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Invited Mini Review

Remodeling of host glycoproteins during bacterial infection

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Protein glycosylation is a common post-translational modification found in all living organisms. This modification in bacterial pathogens plays a pivotal role in their infectious processes including pathogenicity, immune evasion, and host-pathogen interactions. Importantly, many key proteins of host immune systems are also glycosylated and bacterial pathogens can notably modulate glycosylation of these host proteins to facilitate pathogenesis through the induction of abnormal host protein activity and abundance. In recent years, interest in studying the regulation of host protein glycosylation caused by bacterial pathogens is increasing to fully understand bacterial pathogenesis. In this review, we focus on how bacterial pathogens regulate remodeling of host glycoproteins during infections to promote the pathogenesis. [BMB Reports 2021; 54(11): 541-544]

INTRODUCTION

Protein glycosylation, a well-known post-translational modification found in all living organisms, affects a wide range of protein properties including folding, stability, enzyme activity, interactions, signal transduction, tissue targeting, and resistance to proteolysis (1-3). Protein glycosylation plays an essential role in diverse functions of the immune system. Therefore, glycans are reasonable targets for bacterial pathogenesis. Glycans in the immune system have various roles such as protecting proteins from proteases, regulating protein interactions, and contributing to protein activity and stability (4, 5). In eukaryote organisms, protein glycosylation has two major forms: N-linked and O-linked glycosylation. Both glycosylation systems have been also identified in pathogenic bacteria (6, 7). Glycosylated molecules such as glycoproteins, capsular polysaccharides, and lipooligosaccharides or lipopolysaccharides on pathogenic bacteria are presented to the host. They are involved in the colonization, pathogenicity, and virulence (8). Glycans on the host cell surface are used by many bacterial pathogens for adhesion, nutrients, and targets of toxins (1, 8-10). Recently, studies on the mechanisms by which pathogenic bacteria can regulate host glycosylation are increasing to understand the pathogenic mechanism in host immune system. Bacterial glycosyltransferases and glycosidases can modify host protein glycosylation for the pathogenic process. Furthermore, pathogenic bacterial infection can modify host glycans by activating host glycosyltransferases and glycosidases. In this short review, we will discuss how bacterial infections remodel host protein glycosylation that has a pivotal role in bacterial pathogenesis and host immune system.

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ALTERATIONS IN HOST GLYCOSYLATION BY BACTERIAL GLYCOSYLTRANSFERASES AND GLYCOSIDASES

Bacterial pathogens can modify host protein glycosylation using various bacterial glycosyltransferases and glycosidases (Table 1). The modification of host glycans gives bacterial pathogens host adaptation functions including nutrients acquisition and cell attachment (8). Neuraminidases (sialidases) are well-known modifying enzymes that can cleave sialic acid from glycans. Many types of bacteria produce neuraminidase with various specificities (11). *Streptococcus pneumoniae*, a common cause of sepsis, can produce neuraminidase to induce rapid desialylation and clearance of platelets during systemic *S. pneumoniae* infection (12). Host danger-associated molecular patterns (DAMPs) can diminish pro-inflammatory TLR signaling by forming a complex with sialylated CD24 and SiglecG/10. However, sialidases from *S. pneumoniae* can disrupt the CD24-SiglecG/10 inhibitory complex and lead to elevated cytokine production through cleaving sialic acids on CD24 during *S. pneumoniae* sepsis (13, 14). A cell surface neuraminidase of *Treponema denticola*, an oral spirochete, can remove sialic acids on human serum glycoprotein for bacterial growth (15).

Besides bacterial neuraminidases that are well characterized, other bacterial glycosidases can also modify host glycoproteins. Endoglycosidase S (EndoS) from *Streptococcus pyogenes*, a cause of necrotizing fasciitis and streptococcal toxic shock, can hydrolyze glycans from host IgG to evade host adaptive immunity (16, 17). EndoE from *Enterococcus faecalis*, a cause of nosocomial infection, can cleave glycans of host IgG, RNase B,

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Table 1. Bacterial glycosyltransferases and glycosidases discussed in this review

Bacterial pathogen	Bacterial glycosyltransferase or glycosidase	Host substrate	Reference
Streptococcus pneumoniae	Sialidase	Platelets, CD24	(12-14)
Treponema denticola	Sialidase	Serum glycoprotein	(15)
Streptococcus pyogenes	Endoglycosidase S (EndoS)	IgG	(16, 17)
Enterococcus faecalis	Endoglycosidase E (EndoE)	IgG, RNase B, lactoferrin	(18, 19)
Capnocytophaga canimorsus	Endo-β-N-acetylglucosaminidase (GpdG)	IgG	(20)
Enteropathogenic E. coli	arginine glycosyltransferase NleB	Fas-associated via death domain (FADD) proteins	(21-23)
Photorhabdus asymbiotica	PaTox	Rho GTPases	(24)
Legionella pneumophila	*Legionella* glucosyltransferase	eEF1A	(25, 26)
Clostridium difficile	TcdA and TcdB glucosyltransferase	Rho (RhoA/B/C), Rac (Rac1−3), and Cdc42	(27, 28)

Table 2. Bacterial pathogen-induced activation of host glycosyltransferases and glycosidases discussed in this review

Bacterial pathogen	Host glycosyltransferase or glycosidase	Host substrate	Reference
Helicobacter pylori	β1,3-galactosyltransferase	IgA	(29, 30)
Salmonella enterica Typhimurium	Sialidase	Intestinal alkaline phosphatase	(32)
Salmonella, E. coli	Sialidase	Circulating alkaline phosphatase isozymes	(33)
Francisella tularensis	B3GNT2, B3GNT3, B4GALT1, B4GALT3, B4GALT5, C1GALT1, GALNT2, GALNT11, ST3GAL1, Hexosaminidase A, EDEM1, EDEM2, EDEM3, GANAB	Various N-glycosyproteins and O-glycosylproteins	(34)
Salmonella typhimurium, *Helicobacter bilis*, *Citrobacter rodentium*	Fucosyltransferase 2	Intestinal epithelial glycoproteins	(35-38)

and lactoferrin for modulating host immune responses and bacterial growth (18, 19). *Capnocytophaga canimorsus* is detected in the saliva of healthy dogs and cats. However, it can cause illness in humans. Endo-β-N-acetylglucosaminidase (GpdG) of the N-glycan glycoprotein deglycosylation complex from *C. canimorsus* can deglycosylate human IgG to use released sugars as nutrients for bacterial growth (20).

Enteropathogenic *E. coli* use type III secretion systems for translocating effector proteins into host cells. One such effector is arginine glycosyltransferase NleB that catalyzes arginine GlcNAcylation of Fas-associated via death domain (FADD) proteins to block host defense (21-23). Entomopathogenic *Photorhabdus asymbiotica* is an emerging human pathogen. *P. asymbiotica* protein toxin (PaTox) with a glycosyltransferase domain can induce tyrosine-O-glycosylation of host Rho GTPases by using UDP-GlcNAc, resulting in actin disassembly, inhibition of phagocytosis, and toxicity toward host cells (24). *Legionella pneumophila* infection causes Legionnaires' disease pneumonia. *Legionella* glucosyltransferase proteins are *Legionella* virulence factors with UDP-glucosyltransferase activity. They can inhibit host protein synthesis through eEF1A (eukaryotic elongation factor 1A) glucosylation, resulting in host cell death (25, 26). *Clostridium difficile* is associated with hospital-acquired infectious diarrhea and pseudomembranous colitis. It produces toxin A (TcdA) and toxin B (TcdB) as predominant virulence factors (27). TcdA and TcdB are internalized into host cells. The glycosyltransferase domain of these toxins is then released into the cytosol, where Rho GTPases including Rho (RhoA/B/C), Rac (Rac1−3), and Cdc42 are mono-O-glucosylated and inactivated, resulting in impaired epithelial barrier functions, inflammation, and host cell death (28).

REMODELING OF HOST GLYCOPROTEINS BY THE ACTIVATION OF HOST GLYCOSYLTRANSFERASES AND GLYCOSIDASES DURING BACTERIAL INFECTIONS

Bacterial pathogens can modify host protein glycosylation by modulating the expression of numerous host glycosyltransferases and glycosidases (Table 2). *Helicobacter pylori*, a cause of gastrointestinal diseases such as chronic gastritis and gastric cancer, is related to IgA nephropathy. Cytotoxin associated gene A protein (CagA), a major virulence factor of *Helicobacter pylori*, can promote abnormal glycosylation of host IgA by downregulating host β-1,3-galactosyltransferase. Abnormal glycosylation of IgA is involved in the pathogenesis of IgA nephro-

pathy (29, 30). Recurrent nonlethal gastric infections of *Salmonella enterica* Typhimurium, a leading cause of human food poisoning, can induce chronic intestinal inflammation in a mouse model. The disease mechanism involves the deficiency of intestinal alkaline phosphatase (IAP), which can dephosphorylate and detoxify the lipopolysaccharide (LPS) endotoxin produced by commensal Gam-negative microbiota in the host (31, 32). Recurrent *S. enterica* Typhimurium reinfection can induce host endogenous neuraminidase activity, which accelerates the desialylation and clearance of IAP. The administration of zanamivir, an antiviral neuraminidase inhibitor, has therapeutic effect through maintaining IAP abundance and function (32). In mouse experimental sepsis elicited by Gram-negative *Salmonella* and *E. coli*, a host protective mechanism through LPS detoxification by circulating alkaline phosphatase (AP) isozymes is debilitated through host neuraminidase induction (33). Increased neuraminidase activity can accelerate the clearance of AP isozymes mediated by the hepatic lectin Ashwell-Morell receptor. The inhibition of neuraminidase activity can diminish inflammation and promote host survival (33). The bacterial pathogen *Francisella tularensis* is an agent of zoonotic disease tularemia. It can modulate numerous host glycosyltransferases and glycosidases such as β-N-acetylglucosaminyltransferase B3GNT2, B3GNT3, β-galactosyltransferase B4GALT1, B4GALT3, B4GALT5, N-acetylgalactosamine-β-galactosyltransferase C1GALT1, N-acetylgalactosaminyltransferase GALNT2, GALNT11, α-2,3-Sialyltransferase ST3GAL1, Hexosaminidase A, ER Degradation Enhancing Alpha-Mannosidase Like Protein EDEM1, EDEM2, EDEM3, and glucosidase II α subunit GANAB. It can also modify various N-glycosyproteins and O-glycosylproteins, including the multifunctional ER chaperone binding immunoglobulin protein (BiP) (34). Pathogenic bacteria such as *Salmonella typhimurium*, *Helicobacter bilis*, and *Citrobacter rodentium* can induce intestinal epithelial fucosyltransferase 2 expression and α1,2-fucosylation. The intestinal epithelial α1,2-fucosylation is important for various immune reactions, including host defense and host-commensal bacteria interplay (35-38).

CONCLUDING REMARKS

A large number of pathogenic bacterial glycosyltransferases and glycosidases have been discovered and characterized. Functions of these enzymes on glycans of host key proteins in the immune system contribute to the pathogenesis of bacterial pathogens through increased adhesion, nutrient acquisition, targets of bacterial toxins, evading the immune response, and persisting bacterial survival in the host. In addition, bacterial pathogens can modify glycans on many key proteins in host immune system through inducing various host glycosyltransferases and glycosidases, thus contributing to the pathogenesis. Alteration in protein glycosylation can affect protein activity, abundance, stability, and interaction with other proteins regardless whether glycosyltransferases and glycosidases come from bacterial pathogens or hosts. Thus, it is an essential step to analyze remodeling of host glycoprotein during bacterial infection to fully understand the pathogenesis. Although it is difficult to understand bacterial modulation of host glycosylation while bacterial infections induce various host glycosyltransferases and glycosidases, recent advances in glycoengineering make it possible to thoroughly analyze remodeling of host glycans. Taken together, this study about remodeling of host glycoproteins during bacterial infection provides potentially a new insight into bacterial pathogenesis and an opportunity to develop novel therapeutic and preventive strategies to fight infectious diseases.

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CONFLICTS OF INTEREST

The authors have no conflicting interests.

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