JCI The Journal of Clinical Investigation

Surprise? Bacteria glycosylate proteins too.

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J Clin Invest. 1996;98(12):2659-2660. https://doi.org/10.1172/JCI119087.

Editorial

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The dogma said that it couldn't be done: eubacteria were thought not capable of coupling carbohydrate to protein. Perhaps a few archaebacteria could make glycoproteins but, certainly, bacterial pathogens couldn't. Yet, some 20 years ago, the hints were already in the literature that this might be an erroneous assessment of eubacterial skills. Rarely, eubacteria were reported to contain proteins that stained with periodic acid-Schiff or demonstrated affinity for lectins (for review see reference 1). Finally, in the 1990's, with the application of the most current methods of carbohydrate analysis, incontrovertible evidence has been obtained that carbohydrates can be covalently linked to proteins from bacteria (1–4). Several of these bacteria are significant pathogens, including *Neisseria, Mycobacteria,* and *Streptococci.* This has opened up a new aspect of microbial pathogenesis as demonstrated by the growing number of reports suggesting not only that many bacteria glycosylate their surface proteins but also that this process can be critical to pathogenicity.

In this issue of *The Journal,* Kuo et al. (5) demonstrate that the major structural component on the surface of the intracellular pathogen, *Chlamydia trachomatis*, is a high mannose type N-linked glycoprotein. This finding adds a new class of bacteria to the growing list of those capable of this basic biochemical process, in this case an obligate intracellular bacterium with no classical peptidoglycan cell wall. This study is of particular importance, however, because the authors extended the biochemistry into the arena of pathogenesis by demonstrating that the high-mannose type oligosaccharide on the protein mediated attachment and infectivity of *Chlamydia* for an epithelial cell line. This should provoke new questions for understanding the basic biology of sexually transmitted chlamydial disease and add fuel to the fire of the smoldering potential association of *Chlamydia* with atherosclerosis.

Bacteria have extensive polysaccharide structures on their surfaces. Pure polysaccharides form the bacterial capsules that play a major role in resisting phagocytosis and killing by host leukocytes and for most invasive pathogens, capsules are perhaps the most significant virulence determinants. A second class of surface carbohydrates is the macromolecular network of poly-*N*-acetylglucosaminyl-*N*-acetylmuramic acid that constitutes the eubacterial cell wall. This component functions as the bacterial exoskeleton as well as a repository of significant inflammatory components important in inciting the acute phase response to infection. Glycolipids are a third class of carbohydrate-bearing species on bacterial surfaces, the most nefarious of which are lipopolysaccharide in Gram negative bacteria and lipoteichoic acids in Gram positive bacteria. These various carbohydrates are collectively important to bacterial structure and triggering host inflammation and immunity. Yet, when it came down to assigning the nitty gritty elements necessary for bacterial adherence and invasion, proteins were the only standard, accepted primary players, i.e. bacterial surface adhesins functioned as lectins and recognized specific carbohydrates on the human cell surface. Now the sugar is on the other foot. *Chlamydia* presents a glycoprotein as an adhesin and the host recognizes and binds the "glyco" determinant, presumably by a human surface lectin. Perhaps this role reversal could have been anticipated by remembering the example of leukocyte trafficking (6, 7). E and P selectins on activated endothelial cells recognize carbohydrates on leukocytes and promote recruitment to a site of infection. However, L selectin achieves the same end in the reverse manner, i.e. the selectin is found on the leukocyte and its cognate carbohydrate is displayed on the endothelial cell. The lectin-carbohydrate adhesion paradigm works either way.

The glycosylation of bacterial adhesins has taken on added significance because it appears to be variable and highly regulated. Bacteria spend time and energy on this process. *Neisseria meningitidis* exemplifies just how useful reversible glycosylation of surface structures can be. Glycosylation is a phase variable characteristic such that the adhesive fimbriae can be posttranslationally sugar-coated or sugar-free depending on the presence or absence of an O-linked glycosylation site in the pilin structural subunit (3, 4). Sugar coating enhances adherence and presumably also disguises this critical bacterial appendage from the host immune response. Similar variable glycosylation occurs on the lipopolysaccharide (8). Here, the choice of carbohydrate, lacto-*N*-neotetraose, is significant in that it mimics host cell determinants, further confusing detection by host immune mechanisms. *Chlamydia* also appears to employ a human glycosyl determinant, one of the high mannose class, as an adjustable disguise, in this case on an adhesive glycoprotein.

That bacteria can in fact glycosylate proteins is now clearly established. That this is important to pathogenesis is also increasingly obvious. It remains to be determined how and where this process takes place in or on a bacterial cell and how it is regulated in response to host environments. Perhaps, it will be possible to purposefully use this newly recognized manufacturing skill to naturally engineer protein adducts onto polysaccharide antigens in vaccines to expand their efficacy to young children or even to more properly express eukaryotic glycoproteins in recombinant form.

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References

1. Erickson, P., and M. Herzberg. 1993. Evidence for covalent linkage of a carbohydrate polymers to a glycoprotein from *Streptococcus sanguis. J. Biol. Chem.* 268:23780–23783.

2. Dobos, K., K. Khoo, K. Swiderek, P. Brennan, and J. Belisle. 1996. Definition of the full extent of glycosylation of the 45-kD glycoprotein of *Mycobacterium tuberculosis*. *J. Bacteriol.* 178 2498–2506.

3. Virji, M., J. Saunders, F. Sims, K. Makepeace, D. Maskell, and D. Ferguson. 1993. Pilus-facilitated adherence of *Neisseria meningitidis* to human epithelial and endothelial cells: modulation of adherence phenotype occurs concurrently with changes in primary amino acid sequence and the glycosylation status of pilin. *Mol. Microbiol.* 10:1013–1028.

4. Stimson, E., M. Virji, S. Barker, M. Panico, I. Blench, J. Saunders, G. Payne, E. Moxon, A. Dell, and H. Morris. 1996. Discovery of a novel protein modification: alpha-glycerophosphate is a substituent of meningococcal pilin. *Biochem. J.* 316:29–33.

J. Clin. Invest.

0021-9738/96/12/2659/02 $2.00
Volume 98, Number 12, December 1996, 2659–2660

5. Kuo, C., N. Takahashi, A. Swanson, Y. Oziki, and S. Hakomori. 1996. An N-linked high-mannose type oligosaccharide, expressed at the major outer membrane protein of *Chlamydia trachomatis*, mediates attachment and infectivity of the microorganism to HeLa cells. *J. Clin. Invest.* 98:2813–2818.

6. Lasky, L.A. 1992. Selectins: interpreters of cell-specific carbohydrate information. *Science (Wash. DC).* 258:964–969.

7. Springer, T.A., and L.A. Lasky. 1991. Cell adhesion. Sticky sugars for selectins. *Nature (Lond.).* 349:196–197.

8. Jennings, M., D. Hood, I. Peak, M. Virji, and E. Moxon. 1995. Molecular analysis of a locus for the biosynthesis and phase-variable expression of the lacto-N-neotetraose terminal lipopolysaccharide structure in *Neisseria meningitidis*. *Mol. Microbiol.* 18:729–740.