MiniReview

Molecular mimicry of host structures by bacterial lipopolysaccharides and its contribution to disease

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Abstract

The core oligosaccharides of low-molecular-weight lipopolysaccharide (LPS), also termed lipooligosaccharide (LOS), of pathogenic Neisseria spp. mimic the carbohydrate moieties of glycosphingolipids present on human cells. Such mimicry may serve to camouflage the bacterial surface from the host. The LOS component is antigenically and/or chemically identical to lactoneoseries glycosphingolipids and can become sialylated in Neisseria gonorrhoeae when the bacterium is grown in the presence of cytidine 5'-monophospho-N-acetylneuraminic acid, the nucleotide sugar of sialic acid. Strains of Neisseria meningitidis and Haemophilus influenzae also express similarly sialylated LPS. Sialylation of the LOS influences susceptibility to bactericidal antibody, may decrease or prevent phagocytosis, cause down-regulation of complement activation, and decrease adherence to neutrophils and the subsequent oxidative burst response. The core oligosaccharides of LPS of Campylobacter jejuni serotypes which are associated with the development of the neurological disorder, Guillain–Barré syndrome (GBS), exhibit mimicry of gangliosides. Cross-reactive antibodies between C. jejuni LPS and gangliosides are considered to play an important role in GBS pathogenesis. In contrast, the O-chain of a number of Helicobacter pylori strains exhibit mimicry of Lewis χ and Lewis ψ blood group antigens. The role of this mimicry remains to be investigated, but may play a role in bacterial camouflage, the induction of autoimmunity and immune suppression in H. pylori-associated disease.

Keywords: Neisseria spp.; Haemophilus influenzae; Campylobacter jejuni; Helicobacter pylori; Lipopolysaccharide; Molecular mimicry; Guillain–Barré syndrome

1. Introduction

Lipopolysaccharides (LPS) are a family of toxic glycolipids present in the outer membrane of Gram-negative bacteria and are essential for the physical integrity and functioning of that membrane [1,2].

These glycolipids are the main surface antigens (somatic O-antigens) of Gram-negative bacteria and are also potent immunostimulating and immunomodulating compounds [2,3]. Furthermore, variations in the structure of the saccharide moiety of LPS can contribute to the virulence of bacterial strains [3]. Mimicry of host structures by LPS has been reported to contribute to the pathogenesis of certain bacteria, in particular, mucosal pathogens. Of these, the mimicry exhibited by Neisseria gonorrhoeae,
Neisseria meningitidis and Haemophilus influenzae has been the most intensively studied [4]. However, studies within the last half-decade show that LPS of other medically important bacteria also mimic host structures. Campylobacter jejuni which is a common cause of acute gastroenteritis in humans [5] and Helicobacter pylori which is the causal agent of active chronic gastritis and a cofactor in the development of peptic ulcers and gastric cancer [6-8] exhibit mimicry in their LPS which contributes to virulence in these infections.

The aim of this review is to discuss the basis within LPS for the molecular mimicries exhibited by the various bacterial species. Also, the contribution of molecular mimicry to the outcome of infection and disease development will be addressed.

2. Structure of LPS

Chemically LPS, as characterized by enterobacterial LPS, is composed of a poly- or oligosaccharide covalently linked to a lipid component, termed lipid A (Fig. 1) [2,3]. High-molecular weight (M,) smooth-form LPS consist of an O-specific polysaccharide chain, which is a polymer of repeating oligosaccharide units, a core oligosaccharide, and lipid A; whereas low-M, rough-form LPS lack the O chain [3]. Like wild-type strains of the Enterobacteriaceae, H. pylori strains produce high-M, LPS [9,10] (Fig. 1A). In contrast, Neisseria and Haemophilus spp. produce a 10^-44, LPS, also termed lipooligosaccharide (LOS), which has properties distinct from those of enterobacterial rough-form LPS, particularly antigenic diversity [4,11] (Fig. 1C). Wild-type strains of C. jejuni produce high-M, LPS, structurally distinct low-M, LPS resembling those of Neisseria and Haemophilus spp., or both [12,13] (Fig. 1A, B).

3. N. gonorrhoeae, N. meningitidis and H. influenzae LPS

3.1. Molecular mimicry of glycolipids and glycosphingolipids

The first reported structure of an oligosaccharide (OS) moiety of neisserial LOS was that of N. meningitidis L3,7,9 (Table 1, structure 1, Ref. [14]). The non-reducing end of the OS is composed of the same tetrasaccharide, lacto-N-neotetraose (Galβ1-4GlcNAcβ1-3Galβ1-4Glc), as that present in paragloboside (Fig. 2A) which is the precursor of the ABH glycolipid antigens on human erythrocytes. Chemical structural studies have shown that this same terminal tetrasaccharide is present in LOS of N. meningitidis 1.2 and L5 [15,16]. The terminal trisaccharide lactotriaose (Galβ1-4GlcNAcβ1-3Gal) is common among LOS of pathogenic Neisseria spp., since both serological and structural studies have shown that most serogroup B and C strains of meningococci and most gonococcal strains possess this trisaccharide [4,17]. In turn, lactotriaose is a precursor of lacto-N-neotetraose, the precursor of lacto-oligosaccharides.

Although the parent strain of N. gonorrhoeae 1291 has an LOS containing a paragloboside-like terminal OS, globotriaose (Galα1-4Galβ1-4Glc) has been identified as the terminal trisaccharide in LOS of the pyocin-resistant mutant strain 1291B [18]. The longest oligosaccharide chain in LOS of N. meningitidis L1 is identical to globotriaose which is the OS moiety in the P^k glycosphingolipid [17] (Fig. 2B). With an anti-P^k monoclonal antibody (Mab), a P^k-like antigen was found on 10% and 50% of meningococcal and gonococcal strains, and on nontypable and type b H. influenzae [19].

An additional type of mimicry in N. gonorrhoeae F62 involves a pentasaccharide with an N-acetylgalactosamine (GlcNAc) residue β1-3-linked to the terminal galactose (Gal) of a lacto-N-neotetraose OS [20]. This pentasaccharide is identical to the desialylated OS of glycosphingolipids X_2 and asialo G_1.
Fig. 2. Structures of glycosphingolipids whose saccharide moieties are similar to those of some neisserial LOS include (A) paragloboside, (B) P1, (C) Xa and asialoG1, and (D) asialoGM2. Abbreviations: Gal, galactose; Glc, glucose; GalNAc, N-acetylgalactosamine; GlcNAc, N-acetylglucosamine; Cer, ceramide.

(Fig. 2C) on erythrocytes [4]. An anti-asialoGM2 (Fig. 2D) Mab bound OS of N. gonorrhoeae F62 LOS and those of > 50% of gonococcal strains, but the epitope was absent in meningococci and non-pathogenic Neisseria spp. [19].

Anti-lactoneoseries monoclonal antibodies bind to strains of Haemophilus ducreyi, the causative agent of chancroid in humans, and the mimicry in the LOS has been verified structurally [4,21,22]. These same antibodies bind to non-typable and type b H. influenzae LOS and the terminal OS of both H. ducreyi and H. influenzae LOS may be sialylated endogenously [23–25].

3.2. Potential role in camouflage and resistance to the bactericidal effect of serum and to phagocytosis

The expression of structures within LOS resembling those of the host may serve to camouflage the bacterial surface from the host in a similar way to that described for capsular polysaccharides [26]. For example, the Pk antigen (Fig. 2B) is present in a number of human tissues or cells relevant to infection by mucosal pathogens including Neisseria spp., such as uroepithelial cells [27]. Also, the ganglioseries-like LOS of N. gonorrhoeae are of interest since human glycoconjugates with similar terminal OS serve as precursors for synthesis of carbohydrates in human cervical mucins [28].

Fresh clinical isolates of gonococci from urethral exudates possess a virulence factor that is lost upon subculturing strains in vitro [29] but when such strains are incubated in human fluids and secretions, the gonococci can be converted from serum-sensitivity to resistance which is associated with a change in LOS structure [30]. The inducing factor is concentrated in an environment relevant to N. gonorrhoeae infection since Patel et al. [31] found a higher resistance-inducing capacity in leukocytes than in whole blood. Both a high- and low-Mr resistance-inducing factor have been detected but the low-Mr resistance-inducing factor was identified as cytidine 5'-monophospho-N-acetylneuraminic acid (CMP–Neu5Ac), the nucleotide sugar of N-acetylneuraminic (sialic) acid [32]. Furthermore, studies suggested that the enzymes for sialylation were in the outer bacterial layer, that sufficient concentrations of CMP–Neu5Ac might be present in vivo to sialylate LOS and thus induce serum resistance [4]. The major LOS component modified by sialylation was identified as a 4.5 kDa component that binds a Mab which recognizes the lactoneoseries of glycolipids including lacto-N-neotetraose and lactotriose [33]. This LOS molecule is expressed in greater quantities in anaerobically grown than in aerobically grown gonococci [34]. Most strains of meningococci that synthesize a capsule containing sialic acid (serogroups B, C, W and Y) and a 4.5 kDa LOS also sialylate their LOS endogenously [4,35]. Determination of the chemical structure of sialylated N. meningitidis L3 has confirmed the presence of terminal sialic acid on a lacto-N-neotetraose-like OS [36] and the CMP–Neu5Ac synthetase of group B meningococci has been cloned and sequenced [37]. The potential 4.5 kDa LOS sialic acid-acceptor is present on type B and non-typable H. influenzae and H. ducreyi [23,25] and H. influenzae strains are endogenously sialylated as described above. In contrast, meningococci that cannot synthesize sialic acid (e.g., serogroups A and X) and non-pathogenic Neisseria spp., although they may express the 4.5 kDa LOS, do not endogenously sialylate LOS [4]. Moreover, all strains of pathogenic Neisseria have an LOS-specific sialyltransferase [4,38].

Although some N. gonorrhoeae strains remain serum-resistant in vitro without the addition of CMP–Neu5Ac whereas others remain serum-sensitive after growth in CMP–Neu5Ac, the primary role of LOS sialylation may be somewhat different than protecting strains from the lytic effects of serum antibody and complement [4,39]. Sialylation of LOS may decrease or prevent, phagocytosis of gonococci and meningococci by human neutrophils [40,41].
Furthermore, bacterial surface sialylation can cause a down-regulation of complement activation, e.g., the C3 convertase of the alternative pathway is down-regulated by the presence of sialic acid-containing structures [42]. Compared to non-sialylated gonococci, sialylated strains have a decreased ability to induce an oxidative burst in neutrophils, and to adhere to neutrophils in the absence of complement and specific antibody [40]. Therefore, the influence of LOS sialylation may play a pivotal role in the survival of *Neisseria* spp. in the mucosal ecological niche.

### 4. *C. jejuni* LPS

#### 4.1. Role in the development of Guillain–Barré syndrome

Guillain–Barré syndrome (GBS) is an acute, inflammatory and demyelinating paralytic disease of the peripheral nervous system, and although of infrequent occurrence, is now the most common cause of generalized paralysis. In up to 75% of GBS cases, the syndrome develops following various respiratory and gastrointestinal infections [43]. *C. jejuni* has been identified as the most common single pathogen associated with the development of GBS (20–50% of patients), particularly with a severe form of the disease [43-45]. With the heat-stable antigen serotyping system of *C. jejuni* which is based on LPS [12,13], a predominance of *C. jejuni* O:19, an uncommon serotype in gastroenteritis patients, has been found in Japanese GBS patients [46], and has even been reported in a familial outbreak of GBS [17]. This same serotype has been associated with the development of GBS in patients in the USA [48] and in the Netherlands [49]. Other *C. jejuni* serotypes that have been reported to be associated with antecedent infection in GBS patients include serotypes O:2, O:2/44, O:4/59, O:15, O:18, O:21, O:24, O:30, O:37, and O:53 [46,49]. Serotypes O:2 and O:23 have been found in association with Miller Fisher syndrome (MFS), a variant of GBS, comprising of ataxia, areflexia and ophthalmoplegia [50,51]. These results, therefore, suggested a possible link between specific *C. jejuni* serotypes expressing certain LPS structures and the induction of GBS.

Moreover, serum antibodies against gangliosides have been observed in about 30% of GBS patients [43,52]. Sera from GBS patients with antecedent infection with *C. jejuni* enteritis frequently have autoantibodies to gangliosides, especially GM1, ganglioside (Fig. 3A). during the acute phase of illness [49,53,54]. These anti-neural antibodies may function in the development of GBS since plasma exchange elicits a beneficial response in these patients [52] and some individuals have developed GBS-like symptoms after the administration of gangliosides [55,56]. Furthermore, Illa et al. [56] demonstrated that purified anti-GM, antibodies from patients who exhibited acute GBS with axonal degeneration after immunization with a ganglioside preparation recognized epitopes at the nodes of Ranvier and the presynaptic nerve terminals of motor end-plates. Accumulations of these antibodies at the nodes of Ranvier can suppress voltage-sensitive Na⁺ currents and thus interfere with the nerve impulse [57]. Since both monoclonal and polyclonal antibodies against gangliosides, including sera from patients, cross-react with LPS of *C. jejuni* serotypes associated with GBS [49,54,58-60], it was suggested that molecular mimicry between *C. jejuni* LPS and host antigens might act as a trigger for autoimmune mechanisms in the pathogenesis of GBS [54,58].

#### 4.2. Molecular mimicry of gangliosides

Serological analysis by Yuki et al. [58] demonstrated antibody cross-reactions between LPS of *C.
jejuni O:19 and GM₁ ganglioside indicating the potential presence of molecular mimicry in this LPS. In concurrence with these findings, structural analyses have shown that the core OS of C. jejuni O:19 LPS, including those from GBS-associated isolates, contain tetra- and pentasaccharide moieties identical to those of GM₁ and GD₁₂ gangliosides, respectively [61–63] (Fig. 4A). Molecular mimicry of GT₁₃ and GD₃ gangliosides by the terminal hexasaccharides and trisaccharides, respectively, of LPS of some GBS-associated C. jejuni O:19 isolates has also been reported [62] (Fig. 4B, C). Analysis with anti-ganglioside antibodies has verified the presence of GM₁-, GT₁₃- and GD₃-like epitopes in LPS of GBS-associated C. jejuni O:19 strains [64].

In addition to C. jejuni O:19, other serotypes possess sialylated LPS [65,66]. Chemical structural studies on LPS have shown that the terminal pentasaccharide of the core OS of C. jejuni serostain (serotype-reference strain) O:4 mimics that of GD₁₂ ganglioside [67]. The presence of both GD₁₂- and GM₁-like epitopes in this LPS has been shown serologically [60]. LPS of C. jejuni O:41 GBS-associated isolates is sialylated and bears a GM₁-like epitope (M.M. Prendergast, unpublished results). Other forms of ganglioside mimicry are exhibited by C. jejuni serostains. The non-reducing ends of the core OS of LPS of C. jejuni O:23 and O:36 are composed of the same tetrasaccharide as that present in GM₂ ganglioside (Fig. 3B), whereas in LPS of C. jejuni serostain O:1 the extent of mimicry of GM₂ ganglioside is limited to a terminal trisaccharide [67]. Although C. jejuni O:2 is associated with the development of GBS, mimicry of gangliosides is limited to that of a

Fig. 4. Structures of the core OS of C. jejuni LPS of (A) serostain O:19, enteritis strain 98 and GBS isolates 101 and 157 [62,63], (B) GBS isolate OH 4384 [62], and (C) GBS isolate OH 4382 [62] showing homology with the saccharide moieties of GD₁₂, GM₁, GT₁₃, and GD₃. Abbreviations: P, O-phosphoryl group; PEA, O-phosphoethanolamine; KDO, 3-deoxy-D-manno-2-octulosonic acid; LDHep, L-glycero-D-manno-heptose; Glc, glucose; Gal, galactose; GalNAc, N-acetylgalactosamine; Neu5Ac, N-acetylneuraminic acid.
terminal disaccharide (Neu5Acα2→3Gal) [68] which is present in GM₃ ganglioside (Fig. 3C), but also in other gangliosides (e.g., GD₄, GT₂, and GM₂). Despite this, asialoGM₁-antibody can bind to both O:2 and O:19 LPS indicating a shared epitope, not dependent on ganglioside mimicry [54]. The latter shared epitope may, therefore, explain the involvement of C. jejuni O:2 in GBS pathogenesis. This should be emphasized since C. jejuni O:3 has not been associated with the induction of GBS, and whose LPS has been used as a negative control in experiments with anti-ganglioside antibodies [54] is not sialylated [65,66] and does not exhibit any mimicry of gangliosides [69].

On the other hand, mimicry of gangliosides by the core OS of C. jejuni O:19 LPS, is not limited to strains that are associated with GBS but is also present in strains that are isolated from individuals with enteritis but who do not develop GBS [63]. Some other attribute of the host and/or of the bacterium, in addition to mimicry of gangliosides, may contribute to the development of GBS. The LPS of the O:19 serostrain and GBS-associated O:19 isolates contain identical O-specific polysaccharide chains of a hyaluronic acid-like polymer [70]. This polymer consists of disaccharide-repeating units containing residues of β-D-glucuronic acid amidated with 2-amino-2-deoxyglycerol and linked to β-D-N-acetylglucosamine (Fig. 5). Expression of this hyaluronic acid-like O-chain is greater in GBS-associated O:19 isolates than in isolates from patients with enteritis alone [63]. The finding that the O-chain reflects in structure hyaluronic acid, a common human tissue component, indicates that it would be imprudent to preclude the O-chain as a contributing factor in the development of GBS until further investigations are undertaken. Conversely, an association has been reported between certain human leukocyte antigen types, e.g. HLA-B35 [71], and the development of GBS after C. jejuni infection. Thus, it can be speculated that infection with C. jejuni strains (e.g., O:19) bearing ganglioside-like epitopes in their LPS might induce high production of anti-ganglioside autoantibodies in patients with certain immunogenetic backgrounds, such as the HLA-B35 antigen, due to the abolition of tolerance [72].

5. H. pylori LPS

5.1. Molecular mimicry of Lewis blood group antigens

Compositional analysis has revealed that LPS of a number of H. pylori strains are fucosylated [9]. The O-specific polysaccharide chains of H. pylori LPS have been found upon structural analysis to exhibit mimicry of fucosylated Lewis⁴ (Le⁴) or Lewis⁵ (Le⁵) blood group antigens [73,74].

The structure of the O-chain of LPS of H. pylori NCTC 11637 (ATCC 43504), the type strain of H. pylori, was the first to be established [75] and is composed of repeating units that exhibit mimicry of Le⁵ [75,76] (Fig. 6A). The O-chain of another strain,
C1, also exhibits mimicry of \( \text{Le}^x \) units [77]. However, antigenic differences between the LPS from these two strains has been detected by immunoblotting and passive haemagglutination assays [78] and may reflect the presence of structurally different core LPS regions [77]. The O-polysaccharide of another strain, P466, differs from that of the type strain in termination by a \( \text{Le}^y \) determinant, but also has internal \( \text{Le}^x \) determinants [79] (Fig. 6B). In contrast the O-chain of \textit{H. pylori} MO19 consists of a single \( \text{Le}^y \) unit [73,79] (Fig. 6C). Thus, the expression of \( \text{Le}^x \) or \( \text{Le}^y \) determinants and the degree of O chain extension may vary in LPS of different \textit{H. pylori} strains. Nevertheless, analysis of \textit{H. pylori} strains with Mab against Lewis blood group antigens has demonstrated the presence of \( \text{Le}^x \) and/or \( \text{Le}^y \) determinants on 81% of the strains examined [80].

5.2. Potential role in immune suppression and autointimunity

Although it has been known for some years that A, B, and H blood group structures are present on certain Gram-negative bacteria [81,82], the expression of Lewis blood group antigens on the surface of \textit{H. pylori} is a novel property of the bacterium and has important biological implications. Lewis blood group antigens are expressed in normal human gastric mucosa and human gastric carcinoma [83]. The expression of host structures on the bacterial surface may camouflage \textit{H. pylori} for a period after infection, thereby aiding survival of the bacterium in the gastric mucosa [74]. Moreover, it could be considered that this bacterium may have evolved this characteristic during its evolution as a successful human colonizer. This is partly supported by the report of Chan et al. [84] who studied the biosynthetic pathways involved in the expression of \( \text{Le}^x \) on the surface of the bacterium. With acceptor molecules for fucosylation, \textit{H. pylori} was shown to contain \( \alpha_1,3\)-fucosyltransferase and \( \beta_1,4\)-galactosyltransferase activities, and analysis of the enzyme reaction products showed that biosynthesis of \( \text{Le}^x \) in \textit{H. pylori} is strictly ordered, i.e. addition of galactose is followed by that of fucose, and is therefore identical to that found in humans. Although we independently detected \( \alpha_1,3\)-fucosyltransferase activity in \textit{H. pylori} strains expressing \( \text{Le}^x \), \( \alpha_1,2\)-fucosyltransferase activity was not detectable in strains expressing \( \text{Le}^y \) [85]. The most general acceptor molecule known for \( \alpha_1,2\)-fucosyltransferase activity was used in our studies, and therefore it may be possible that the enzyme in \textit{H. pylori} is a rare class of fucosyltransferase.

During the course of prolonged infection, seropositivity against \textit{H. pylori} has been found to correlate with the presence of autoantibodies against human antral gastric mucosa, and antibodies cross-reacting with antigens of the gastric mucosa have been demonstrated in mice immunized with \textit{H. pylori} [86]. Therefore, with the progression of infection and the induction of an immune response, the presence of \( \text{Le}^x \)-bearing structures on \textit{H. pylori} might explain the development of autoantibodies. Supporting this, anti-\( \text{Le}^x \) and -\( \text{Le}^y \) have been found in patients infected with \textit{H. pylori} [87]. Moreover, anti-\( \text{Le}^x \) antibodies have been induced post-infection in a \textit{H. pylori} mouse model with a strain bearing the \( \text{Le}^x \) determinant, and \textit{H. pylori}-induced anti-\( \text{Le}^x \) and -\( \text{Le}^y \) Mab reacted with the gastric mucosa [85].

Chronic gastritis has been classified as two major types: chronic superficial gastritis without glandular loss and chronic atrophic gastritis with destruction of the glands [88]. On the basis of the prevalence of these two types of gastritis in different age groups, it was deduced that the superficial form may develop to the atrophic form [89,90]. \textit{H. pylori} is the primary cause of chronic superficial gastritis [6], whereas the pathogenic mechanisms triggering chronic atrophic gastritis include autointimy [91]. Further studies, therefore, are required to determine the role of Lewis antigen mimicry by LPS in the induction of autointimy in \textit{H. pylori}-associated disease.

Another and less controversial consequence of \( \text{Le}^x \) expression by \textit{H. pylori} concerns the down-regulation of the T-lymphocyte response in \textit{H. pylori} gastritis. T-helper lymphocytes (\( T_h \) cells) can be subdivided into \( T_{h1} \) and \( T_{h2} \) cells, and suppressed \( T_{h1} \) and enhanced \( T_{h2} \) responses in \textit{H. pylori} infection may be involved in the immunopathogenesis of this chronic infection [92]. \( \text{Le}^x \) is also found as a surface antigen on the eggs of the parasitic worm \textit{Schistosoma mansoni} which also down-regulates the T-lymphocyte response during infection [93]. The eggs of \textit{S. mansonii} trigger an alteration in the T-lymphocyte response, shifting immunity from
cell-mediated to antibody-mediated which, as in *H. pylori* infection, is ineffective in combating *S. mansoni* infection [94]. The polymeric Le"-containing structure of *S. mansoni* stimulates a B-lymphocyte-enriched population of spleen cells to produce large amounts of interleukin 10 and prostaglandin E₂, which down-regulate Tₘ responses, thereby suppressing cell-mediated immunity [93]. Whether a similar phenomenon occurs in *H. pylori*-strains expressing Le" requires investigation.

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### References

[1] Nikaido, H and Vaara, M (1987) Outer membrane In: *Escherichia coli and Salmonella typhimurium*. Cellular and Molecular Biology, Vol. 1 (Neidhardt, F.C., Ed.), pp. 7–22. American Society for Microbiology, Washington, DC.

[2] Moran, A.P. (1994) Structure-bioactivity relationships of bacterial endotoxins. *J. Toxicol. Toxin Rev.* 14, 47–83.

[3] Rietschel, E.T., Brade, L., Holst, O., Kulshin, V.A., Lindner, B., Moran, A.P., Schade, U.F., Zahringer, U. and Brade, H. (1990) Molecular structure of bacterial endotoxin in relation to bioactivity. In: *Endotoxin Research Series, Vol. 1. Cellular and Molecular Aspects of Endotoxin Reactions* (Nowotny, A., Spitzer, J.J. and Ziegler, E.J., Eds.), pp. 15–32. Elsevier Science Publishers B.V., Amsterdam.

[4] Mandrell, R.E. and Apicella, M.A. (1993) Lipooligosaccharides (LOS) of mucosal pathogens: molecular mimicry and host-modification of LOS. *Immunobiology* 187, 382–402.

[5] Nachamkin, I., Blaser, M.J. and Tompkins, L.S. (1992) *Campylobacter jejuni*: Current Status and Future Trends. *American Society for Microbiology*, Washington, DC.

[6] Marshall, B.J. and Warren, J.R. (1984) Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. *Lancet* i, 1311–1315.

[7] Rawws, E.A.I. and Tytgat, G.N.J. (1990) Cure of duodenal ulcer associated with eradication of *Helicobacter pylori*. *Lancet* 335, 1233–1235.

[8] Forman, D., Newell, D.G., Fullerton, F., Yarnell, J.W., Stacey, A.R., Wald, N. and Sitars, F. (1991) Association between infection with *Helicobacter pylori* and risk of gastric cancer: evidence from a prospective investigation. *Br. Med. J.* 302, 1302–1305.

[9] Moran, A.P., Helander, I.M. and Kosunen, T.U. (1992) Compositional analysis of *Helicobacter pylori* rough-form lipopolysaccharides. *J. Bacteriol.* 174, 1370–1377.

[10] Moran, A.P. (1995) Cell surface characteristics of *Helicobacter pylori*. *FEMS Immunol. Med. Microbiol.* 10, 271–280.

[11] Mandrell, R.E., Schneider, H., Apicella, M., Zollinger, W., Rice, P.A. and Griffiss (1986) Antigenic and physical diversity of *Neisseria gonorrhoeae* lipopolysaccharides. *Infect. Immun.* 54, 63–69.

[12] Preston, M.A. and Penner, J.L. (1987) Structural and antigenic properties of lipopolysaccharides from serotype reference strains of *Campylobacter jejuni*. *Infect. Immun.* 55, 1806–1812.

[13] Moran, A.P. and Kosunen, T.U. (1989) Serological analysis of the heat-stable antigens involved in serotyping *Campylobacter jejuni* and *Campylobacter coli*. *APMIS* 97, 253–260.

[14] Jennings, H.J., Lugowski, C. and Ashton, F.E. (1983) The structure of an R-type lipooligosaccharide core obtained from some lipopolysaccharides of *Neisseria meningitidis*. *Carbohydr. Res.* 121, 233–241.

[15] Michon, F., Beurret, M., Gamian, A., Brisson, J.-R. and Jennings, H.J. (1990) Structure of the L5 lipopolysaccharide core oligosaccharides of *Neisseria meningitidis*. *J. Biol. Chem.* 265, 7243–7247.

[16] Gamian, A., Beurret, M., Michon, F., Brisson, J.-R. and Jennings, J.H. (1992) Structure of the L2 lipopolysaccharides core oligosaccharides of *Neisseria meningitidis*. *J. Biol. Chem.* 267, 922–925.

[17] Di Fabio, J.L., Michon, F., Brisson, J.-R. and Jennings, H.J. (1990) Structure of the L1 and L6 core oligosaccharide epitopes of *Neisseria meningitidis*. *Can. J. Chem.* 68, 1029–1034.

[18] John, C.M., Griffiss, J.M., Apicella, M.A., Mandrell, R.E. and Gibson, B.W. (1991) The structural basis for pyocin-resistance in *Neisseria gonorrhoeae* lipopolysaccharides. *J. Biol. Chem.* 266, 19303–19311.

[19] Mandrell, R.E. (1992) Further antigenic similarities of *Neisseria gonorrhoeae* lipopolysaccharides and human glycosphingolipids. *Infect. Immun.* 60, 3017–3020.

[20] Yamasaki, R., Bacon, B.E., Nasheild, W., Schneider, H. and Griffiss, J.M. (1991) Structural determination of olsogalssaccharides derived from lipopolysaccharide of *Neisseria gonorrhoeae* F62 by chemical, enzymatic, and two-dimensional NMR methods. *Biochemistry* 30, 10566–10575.

[21] Borrelli, S., Roggen, E.L., Hendriksen, D., Jonasson, J., Ahmed, H.J., Floy, P., Jansson, P.-E. and Lindberg, A.A. (1995) Monoclonal antibodies against *Haemophilus* lipopolysaccharides: clone DF8 specific for *Haemophilus ducreyi* and clone DH24 binding to lacto-N-neotetraose. *Infect. Immun.* 63, 2665–2673.

[22] Schweda, E.K.H., Sundström, A.C., Eriksson, L.M., Jonasson, J.A. and Lindberg, A.A. (1994) Structural studies of the
cell envelope lipopolysaccharides from Haemophilus ducreyi strains ITM 2665 and ITM 4747. J. Biol. Chem. 260, 12040–12048.

[23] Mandrell, R.E., McLaughlin, R., Kwaik, Y.A., Lesse, A., Yamasaki, R., Gibson, B., Spinola, S.M. and Apicella, M.A. (1992) Lipooligosaccharides (LOS) of some Haemophilus species mimic human glycosphingolipids, and some LOS are sialylated. Infect. Immun. 60, 1322–1328.

[24] Gibson, B.W., Melaugh, W., Phillips, N.J., Apicella, M.A., Campagnari, A.A. and Griffin, J.M. (1993) Investigation of the structural heterogeneity of lipooligosaccharides from pathogenic Haemophilus and Neisseria species and of R-type lipopolysaccharides from Salmonella typhimurium by electrospray mass spectrometry. J. Bacteriol. 175, 2702–2712.

[25] Melaugh, W., Phillips, N.J., Campagnari, A.A. and Tullius, M.V. (1994) Structure of the major oligosaccharide from the lipooligosaccharide of Haemophilus ducreyi strain 35000 and evidence for additional glycoforms. Biochemistry 33, 13070–13078.

[26] Jann, B., Rodriguez, M.-L., Finke, A., Kröncke, K.-D. and Jann, K. (1991) Chemical characterization of E.coli capsules and analysis of their expression. In: FEMS Symposium, No. 51. Microbial Surface Components and Toxins in Relation to Pathogenesis (Rou, E.Z. and Ruten, S., Eds.), pp. 151–160. Plenum Press, New York.

[27] Kasai, K., Galton, J., Terasaki, P.I., Wakisaka, K., Kawahara, M., Root, T. and Hakomori, S.-I. (1985) Tissue distribution of the Pα antigen as determined by a monoclonal antibody. J. Immunogen. 12, 213–220.

[28] Yurewicz, E.C., Matsuura, F. and Moghissi, K.S. (1982) Structural characterization of neutral oligosaccharides of human midcyclical mucin. J. Biol. Chem. 257, 2314–2322.

[29] Ward, M.E., Watt, P.J. and Glynne, A.A. (1970) Gonococci in urethral exudates possess a virulence factor lost on subculture. Nature (London) 227, 382–384.

[30] Tan, E.L., Patel, P.V., Parsons, N.J., Martin, P.M.V. and Smith, H. (1986) Lipopolysaccharide alteration is associated with induced resistance of Neisseria gonorrhoeae to killing by human serum. J. Gen. Microbiol. 132, 1407–1413.

[31] Patel, P.V., Parsons, N.J., Andrade, J.R.C., Nairn, C.A., Tan, E.L., Glodner, M., Cole, J.A. and Smith, H. (1988) White blood cells including polymorphonuclear phagocytes contain a factor which induces gonococcal resistance to complement-mediated serum killing. FEMS Microbiol. Lett. 50, 173–176.

[32] Parsons, N.J., Andrade, J.R.C., Patel, P.V., Cole, J.A. and Smith, H. (1989) Sialylation of lipopolysaccharide and loss of absorption of bactericidal antibody during conversion of gonococci to serum resistance by cytokine 5'-monophospho-N-acetylneuraminic acid. Microb. Pathog. 7, 63–72.

[33] Mandrell, R.E., Lesse, A.J., Sugai, J.V., Shero, M., Griffin, J.M., Cole, J.A., Parsons, N.J., Smith, H., Morse, S.A. and Apicella, M.A. (1990) In vitro and in vivo modification of Neisseria gonorrhoeae lipooligosaccharide epitope structure by sialylation. J. Exp. Med. 171, 1649–1664.

[34] Frangipane, J.V. and Rest, R.F. (1993) Anaerobic growth and cytidine 5'-monophospho-N-acetylneuraminic acid act synergistically to induce high-level serum resistance in Neisseria gonorrhoeae. Infect. Immun. 61, 1657–1666.

[35] Mandrell, R.E., Kim, J.J., John, C.M., Gibson, B.W., Sugai, J.V., Apicella, M.A., Griffin, J.M. and Yamasaki, R. (1991) Endogenous sialylation of the lipooligosaccharides of Neisseria meningitidis. J. Bacteriol. 173, 2823–2832.

[36] Pavliak, V., Brisson, J.-R., Michon, F., Uhrin, D. and Jennings, H.J. (1993) Structure of the sialylated L3 Lipopolysaccharide of Neisseria meningitidis. J. Biol. Chem. 268, 14146–14152.

[37] Ganguli, A., Zapata, G., Wallis, T., Reid, C., Boulnois, G., Vann, W.F. and Roberts, I.S. (1994) Molecular cloning and analysis of genes for sialic acid synthesis in Neisseria meningitidis group B and purification of the meningococcal CMP-NeuNac synthetase enzyme. J. Bacteriol. 176, 4583–4589.

[38] Mandrell, R.E., Smith, H., Jarvis, G.A., Griffiss, J.M. and Cole, J.A. (1993) Detection and some properties of the sialyltransferase implicated in the sialylation of lipopolysaccharide of Neisseria gonorrhoeae. Microb. Pathog. 14, 307–313.

[39] de la Paz, H., Cooke, S.J. and Heckels, J.E. (1995) Effect of sialylation of lipopolysaccharide of Neisseria gonorrhoeae on recognition and complement-mediated killing by monoclonal antibodies directed against different outer-membrane antigens. Microbiology 141, 913–920.

[40] Rest, R.F. and Frangipane, J.V. (1992) Growth of Neisseria gonorrhoeae in CMP-N-acetylneuraminic acid inhibits nonsonic (opacity-associated outer membrane protein-mediated) interactions with human neutrophils. Infect. Immun. 60, 989–997.

[41] Wetzler, L.M., Barry, K., Blake, M.S. and Gotschlich, E.C. (1992) Gonococcal lipooligosaccharide sialylation prevents complement-dependent killing by immune sera. Infect. Immun. 60, 39–43.

[42] Meri, S. and Pangburn, M.K. (1990) Discrimination between activators and nonactivators of the alternative pathway of complement: regulation via a sialic acid/polyanion binding site on factor H. Proc. Natl. Acad. Sci. USA 87, 3982–3986.

[43] Mishu, B. and Blaser, M.J. (1993) Role of infection due to Campylobacter jejuni in the initiation of Guillain–Barré syndrome. Clin. Infect. Dis. 17, 104–108.

[44] Mishu, B., Ilyas, A.A., Koski, C.L., Vitsendorp, Cook, S.D., Mithen, F.A. and Blaser, M.J. (1993) Serologic evidence of previous Campylobacter jejuni infection in patients with the Guillain–Barré syndrome. Ann. Intern. Med. 118, 947–953.

[45] Rees, J.H., Soudain, S.E., Gregson, N.A. and Hughes, R.A.C. (1995) Campylobacter jejuni infection and Guillain–Barré syndrome. New Engl. J. Med. 333, 1374–1379.

[46] Kuroki, S., Saida, T., Nukina, M. et al. (1993) Campylobacter jejuni strains from patients with Guillain–Barré syndrome belong mostly to Penner serogroup 19 and contain β-N-acetylgalcosamine residues. Ann. Neurol. 33, 243–247.
Acute axonal polyneuropathy associated with anti-GM, anti-Illa, I., Ortiz, N., Gallard, E., Juarez, C., Grau, J.M. and Laporte. J.R. (1992) Bovine gangliosides and acute motor toxin Res. 2, 395-403.
Wirguin, I., Suturkova-Milosevic, L., Della-Latta, P., Fisher, T., Brown, R.H and Latov, N. (1994) Monoclonal IgM antibodies to GM1 and asialo-GM1 in chronic neuropathies cross-react with Campylobacter jejuni lipopolysaccharides. Ann. Neurol. 35, 698-703.

Yuki, N., Taki, T., Takahashi, M., Saito, K., Tai, T., Miyatake, Y. and Handa, S. (1994) Penner's serotype 4 of Campylobacter jejuni has a lipopolysaccharide that bears a GM1 ganglioside epitope as well as one that bears a GD1a epitope. Infect. Immun. 62, 2101-2103.

Yuki, N., Taki, T., Inagaki, F., Kasama, T., Takahashi, M., Saito, K., Handa, S. and Miyatake, T. (1993) A bacterium lipopolysaccharide that elicits Guillain–Barré syndrome has a GM1 ganglioside-like structure. J. Exp. Med. 178, 1771-1775.

Aspinall, G.O., McDonald, A.G., Pang, H., Kurjanczyk, L.A. and Penner, J.L. (1994) Lipopolysaccharides of Campylobacter jejuni serotype O:19: structures of core oligosaccharide regions from the serostrain and two bacterial isolates from patients with the Guillain–Barré syndrome. Biochemistry 33, 241-9.

Moran, A.P. and O’Malley, D.T. (1995) Potential role of lipopolysaccharides of Campylobacter jejuni in the development of Guillain–Barré syndrome. J. Endotoxin Res. 2, 233-235.

Yuki, N., Handa, S., Tai, T., Takahashi, M., Saito, K., Tsuji, Y. and Taki, T. (1995) Ganglioside-like epitopes of lipopolysaccharides from Campylobacter jejuni (PEN 19) in three isolates from patients with Guillain–Barré syndrome. J. Neuro. Sci. 130, 112-116.

Moran, A.P., Rietschel, E.T., Kosunen, T.U. and Zähringer, U. (1991) Chemical characterization of Campylobacter jejuni lipopolysaccharides containing N-acetylenuraminic acid and 2,3-diamino-2,3-dideoxy-D-glucose. J. Bacteriol. 173, 618-626.

Moran, A.P. (1995) Biological and serological characterization of Campylobacter jejuni lipopolysaccharides with deviating core and lipid A structures. FEMS Immunol. Med. Microbiol. 11, 121-130.

Aspinall, G.O., McDonald, A.G., Raju, T.S., Pang, H., Moran, A.P. and Penner, J.L. (1993) Chemical structure of the core regions of Campylobacter jejuni serotypes O:1, O:4, and O:23 and O:36 lipopolysaccharides. Eur. J. Biochem. 213, 1017-27.

Aspinall, G.O., Lynch, C.M., Pang, H. Shaver, R.T. and Moran, A.P. (1995) Chemical structures of the core region of Campylobacter jejuni O:3 lipopolysaccharide and an associated polysaccharide. Eur. J. Biochem. 231, 570-578.

Aspinall, G.O., McDonald, A.G. and Pang, H. (1994) Lipopolysaccharides of Campylobacter jejuni O:3 observed of O antigen chains from the serostrain and two bacterial isolates from patients with the Guillain–Barré syndrome. Biochemistry 33, 250-255.

Yuki, N., Sato, S., Itoh, T. and Miyatake, T. (1991) HLA-B35 and acute axonal polyneuropathy following Campylobacter jejuni infection. Neurology 41, 1561-1563.

Yuki, N. (1994) Pathogenesis of axonal Guillain–Barré syndrome: hypothesis. Muscle Nerve 17, 680-687.

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eral structures of lipopolysaccharides: a window on strain to strain variations in \textit{H. pylori}. Gut 37 (Suppl. 1), A17.

[74] Moran, A.P. (1996) The role of lipopolysaccharide in \textit{Helicobacter pylori} pathogenesis. Aliment. Pharmacol. Ther. 10, Suppl. 1, 39–50.

[75] Aspinall, G.O., Monteiro, M.A., Pang, H., Walsh, E.J. and Moran, A.P. (1994) O antigen chains in the lipopolysaccharide of \textit{Helicobacter pylori} NCTC 11637. Carbohydr. Lett. 1, 151–156.

[76] Aspinall, G.O., Monteiro, M.A., Pang, H., Walsh, E.J. and Moran, A.P. (1996) Lipopolysaccharide of the \textit{Helicobacter pylori} type strain NCTC 11637 (ATCC 43504): structure of the O antigen chain and core oligosaccharide regions. Biochemistry 35, 2489–2497.

[77] Aspinall, G.O., Monteiro, M.A., Moran, A.P., Pang, H., Penner, J.L. and Shaver, R.T. (1996) Lipopolysaccharides from \textit{Helicobacter pylori}. Prog. Clin. Biol. Res. 392, 93–101.

[78] Mills, S.D., Kurjanczyk, L.A. and Penner, J.L. (1992) Antigenicity of \textit{Helicobacter pylori} lipopolysaccharides. Infect. Immun. 60, Suppl. 1, 1–50.

[79] Aspinall, G.O. and Monteiro, M.A. (1996) Lipopolysaccharides of \textit{Helicobacter pylori} strains P466 and M019: structures of the O antigen and core oligosaccharide regions. Biochemistry 35, 2498–2504.

[80] Simoons-Smit, I.M., Appelmelk, B.J., Verboom, T., Negrini, R., Penner, J.L., Aspinall, G.O., Forte, J.G., De Vries, T., Quan, H., Verboom, T., Maaskant, J.J., Ghiara, P., Koipers, E.J., Bloemen, E., Tadema, T.M., Townsend, R.R., Tyagarajan, K., Crothers, J.M., Monteiro, M.A., Savio, A. and De Graaff, J. (1996) Potential role of molecular mimicry between \textit{Helicobacter pylori} lipopolysaccharide and host Lewis blood group antigens in autoimmunity. Infect. Immun. 64, 2031–2040.

[81] Appelmelk, B.J., Simoons-Smit, I., Negrini, R., Moran, A.P., Aspinall, G.O., Forte, J.G., De Vries, T., Quan, H., Verboom, T., Maaskant, J.J., Ghiara, P., Koipers, E.J., Bloemen, E., Tadema, T.M., Townsend, R.R., Tyagarajan, K., Crothers, J.M., Monteiro, M.A., Savio, A. and De Graaff, J. (1996) Potential role of molecular mimicry between \textit{Helicobacter pylori} lipopolysaccharide and host Lewis blood group antigens in autoimmunity. Infect. Immun. 64, 2031–2040.

[82] Negrini, R., Lisato, L., Zanella, L., Cavazzini, L., Gullini, S., Villanacci, V., Poiesi, C., Albertini, A. and Ghelmi, S. (1991) \textit{Helicobacter pylori} infection induces antibodies cross-reacting with human gastric mucosa. Gastroenterology 101, 437–445.

[83] Aspinall, G.O., Monteiro, M.A., Moran, A.P., Pang, H., Penner, J.L. and Shaver, R.T. (1996) Lipopolysaccharides from \textit{Helicobacter pylori}. Prog. Clin. Biol. Res. 392, 93–101.

[84] Mills, S.D., Kurjanczyk, L.A. and Penner, J.L. (1992) Antigenicity of \textit{Helicobacter pylori} lipopolysaccharides. Infect. Immun. 60, Suppl. 1, 1–50.

[85] Appelmelk, B.J., Simoons-Smit, I., Negrini, R., Moran, A.P., Aspinall, G.O., Forte, J.G., De Vries, T., Quan, H., Verboom, T., Maaskant, J.J., Ghiara, P., Koipers, E.J., Bloemen, E., Tadema, T.M., Townsend, R.R., Tyagarajan, K., Crothers, J.M., Monteiro, M.A., Savio, A. and De Graaff, J. (1996) Potential role of molecular mimicry between \textit{Helicobacter pylori} lipopolysaccharide and host Lewis blood group antigens in autoimmunity. Infect. Immun. 64, 2031–2040.

[86] Negrini, R., Lisato, L., Zanella, L., Cavazzini, L., Gullini, S., Villanacci, V., Poiesi, C., Albertini, A. and Ghelmi, S. (1991) \textit{Helicobacter pylori} infection induces antibodies cross-reacting with human gastric mucosa. Gastroenterology 101, 437–445.

[87] Sherburne, R. and Taylor, D.E. (1995) \textit{Helicobacter pylori} expresses a complex surface carbohydrate. Lewis X. Infect. Immun. 63, 4564–4568.

[88] Kekki, M., Siurala, M., Varis, K., Sipponen, P., Sistonen, P. and Nevanlinna, H.R. (1987) Classification principles and genetics of chronic gastritis. Scand. J. Gastroenterol. 22 (Suppl. 141), 1–28.

[89] Siurala, M., Isokoski, M., Varis, K. and Kekki, M. (1968) Prevalence of gastritis in a rural population. Biologic study of subjects selected at random. Scand. J. Gastroenterol. 3, 211–223.

[90] Kekki, M., Villako, K., Tammi, A. and Siurala, M. (1977) Dynamics of antral and fundal gastritis in an Estonian rural population sample. Scand. J. Gastroenterol. 12, 321–4.

[91] Strickland, R.G. and Makay, I.R. (1973) A reappraisal of the nature and significance of chronic atrophic gastritis. Dig. Dis. 18, 426–440.

[92] Fan, X.G., Yahboob, J., Fan, X.J. and Keeling, P.W.N. (1996) Enhanced T-helper 2 lymphocyte responses: immune mechanism of \textit{Helicobacter pylori} infection. Ir. J. Med. Sci. 165, 37–39.

[93] Velupillai, P. and Harn, D.A. (1994) Oligosaccharide-specific induction of interleukin 10 production by B220+ cells from schistosome-infected mice: a mechanism for regulation of CD4+ T-cell subsets. Proc. Natl. Acad. Sci. USA 91, 18–22.

[94] Mosmann, T.R. and Coffman, R.L. (1989) Heterogeneity of cytokine secretion patterns and functions of helper T cells. Adv. Immunol. 46, 111–147.