Remodeling of host glycoproteins during bacterial infection

Yeolhoe Kim1,2, Jeong Yeon Ko1,2 & Won Ho Yang1,2,∗
1Department of Systems Biology, BK21 Plus Project, College of Life Science and Biotechnology, Yonsei University, Seoul 03722, Korea
2Glycosylation Network Research Center, Yonsei University, Seoul 03722, Korea

INTRODUCTION

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]

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 glycidosidases 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)      |
| Treptococcus pyogenes               | Endoglycosidase S (EndoS)                     | IgG                                 | (16, 17)  |
| Enterococcus faecalis               | Endoglycosidase E (EndoE)                     | IgG, RNase B, lactoferrin           | (18, 19)  |
| Capnocytophaga canimorsus           | Endoβ-N-acetylglucosaminidase (GpdG)          | IgG                                 | (20)      |
| Entropathogenic E. coli             | Arginine glycosyltransferase NleB             | Fas-associated via death domain (FADD) proteins | (21-23) |
| Photobacteroides 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, 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. Endoβ-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).

Entropathogenic 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 Photobacteroides 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 glucosyltransferase 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. Cytotoxic associated gene A protein (CagA), a major virulence factor of Helicobacter pylori, can promote abnormal glycosylation of host IgA by downregulating host β1,3-galactosyltransferase. Abnormal glycosylation of IgA is involved in the pathogenesis of IgA nephropathy.
pathy (29, 30). Recurrent nonlethal gastric infections of *Salmo-
ella 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 dephospho-
rylate and detoxify the lipopolysaccharide (LPS) endotoxin
produced by commensal Garn-negative microbiota in the host
(31, 32). Recurrent *S. enterica* Typhimurium reinfection can
induce host endogenous neuraminidase activity, which acceler-
ates the desialylation and clearance of IAP. The administra-
tion 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 induc-
tion (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 zoono-
tic disease tularemia. It can modulate numerous host glyco-
syltransferases and glycosidases such as β-N-acetylglucosamyl-
transferase B3GNT2, B3GNT3, β-galactosyltransferase B4GALT1,
B4GALT3, B4GALT5, N-acetylgalactosamine-β-galactosyltrans-
ferase 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-glycosyl-
proteins, 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, includ-
ing 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 glycosyltrans-
ferases 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 glycosyla-
tion while bacterial infections induce various host glycosyltrans-
f erases 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.

**REFERENCES**

1. Bhat AH, Maity S, Giri K and Ambatipudi K (2019) Protein
glycosylation: sweet or bitter for bacterial pathogens? Crit
Rev Microbiol 45, 82-102
2. Moremen KW, Tiemeyer M and Nairn AV (2012) Verte-
brate protein glycosylation: diversity, synthesis and func-
tion. Nat Rev Mol Cell Biol 13, 448-462
3. Pinho SS and Reis CA (2015) Glycosylation in cancer:
mechanisms and clinical implications. Nat Rev Cancer
15, 540-555
4. Rudd P, Elliott T, Cresswell P, Wilson I and Dwek R
(2001) Glycosylation and the immune system. Science
291, 2370-2376
5. Sjögren J and Collin M (2014) Bacterial glycosidases in
pathogenesis and glycoengineering. Future Microbiol 9,
1039-1051
6. Nothaft H and Szymanski CM (2010) Protein glycosyla-
tion in bacteria: sweeter than ever. Nat Rev Microbiol 8,
765-778
7. Szymanski CM and Wren BW (2005) Protein glycosyla-
tion in bacterial mucosal pathogens. Nat Rev Microbiol 3,
225-237
8. Poole J, Day CJ, von Itzstein M, Paton JC and Jennings MP
(2018) Glycointeractions in bacterial pathogenesis. Nat
Rev Microbiol 16, 440-452
9. Jank T, Belyi Y and Aktories K (2015) Bacterial glycosyl-
transferase toxins. Cell Microbiol 17, 1752-1765
10. Lu Q, Li S and Shao F (2015) Sweet talk: protein glyco-
sylation in bacterial interaction with the host. Trends Micro-
biol 23, 630-641
11. Sudhakara P, Sellamuthu I and Aruni AW (2019) Bacterial
sioglucosidases in virulence and pathogenesis. Pathogens
8, 39
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12. Grewal PK, Uchiyama S, Ditto D et al (2008) The Ashwell receptor mitigates the lethal coagulopathy of sepsis. Nat Med 14, 648-655
13. Chen GY, Chen X, King S et al (2011) Amelioration of sepsis by inhibiting sialidase-mediated disruption of the CD24-SiglecG interaction. Nat Biotechnol 29, 428-435
14. Paulson JC and Kawasaki N (2011) Sialidase inhibitors DAMPen sepsis. Nat Biotechnol 29, 406-407
15. Kurniyati K, Zhang W, Zhang K and Li C (2013) A surface-exposed neuraminidase affects complement resistance and virulence of the oral spirochaete Treponema denticola. Mol Microbiol 89, 842-856
16. Collin M and Olsén A (2001) EndoS, a novel secreted protein from Streptococcus pyogenes with endoglycosidase activity on human IgG. EMBO J 20, 3046-3055
17. Naegeli A, Bratanis E, Karlsson C et al (2019) Streptococcus pyogenes evades adaptive immunity through specific IgG glycan hydrolysis. J Exp Med 216, 1615-1629
18. Collin M and Fischetti VA (2004) A novel secreted endoglycosidase from Enterococcus faecalis with activity on human immunoglobulin G and ribonuclease B. J Biol Chem 279, 22558-22570
19. Garbe J, Sjögren J, Cosgrave EF et al (2014) EndoE from Enterococcus faecalis hydrolyzes the glycans of the biofilm inhibiting protein lactoferrin and mediates growth. PLoS One 9, e91035
20. Renzi F, Manfredi P, Mally M, Soes, Juno P and Cornelis G (2011) The N-glycan glycoprotein deglycosylation complex (Gpd) from Capnocytophaga canimorsus deglycosylates human IgG. PLoS Pathog 7, 17
21. Ding J, Pan X, Du L et al (2019) Structural and functional insights into host death domains inactivation by the bacterial arginine GlcNAcyltransferase effector. Mol Cell 74, 922-935
22. Gao X, Wang X, Pham TH et al (2013) NleB, a bacterial effector with glycosyltransferase activity, targets GAPDH function to inhibit NF-kB activation. Cell Host Microbe 13, 87-99
23. Scott NE, Giogha GL, Pollock CL et al (2017) The bacterial arginine glycosyltransferase effector NleB preferentially modifies Fas-associated death domain protein (FADD). J Biol Chem 292, 17337-17350
24. Jank T, Bogdanovic X, Wirth C et al (2013) A bacterial toxin catalyzing tyrosine glycosylation of Rho and deamidation of Gq and Gi proteins. Nat Struct Mol Biol 20, 1273-1280
25. Belyi Y, Niggeweg R, Opitz B et al (2006) Legionella pneumophila glucosyltransferase inhibits host elongation factor 1A. Proc Natl Acad Sci U S A 103, 16953-16958
26. Tzivelekidis T, Jank T, Pohl C et al (2011) Aminoacyl-tRNA-charged eukaryotic elongation factor 1A is the bona fide substrate for Legionella pneumophila effector glucosyltransferases. PLoS One 6, e29525
27. Kuehne SA, Cartman ST, Hoap JT, Kelly ML, Cockayne A and Minton NP (2010) The role of toxin A and toxin B in Clostridium difficile infection. Nature 467, 711-713
28. Aktories K, Schwan C and Jank T (2017) Clostridium difficile toxin biology. Annu Rev Microbiol 71, 281-307
29. Yang M, Li FG, Xie XS, Wang SQ and Fan JM (2014) CagA, a major virulence factor of Helicobacter pylori, promotes the production and underglycosylation of IgA1 in DAKIKI cells. Biochem Biophys Res Commun 444, 278-281
30. Zhu TT, Wang L, Wang HL, He Y, Ma X and Fan JM (2016) Helicobacter pylori participates in the pathogenesis of IgA nephropathy. Ren Fail 38, 1398-1404
31. Vaishnava S, Hooper LV (2007) Alkaline phosphatase: keeping the peace at the gut epithelial surface. Cell Host Microbe 2, 365-367
32. Yang WH, Heithoff DM, Aziz PV et al (2017) Recurrent infection progressively disables host protection against intestinal inflammation. Science 358, eaao5610
33. Yang WH, Heithoff DM, Aziz PV et al (2018) Accelerated aging and clearance of host anti-inflammatory enzymes by discrete pathogens fuels sepsis. Cell Host Microbe 24, 500-513
34. Barel M, Harduin-Lepers A, Portier L, Slomianny MC and Charbit A (2016) Host glycosylation pathways and the unfolded protein response contribute to the infection by Francisella. Cell Microbiol 18, 1763-1781
35. Goto Y, Obata T, Kunisawa J et al (2014) Innate lymphoid cells regulate intestinal epithelial cell glycosylation. Science 345, 1254009
36. Goto Y, Uematsu S and Kiyono H (2016) Epithelial glycosylation in gut homestasis and inflammation. Nat Immunol 17, 1244-1251
37. Pham TA, Clare S, Goulding D et al (2014) Epithelial IL-22RA1-mediated fucosylation promotes intestinal colonization resistance to an opportunistic pathogen. Cell Host Microbe 16, 504-516
38. Pickard JM, Maurice CF, Kinnebrew MA et al (2014) Rapid fucosylation of intestinal epithelium sustains host-commensal symbiosis in sickness. Nature 514, 638-641