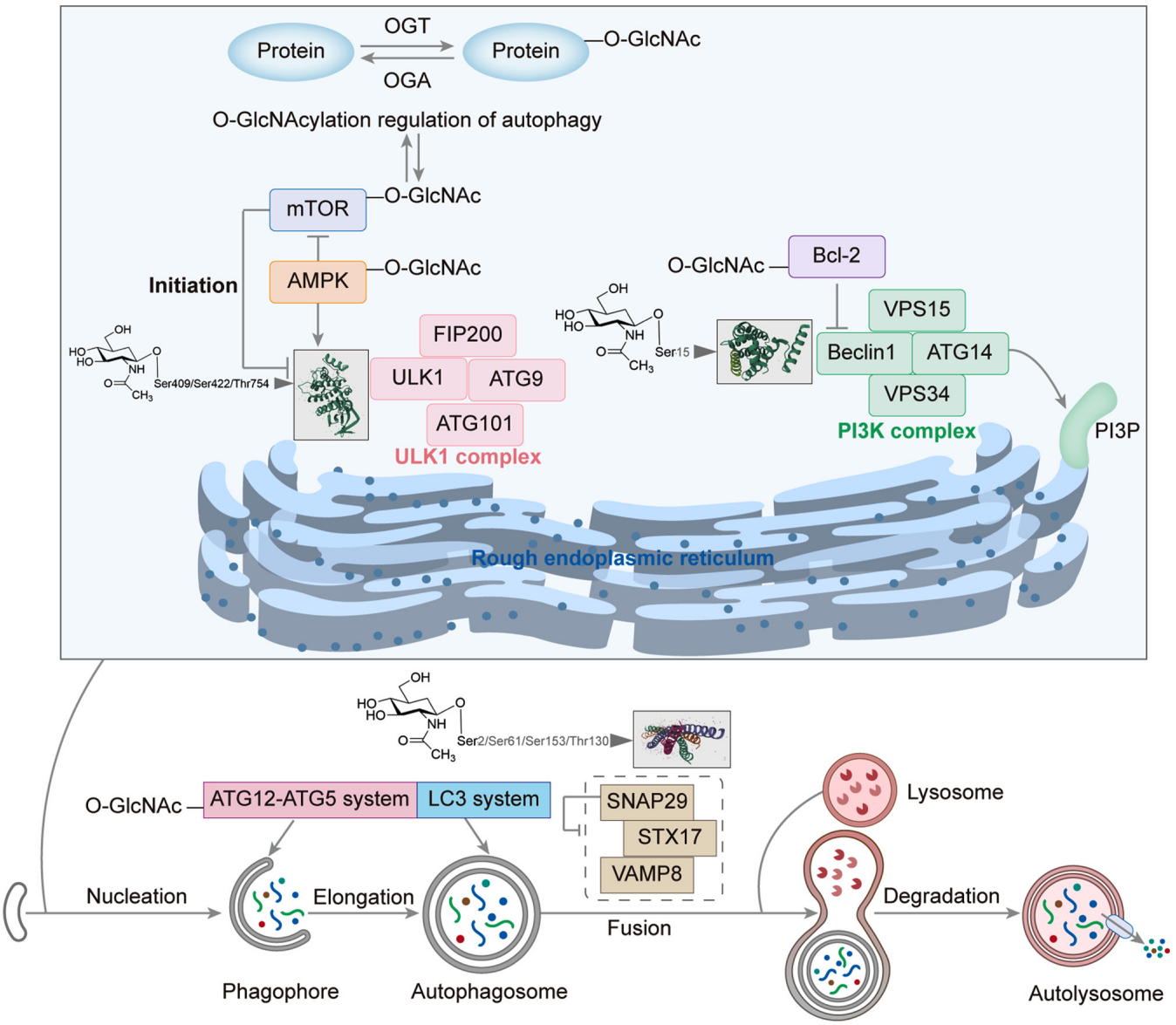


Figure 2. Role of O-GlcNAcylation in the initiation, nucleation, elongation and fusion stages of autophagy and lysosomal activity. AMPK, AMP-activated protein kinase; ATG, autophagy related; FIP200, FAK family kinase-interacting protein of 200 kDa; LC3, microtubule-associated protein 1A/1B-light chain 3; O-GlcnAc, O-linked N-acetylglucosamine; O-GlcNAcylation, attachment of GlcNAc via an oxygen linkage; OGA, O-GlcNAcase; OGT, O-GlcNAc transferase; PI3K, phosphoinositide 3-kinase; PI3P, phosphatidylinositol-3-phosphate; SNAP29, synaptosome-associated protein 29; STX17, syntaxin 17; ULK1, unc-51 like autophagy activating kinase 1; VAMP8, vesicle-associated membrane protein 8; VSP, voltage-sensing phosphatase.

formation of autophagic vesicles and are responsive to signals from multiple signaling pathways. The activity of the ULK1 complex is regulated by both mTOR complex 1 and AMP-activated protein kinase (AMPK) (62,63). Specifically, activation of mTOR via Akt and MAPK signaling inhibits autophagy, while the inhibition of mTOR by AMPK or p53 signaling promotes autophagy. The ULK complex promotes the localized synthesis of phosphatidylinositol-3-phosphate by phosphorylating components of the class III phosphatidylinositol 3-kinase complex, which includes beclin1, vacuolar protein sorting (VPS)15, VPS34 and ATG14 (64). Beclin1 has been identified as a direct target of O-GlcNAcylation, and the O-GlcNAcylation and phosphorylation of beclin1 at the Ser15 site has been shown to regulate autophagy in HTR-8/SVneo cells (48). Bcl-2 inhibits autophagy by interacting with beclin1, and Bcl-2 is also a target of O-GlcNAcylation (49). The O-GlcNAcylation of beclin1 enhances its binding to Bcl-2, thereby suppressing autophagic activity, whereas the O-GlcNAcylation of Bcl-2 regulates autophagy and apoptosis by influencing its expression levels (50,65).

The elongation of phagophores is promoted by two ubiquitin-like conjugation systems: The ATG12-ATG5 system and the microtubule-associated protein 1A/1B-light chain 3 (LC3) system (66). Wang and Hanover (67) demonstrated that the deletion of OGT in *Drosophila* resulted in a reduction in O-GlcNAc levels and a significant increase in the accumulation of GFP-LGG-1 (an ATG8/LC3 homolog) and its phosphatidylethanolamine-modified form under starvation conditions, indicating enhanced autophagosome formation. Furthermore, OGT knockdown upregulated the mRNA expression of ATG1 and ATG5, whereas OGT overexpression

Table I. Summary of O-GlcNAc modification sites and their effects on protein function in autophagy regulation.

| Protein | O-GlcNAc modification sites | O-GlcNAcylation regulatory mechanism | Autophagy phase | (Refs.) |
|---|---|---|---|---|
| Beclin1 | Ser15 | O-GlcNAcylation enhances beclin1 binding to Bcl-2, blocks its independent activity, inhibits autophagosome formation, and reduces basal autophagy levels | Initiation | (48,49) |
| Bcl-2 | Unclear | O-GlcNAcylation upregulates Bcl-2 expression, enhances binding stability with beclin1, inhibits autophagy, promotes apoptosis, and balances cellular stress responses | Initiation | (49,50) |
| AMPK | Unclear | O-GlcNAc modification inhibits AMPK activity, suppressing ULK1 activation and autophagy | Initiation | (28) |
| mTOR | Unclear | Inhibiting OGT enhances autophagy in rat cortical neurons; this effect is further amplified when treated with the mTOR inhibitor rapamycin | Initiation | (51) |
| ULK1 | Thr754, Ser409 and Ser422 | O-GlcNAcylation at Thr754 is critical for VPS34 activation via ATG14L, promoting autophagy; Ser409 modification inhibits phosphorylation at Ser423, stabilizing ULK1; maresin-2 activates GFAT1, enhances O-GlcNAc modification and autophagosome formation via TAK1-TAB1 inhibition, but ULK1 Ser409 and Ser422 mutations counteract this effect | Initiation | (52-54) |
| PINK1 | Unclear | O-GlcNAcylation inhibits PINK1 stability, blocks PARKIN recruitment during mitochondrial depolarization, suppresses mitophagy, and leads to the accumulation of damaged mitochondria | Elongation | (55) |
| SNAP29 | Ser2, Ser61, Thr130 and Ser153 | O-GlcNAcylation blocks SNARE complex assembly with STX17-VAMP8, thereby interfering with membrane fusion and inhibiting autophagy | Fusion | (56-60) |

AMPK, AMP-activated protein kinase; ATG14L, autophagy-related protein 14-like; GFAT1, glutamine:fructose-6-phosphate transaminase 1; O-GlcNAc, O-linked N-acetylglucosamine; O-GlcNAcylation, attachment of GlcNAc via an oxygen linkage; OGT, O-GlcNAc transferase; PINK1, PTEN-induced putative kinase 1; Ser, serine; SNAP29, synaptosome-associated protein 29; STX17, syntaxin 17; TAK1-TAB1, complex formed by transforming growth factor b-activated kinase 1 and TAK1 binding protein 1; Thr, threonine; ULK1, unc-51 like autophagy activating kinase 1; VAMP8, vesicle-associated membrane protein 8; VPS34, voltage-sensing phosphatase 34.

inhibited the transcription of ATG5 and ATG8 (68). These findings suggest that O-GlcNAcylation limits autophagic activity by suppressing the expression of ATG genes. This mechanism may operate synergistically with the stabilization of the beclin1/Bcl-2 complex by O-GlcNAcylation in mammals to maintain the basal autophagy in a low-activity state under normal conditions.

During autophagic fusion, intact autophagosomes fuse with lysosomes to form autolysosomes, which enables the degradation of substances via the action of lysosomal enzymes. O-GlcNAcylation has been shown to regulate the autophagosome-lysosome fusion phase of autophagy in an arsenic-exposed environment by targeting synaptosome-associated protein 29 (SNAP29) (29). In SNAP29-mediated vesicle fusion, autophagosome membranes containing syntaxin 17 (STX17) are linked to lysosomes containing vesicle-associated membrane protein 8 (VAMP8) (69). The O-GlcNAcylation of SNAP29 blocks the assembly of the SNARE complex from STX17, SNAP29 and VAMP8, thereby impairing normal autophagy (70).

## 5. Infection and immune regulation by O-GlcNAc modification

O-GlcNAc modification affects cellular metabolism, autotransduction, translation and signal transduction as a nutrient and stress sensor. The maintenance of proper O-GlcNAcylation is crucial for health, as imbalances in O-GlcNAcylation can result in pathological conditions such as tumors, diabetes and neurodegenerative diseases (71-73). A number of studies have focused on the role of O-GlcNAcylation in the regulation of the immune response and maintenance of homeostasis during infection. The present review offers insights into the role of O-GlcNAcylation in the modulation of immune responses against viral, bacterial, fungal and parasitic infections, and explores its potential as a therapeutic target in sepsis (Fig. 3).

*Function of O-GlcNAcylation in immune cell recognition of bacterial infections*. Neutrophils are key cells of the innate immune system that rapidly migrate to sites of bacterial infection and remove pathogens via phagocytosis, the release

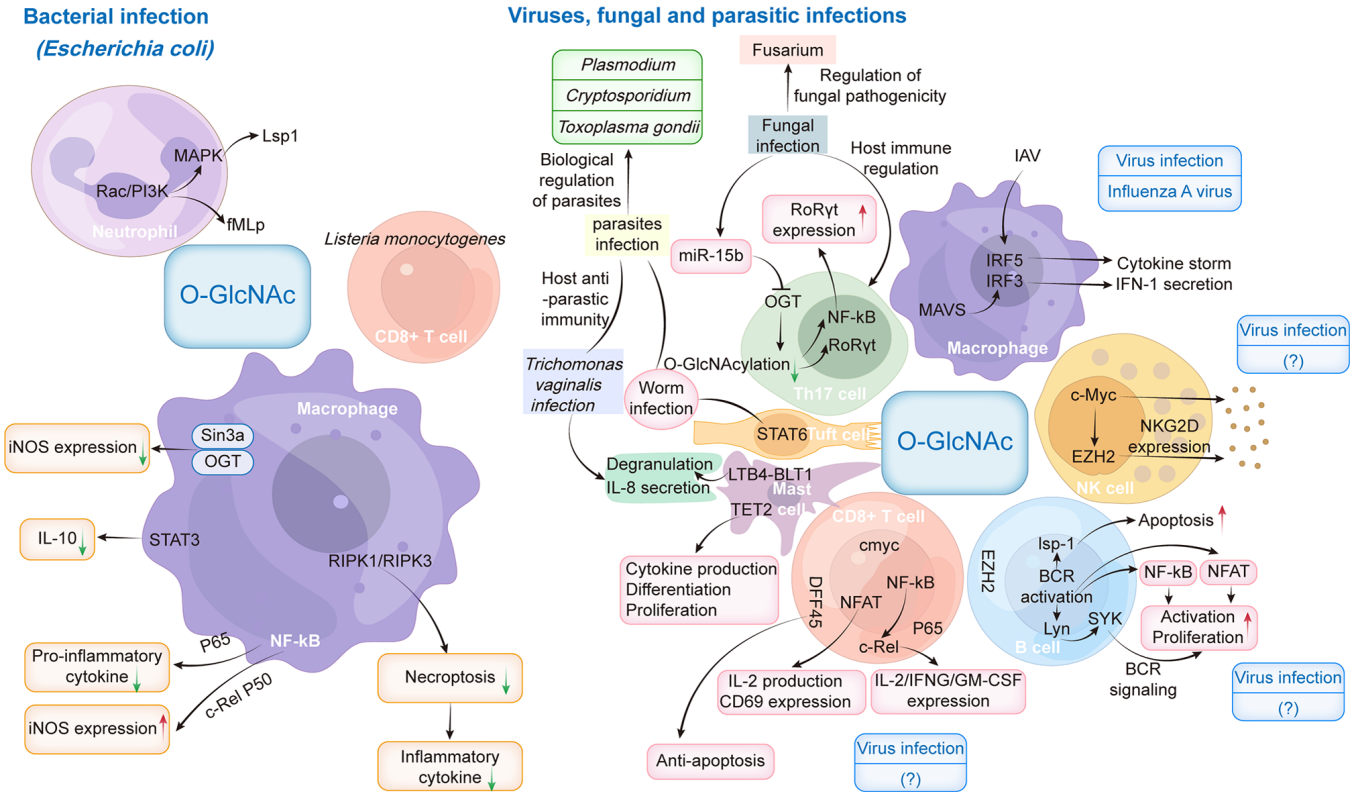


Figure 3. Role of O-GlcNAcylation in the immune response to infection with different pathogens. BCR, B-cell receptor; BLT1, LTB4 receptor 1; c-Rel, cellular-Rel; DFF45, DNA fragmentation factor 45; EZH2, enhancer of zeste 2; fMLP, N-formyl-methionyl-leucyl-phenylalanine; GM-CSF, granulocyte macrophage-colony-stimulating factor; IAV, influenza A virus; IFN, interferon; IFNG, IFN-g; iNOS, inducible nitric oxide synthase; IRF, IFN regulatory factor 3; Lsp1, lymphocyte-specific protein 1; LTB4, leukotriene B4; MAVS, mitochondrial antiviral signaling protein; miR-15b, microRNA-15b; NFAT, nuclear factor of activated T-cells; NK, natural killer; NKG2D, NK group 2D; O-GlcNAc, O-linked N-acetylglucosamine; OGT, O-GlcNAc transferase; PI3K, phosphoinositide 3-kinase; RIPK, receptor-interacting protein kinase; RoRγt, retinoic acid receptor-related orphan receptor gt; TET2, Tet methylcytosine dioxygenase 2; Th17, T helper 17.

of ROS and necrosis. Neutrophils are the initial responders to injury and infection, and the prognosis of sepsis is poor when neutrophil migration is impaired (74). In both animal models and patients with advanced sepsis, neutrophil function is notably compromised, as evidenced by diminished bacterial clearance, reduced reactivity, decreased ROS production and a significant reduction in neutrophil numbers within infected tissues (75).

O-GlcNAcylation has been found to significantly influence neutrophil chemotaxis and cell migration. For example, treatment with the chemoattractant N-formylmethionyl-leucyl-phenylalanine significantly elevates O-GlcNAcylation levels, thereby promoting neutrophil chemotaxis and migration (76). In addition, glucosamine (GlcN) promotes O-GlcNAcylation by increasing the availability of UDP-GlcNAc, which is the donor substrate for OGT; GlcN enters the hexosamine biosynthetic pathway (HBP) downstream of the rate-limiting enzyme glutamine-fructose-6-phosphate transaminase 1, effectively bypassing it and boosting UDP-GlcNAc production (77). Mechanistically, enhanced O-GlcNAcylation promotes Rac- and phosphoinositide 3-kinase-dependent chemotaxis. Rac is an key small GTPase that regulates neutrophil mobilization by activating downstream MAPK signaling and promoting the phosphorylation of lymphocyte specific protein 1 at Ser243 (78-80). These signaling pathways are critical for neutrophil migration and effector functions. O-GlcNAcylation is inducible in neutrophils and modulates their dynamic responses, potentially providing a novel therapeutic target for the treatment of sepsis.

Macrophages play a key role in resistance to bacterial infections by eliminating pathogens through various mechanisms, including the activation of inducible nitric oxide synthase (iNOS) to produce nitric oxide (NO). NO is a gaseous signaling molecule with antibacterial properties, capable of inhibiting bacterial metabolic enzymes, thereby impairing bacterial viability. In response to bacterial infection or inflammatory stimuli, macrophages increase iNOS expression, thereby increasing NO production (81). NF-κB is a key regulator of the inflammatory response in macrophages and can be modified via O-GlcNAcylation. In RAW264.7 macrophage-like cells, the interaction of OGT with murine Sin3A disrupts NF-κB activation and downregulates iNOS gene expression upon LPS stimulation (82). In microglia, O-GlcNAcylation of the NF-κB subunit cellular-Rel (c-Rel) promotes the formation of the c-Rel-p50 heterodimer and increases iNOS production (83). Notably, the response of the NF-κB subunit p65 to O-GlcNAcylation differs markedly from that of c-Rel. Thiamet-G, a potent and selective inhibitor of OGA, exerts anti-inflammatory effects by promoting the O-GlcNAcylation of p65 in microglia, which subsequently modulates its nuclear localization and reduces the expression of inflammatory genes (84).

Inflammatory diseases such as sepsis are characterized by elevated glucose metabolism in immune cells. Despite macrophages exhibiting increased glycolytic activity and pentose phosphate pathway activation during inflammation, endotoxin exposure inhibits HBP activity, resulting in decreased protein O-GlcNAcylation. Loss of OGT promotes the innate immune response and exacerbates inflammation in sepsis. Specifically, OGT-mediated O-GlcNAcylation of receptor-interacting protein kinase (RIPK)3 at Thr467 disrupts its interaction with RIPK1 and RIPK3 proteins, thereby inhibiting downstream innate immune responses, necroptosis and antibacterial activity (85).

$CD8^+$ T cells are essential for cell-mediated immunity. Upon acute infection, naive $CD8^+$ T cells differentiate into effector cells following antigen stimulation. These effector cells eliminate bacteria by releasing granules containing perforins and granzymes, and secreting cytokines such as interferon (IFN)-γ and TNF-α (86,87). This immune response involves the phosphorylation of various intracellular signaling proteins. Protein O-GlcNAcylation often acts synergistically with phosphorylation (16). Lopez Aguilar *et al* (88) demonstrated that O-GlcNAcylation was dynamically elevated in murine $CD8^+$ T cells during Listeria infection and *in vitro* differentiation, with activated effector cells exhibiting increased global levels *in vivo*, and memory-like cells exhibiting even higher levels (including distinct high-molecular weight modifications) *in vitro*. Proteomics revealed that O-GlcNAc in effector-like cells primarily targets transcription/translation machinery (such as ribosomal proteins) to enable rapid proliferation, while in memory-like cells it modifies transcriptional regulators, mRNA processing factors and tRNA synthetases, suggesting roles in establishing a poised state. Notably, O-GlcNAc contributes to the 'histone code' in both subsets, implicating it in epigenetic regulation of T cell function.

O-GlcNAcylation plays a key regulatory role in the immune response triggered by bacterial infection by dynamically modifying inflammation-related proteins. Pathogen-associated molecular patterns, such as bacterial LPS, can increase O-GlcNAcylation levels in endothelial cells, thereby exacerbating inflammation via the activation of inflammatory signaling pathways (89). At the molecular level, the OGT-mediated glycosylation of NLRX1 facilitates its interaction with IKK-α and promotes the expression of IL-1β in M1 macrophages (35). In parallel, O-GlcNAcylation of the NLRP3 inflammasome not only directly regulates pyroptosis but also promotes the release of inflammatory cytokines by enhancing the activity of the NIMA related kinase 7/NLRP3 axis (90,91). Furthermore, this PTM can create a positive feedback loop, whereby the O-GlcNAcylation of STAT3 further amplifies pro-inflammatory signaling by enhancing JAK2/STAT3 pathway signaling activity (92,93). As an upstream regulator, the phase separation process of TNF receptor-associated factor 6 may also contribute to this regulatory network. Notably, inhibition of O-GlcNAcylation has been shown to effectively block STAT3- and forkhead box protein O1-mediated oxidative stress-induced apoptosis (93-95), suggesting that targeting this modification may be a promising strategy for the alleviation of hyperinflammation during bacterial infections.

These findings suggest that targeting O-GlcNAc modifications may represent a novel therapeutic strategy for the treatment of sepsis by optimizing immune cell function and reducing the tissue damage caused by excessive inflammation.

*Influence of O-GlcNAcylation on immune cell detection of fungal infections.* O-GlcNAcylation has been implicated in the differentiation of T helper (Th)17 cells during fungal infections. Naive $CD4^+$ T cells can differentiate into Th1, Th2, Th17 and Treg cells (96). The downregulation of OGT through microRNA-15b has been shown to inhibit Th17 cell differentiation, thereby contributing to the pathogenesis of multiple sclerosis (97). In addition, elevated O-GlcNAc levels have been shown to promote the secretion of IL-17A by Th17 cells and upregulate the production of lipid ligands for the transcription factor RAR-related orphan receptor γt in diet-induced obese mice (98). Furthermore, in Treg cells, O-GlcNAc-mediated post-translational modifications of the T-cell receptor (TCR) have been demonstrated to increase the stability of forkhead box P3 and activate STAT5, effects that act synergistically to control Treg cell homeostasis and function (96).

Notably, fungal O-GlcNAc metabolism itself directly affects pathogenicity. As a key signaling molecule, GlcNAc regulates morphological transitions, the expression of virulence factors and environmental adaptation in a variety of fungi such as *Fusarium*. For example, deletion of the OGT homologous gene FpOGT in *Fusarium proliferatum* inhibits the expression of glucose metabolism-related genes, such as glucokinase, resulting in restricted fungal growth, a downregulated stress response and markedly reduced virulence (99). In addition, GlcNAc has been demonstrated to be a key metabolic target for fungal pathogenesis since it regulates cell wall synthesis, biofilm formation and host tissue invasion pathways (100,101). From a therapeutic perspective, interventions targeting GlcNAc sensing and metabolism, such as GlcNAc analogs or metabolic engineering, have been shown to effectively reduce the virulence of pathogenic fungi (102).

Therefore, in sepsis complicated by fungal infection, the combined modulation of host O-GlcNAc levels to enhance Th17-mediated antifungal immunity while inhibiting fungal GlcNAc-dependent virulence pathways may offer a synergistic therapeutic strategy. Future studies are necessary to further elucidate the molecular mechanisms of the host-fungus O-GlcNAc interaction network and to develop dual regulatory strategies to optimize immunometabolic balance.

*Role of O-GlcNAcylation in immune cell recognition of viral infections.* Macrophages play a crucial role in the innate immune system, particularly for the early detection of and response to viral infections. Research indicates that O-GlcNAcylation in macrophages is essential for the recognition of RNA viruses. These viruses are detected by cytosolic retinoic acid-inducible gene I-like receptors (RLRs), particularly retinoic acid-inducible gene I and melanoma differentiation-associated gene 5. Upon viral recognition, these receptors engage mitochondrial antiviral signaling protein (MAVS), which activates IFN regulatory factor (IRF)3 and promotes the production of type I IFN (103). In mouse bone marrow-derived macrophages, the absence of OGT disrupts MAVS-dependent RLR signaling and reduces inflammatory

cytokine expression (104). Research has further shown that O-GlcNAcylation is crucial for modulating immune responses and increasing infection resistance in macrophages. During influenza A virus infection, O-GlcNAcylation regulates the inflammatory response by modulating the activity of specific transcription factors.

Specifically, O-GlcNAcylation at the Ser430 residue of IRF5 is necessary for its Lys63-linked ubiquitination, which promotes IRF5 activation by facilitating nuclear translocation and interaction with the E3 ubiquitin ligase TRAF6. This modification drives downstream proinflammatory cytokine production during influenza infection (105). Thus, both IRF3 and IRF5 undergo O-GlcNAcylation and ubiquitination, which are crucial for the regulation of macrophage-mediated inflammatory responses following influenza infection. Balancing these modifications is essential to ensure the appropriate intensity of the immune response while preventing excessive inflammation.

Natural killer (NK) cells are crucial components of the innate immune system, responsible for targeting and eliminating virus-infected cells. O-GlcNAcylation has been shown to modulate the function of NK cells as a PTM; specifically, the elevated O-GlcNAcylation of NK cells attenuates their cytotoxicity. Notably, certain molecules, such as the glutathione S-transferase-soluble HLA-G1α chain fusion protein, inhibit O-GlcNAcylation in NK cells, thereby enhancing their cytotoxic function (106).

NK group 2D (NKG2D) is an activating receptor on NK cells that facilitates the recognition and elimination of virus-infected cells presenting stress-induced ligands associated with major histocompatibility complex class I molecules (107). The cytotoxic function of NKG2D-expressing NK cells is regulated by the transcription factor enhancer of zeste 2 (EZH2), a core subunit of polycomb repressive complex 2. Inhibition of EZH2 has been shown to accelerate the maturation of NK cells and improve their killing ability. Notably, EZH2 contains five O-GlcNAcylation sites, which are pivotal for its stabilization and function (108-110).

Another transcription factor that induces cytotoxicity by regulating the O-GlcNAcylation of NK cells is c-Myc. It upregulates the expression of granzyme B, thereby increasing the cytotoxic activity of NK cells against virus-infected cells. O-GlcNAcylation helps to maintain the stability and function of c-Myc. The substrate for this modification, UDP-GlcNAc, is generated through glycolysis and the glutamine metabolic pathway. Glutamine depletion reduces UDP-GlcNAc levels in NK cells, subsequently impacting c-Myc function and diminishing cytotoxic activity (111). Thus, O-GlcNAc modification potentially boosts NK cell immune responses, aiding in the elimination of infected cells and protecting against the progression of sepsis.

B cells are activated via the B-cell receptor (BCR) on their surface, a process that is regulated by O-GlcNAcylation. This PTM affects the YN proto-oncogene, an Src family tyrosine kinase, and its interaction with spleen tyrosine kinase to initiate BCR signaling (112). In addition, the O-GlcNAcylation of nuclear factor of activated T-cells, cytoplasmic 1 (NFATc1) and NF-κB further amplifies B cell activation (113). Following BCR crosslinking, the interaction between O-GlcNAc-modified lymphocyte-specific protein 1 (Lsp1) and protein kinase C-β1 is crucial for the regulation of apoptosis in activated B cells. The O-GlcNAcylation of Lsp1 at Ser209 facilitates its phosphorylation at Ser243, thereby modulating Lsp1 function (114). Also, the dysregulation of EZH2 activity or aberrant O-GlcNAcylation may impair antibody production in B cells, indicating the importance of O-GlcNAcylation in the modulation of B cell function and antibody responses (115).

$CD8^+$ cytotoxic T cells identify and destroy infected cells during viral infections. NF-κB and c-Myc are essential transcription factors in the activation of $CD8^+$ T cells, and TCR-mediated stimulation induces their O-GlcNAcylation. The O-GlcNAcylation of c-Rel enhances its binding to the CD28 response element, resulting in the production of proinflammatory cytokines, including IL-2, IFN-γ and granulocyte macrophage-colony-stimulating factor. In addition, site-specific O-GlcNAcylation stabilizes c-Myc, while the inhibition of OGT decreases c-Myc levels (116,117). Furthermore, NFATc1 is mainly O-GlcNAcylated in the cytosol, and translocates to the nucleus after TCR activation. The O-GlcNAc modification of NFAT has been demonstrated to be crucial for its nuclear translocation and function, as the inhibition of OGT decreases TCR-induced IL-2 production and CD69 expression (113). These findings highlight the importance of O-GlcNAcylation in T cells. The inhibition of OGT has also been shown to affect the transcriptional activity of NF-κB in T cells, with the p65 subunit of NF-κB undergoing O-GlcNAcylation (113,118). In addition, the O-GlcNAcylation of DNA fragmentation factor 45 shields proteins from caspase-mediated cleavage during DNA damage-induced T-cell apoptosis, indicating its protective role against apoptotic cell death in T cells (119).

Modulating O-GlcNAc glycosylation levels or its downstream signaling pathways may help to address immune imbalances in patients with sepsis, suppress excessive inflammation, prevent organ dysfunction and ultimately improve clinical outcomes.

*Role of O-GlcNAcylation in immune cell recognition of parasitic infections*. The dual role of O-GlcNAcylation in host anti-parasitic immunity and parasite self-regulation has become increasingly evident. This involves an interaction between the regulation of host immune cell function and the metabolic dependence of the parasite on O-GlcNAc pathways. In the anti-parasitic immunity of the host, O-GlcNAc contributes to key pathways that regulate type 2 immune responses. For example, the O-GlcNAcylation of STAT6 in intestinal epithelial cells forms the first line of defense against helminth infection by driving tuft cell proliferation and the release of gasdermin C-dependent alarmins (120). Restoration of STAT6 activation partially rescues the impaired immune responses to helminth infection in OGT-deficient mice, which exhibit defective STAT6 signaling and intestinal villus dysplasia (121). In addition, mast cell function is closely associated with O-GlcNAc modification: In *Trichomonas vaginalis* infection, leukotriene B4 (LTB4) secreted by the parasite binds to LTB4 receptor 1 on mast cells, elevates O-GlcNAc levels and promotes NADPH oxidase-dependent migration, degranulation and IL-8 secretion (122). However, Tet methylcytosine dioxygenase 2 (TET2)-mediated O-GlcNAcylation affects mast cell differentiation and cytokine production by regulating chromatin accessibility (123). These findings suggest that

O-GlcNAc contributes to the anti-parasitic response through the multifaceted regulation of host immune cell functions, including Th2 polarization, epithelial barrier defense and mast cell effector functions.

At the biological level, glycosylation modifications, including O-GlcNAc-related pathways, are essential for the survival, development and pathogenicity of parasites. For example, *Plasmodium falciparum* relies on the HBP to produce glycosylphosphatidylinositol-anchored proteins, which are critical for the invasion of red blood cells and immune evasion. Therefore, blocking this pathway can lead to the growth arrest of *Plasmodium* at the schizont stage (124). Although *Cryptosporidium* lacks certain glycosylases, it compensates by hijacking host glycosylation resources to perform its protein modifications (125). In addition, glycosylation in various parasites, such as *Plasmodium* and *Toxoplasma gondii*, affects host immune recognition by altering the function of surface proteins (126,127). Notably, there is an interaction between host and parasite O-GlcNAc metabolism: Parasites may disrupt the glycosylation homeostasis of host immune cells by secreting metabolites such as GlcNAc, while host-targeted drugs against key enzymes involved in parasite glycosylation, such as glutamine:fructose-6-phosphate transaminase (GFAT) in the HBP, can simultaneously inhibit parasite growth and enhance immune clearance (124,127).

In summary, O-GlcNAcylation affects infection outcomes through host-parasite bidirectional regulation: It regulates host type 2 immune responses and effector cell functions through targets such as STAT6 and TET2, while parasites rely on glycosylation pathways to complete their developmental cycles and evade host immunity. Future studies should aim to further elucidate the parasite-specific O-GlcNAc modification network and explore dual intervention strategies, such as the development of GFAT inhibitors combined with immunomodulators, to synergistically enhance anti-parasitic immunity and block pathogen metabolism-dependent virulence mechanisms.

## 6. Discussion

O-GlcNAcylation plays diverse roles in different types of infection by modulating host defense mechanisms and affecting immune cell function. Specifically, macrophage responses to infection reveal a key functional divergence of O-GlcNAcylation: It promotes antiviral defenses but suppresses antibacterial responses. Given the dual role of O-GlcNAcylation in different types of infection, the modulation of O-GlcNAcylation activity may serve as a novel therapeutic strategy. For example, enhancing O-GlcNAcylation may strengthen the host antiviral response, while in bacterial infections, moderate inhibition of O-GlcNAcylation may help to limit inflammatory damage and promote tissue repair. Therefore, targeting O-GlcNAcylation may represent a potential approach for the treatment of infectious diseases such as sepsis.

O-GlcNAc glycosylation is a crucial PTM that influences protein function by interacting with other PTMs, such as phosphorylation and ubiquitination (16). For example, O-GlcNAcylation has been demonstrated to promote protein phosphorylation, including that of Lsp1 in B cells, where it facilitates interaction with F-actin (114). Also, O-GlcNAcylation can modulate the function of ubiquitinated proteins, including macrophage proteins MAVS and IRF5, which depend on downstream ubiquitination signaling for proper immune activation (103-105). Understanding the interplay between O-GlcNAcylation and other PTMs, such as phosphorylation and ubiquitination, is crucial for elucidating the role of O-GlcNAcylation in the regulation of immune cell function in both homeostatic and infectious states.

Intervention strategies targeting O-GlcNAc homeostasis have demonstrated multidimensional potential in the treatment of sepsis. For example, GlcN significantly inhibits LPS-induced activation of the MAPK and NF-κB inflammatory pathways by increasing the O-GlcNAc modification of nucleoplasmic proteins, thereby attenuating lung tissue damage and improving survival in mouse and zebrafish models (128). In addition, OGT-mediated modification of O-GlcNAc at RIPK3 Thr467 has been shown to block the formation of necroptotic complexes and inhibit the inflammatory storm in sepsis (129). Also, an acute increase in overall O-GlcNAc levels, such as that induced by the OGA inhibitor N-butyryl-glucosamine-1,5-lactone O-(phenylcarbamoyl)oxime, significantly reduces mortality in septic shock models by inhibiting the cleavage and activation of GSDMD, a key pyroptosis protein (130,131). At the metabolic level, O-GlcNAcylation regulates metabolic enzymes such as ATP citrate lyase in rat models of juvenile sepsis and helps to modulate systemic inflammatory responses through non-transcriptional pathways, suggesting its multi-target regulatory advantage (132,133). However, the clinical application of OGT/OGA inhibitors faces complex challenges. Specifically, the inhibition of OGT may have off-target effects that interfere with protective mechanisms in sepsis. For example, inhibition of OGT may inadvertently weaken its inhibitory effect on GSDMD-mediated pyroptosis or impair the glutamine-maintained gut mucus barrier by interfering with mucin-type glycosylation, potentially through the cross-inhibition of enzymes such as UDP-GalNAc:polypeptide N-acetylgalact osaminyltransferase (5,24,134). In addition, the compensatory stimulation of OGA or fluctuations in the UDP-GlcNAc metabolic pool triggered by OGT inhibition may disrupt the N-glycosylation of immune receptors such as TLR4, thereby exacerbating inflammatory dysregulation (134-136). However, the spatiotemporal heterogeneity of O-GlcNAcylation, such as the contrasting roles observed between endothelial cells and macrophages, and the lack of cell-specific regulatory tools make it challenging to accurately target the dynamic pathological processes of sepsis (137,138). Future strategies combining nano-targeted delivery and dynamic biomarker monitoring are necessary for the development of spatiotemporally accurate modification approaches that optimize therapeutic benefits while minimizing risks.

In summary, as a key PTM, O-GlcNAcylation acts as a critical link between the immune response to infection and the progression of sepsis. Future studies should aim to fully elucidate the specific role of O-GlcNAcylation in the pathogenesis of sepsis, including the mechanisms by which it activates immune cells, regulates the inflammatory response and controls the autophagic process. In addition, the identification of specific O-GlcNAcylation markers as potential biomarkers may improve the early diagnosis and prognostic assessment of sepsis, providing deeper mechanistic insights. Intervention

strategies targeting O-GlcNAcylation may enable the regulation of autophagy and immune responses, thereby providing new therapeutic options for patients with sepsis. Such approaches may include the development of small-molecule drugs to modulate the activity of OGT and OGA, or the design of interventions targeting specific O-GlcNAcylation sites.

**Acknowledgements**

Not applicable.

**Funding**

The present study was supported by a grant from the National Natural Science Foundation of China (grant no. 82260135).

**Availability of data and materials**

Not applicable.

**Authors' contributions**

ZH and XL wrote and revised this manuscript. PL designed the subject of review. LZ, YL and XM reviewed and revised the manuscript. Data authentication is not applicable. All authors read and approved the final version of the manuscript.

**Ethics approval and consent to participate**

Not applicable.

**Patient consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

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