Molecular Mimicry in Campylobacter jejuni Lipopolysaccharides and the Development of Guillain-Barré Syndrome

To the Editor—Three-quarters of patients develop Guillain-Barré syndrome (GBS) following various respiratory and gastrointestinal infections [1]. Campylobacter jejuni has been identified as the most common single pathogen associated with the development of GBS (in 20%–50% of patients). In a recent article, Yuki [2] described the role of molecular mimicry between gangliosides and lipopolysaccharides (LPSs) of C. jejuni in the induction of anti-ganglioside antibodies, which are considered to play an important role in the pathogenesis of GBS. This article raises a number of points for discussion.

Yuki [2] described the high frequency of C. jejuni O:19 isolates in GBS patients and discussed the importance of mimicry of GM, ganglioside in the LPS core of such isolates for the development of GBS. However, the molecular mimicry is not restricted to C. jejuni O:19. Isolates of other C. jejuni serotypes obtained from GBS patients exhibit mimicry of GM, and other gangliosides (reviewed in [3]).

Nevertheless, molecular mimicry of gangliosides in the core oligosaccharide of LPS may not be sufficient to explain the induction of GBS by C. jejuni. We have shown previously [4] that the LPS core of a C. jejuni O:19 isolate from a patient with enteritis, but who subsequently did not develop GBS, exhibited mimicry of GM, and GD₃, oligosaccharides. In his article, Yuki [2] speculated that the presence of a hyaluronic acid–like repeat unit [5] in the O chain of C. jejuni O:19 LPS helps this GM₁-like LPS to induce the development of anti-GM, antibody in GBS. This was based on data that glycosaminoglycans, including hyaluronic acid, may play an important role in the development of autoimmune disease in general [6]. An argument against this hypothesis is that the antigenic determinants for serotyping C. jejuni O:19 strains occur in the O chain of this LPS [7], and therefore, both enteritis and GBS isolates of this serotype would have to possess hyaluronic acid–like O chains to be serotyped as C. jejuni O:19.

We have addressed this issue in a previous study, in which we examined the expression of the O chain in 2 enteritis and 2 GBS isolates of C. jejuni O:19 that exhibited mimicry of GM₁, and GD₃, gangliosides [4]. To avoid any comparative loss of O chain expression during in vitro cultivation, all isolates were treated identically, and tests were performed after one subculture from frozen stocks of the original isolates. Briefly, when serotyped in passive hemagglutination, all 4 isolates belonged to O:19, but the 2 GBS-associated isolates gave a higher titer than the enteritis isolates (1:5120 vs. 1:640). In repeated parallel immunoblotting with O:19 typing antisera, staining of O chains was more intense in LPS preparations from the GBS isolates. Lectin typing indicated a lower content of sugars associated with the O chain in enteritis isolates compared with GBS isolates. Chemical liberation and purification of O chains gave higher yields from LPS of GBS than of enteritis-associated isolates (14% vs. 6% dry weight).

Collectively, these data indicated a higher expression of the hyaluronic acid–like O chain in LPS of C. jejuni O:19 GBS-associated isolates. Since both the GBS- and enteritis-associated isolates in our study exhibited ganglioside mimicry, differences in the extent of expression of the hyaluronic acid–like O chain, rather than simply its presence as speculated by Yuki [2], may play an important role in the development of C. jejuni–associated GBS.

Furthermore, Yuki suggested (figure 2 in [2]) that the GM₁-like LPS of C. jejuni O:19, with its associated hyaluronic acid–like O chain, alone “induces high production of IgG anti-GM antibodies with help of T helper cells.” The situation may not be so simple. Immune responses against polysaccharides are usually T cell–independent. Glycolipids cannot be bound by major histocompatibility complex (MHC) molecules, suggesting that these compounds cannot directly activate T cells in an MHC-restricted manner. However, a weak association between C. jejuni infections and HLA haplotype in GBS patients suggests some involvement of T cells [8]. An MHC-restricted T cell response to glycolipids may be obtained in the presence of a carrier protein, whereby presentation of the glycolipid-protein complex by MHC could occur and activation of T cells proceed [3].

A potential candidate as a carrier protein for GM₁-like LPS is the GM₁-binding cholera-like enterotoxin produced by some C. jejuni strains [3, 9]. Alternatively, as demonstrated for lipoglycans, presentation to T cells could occur in association with the CD1 molecule [10]. Whether these CD1-dependent, MHC-unrestricted T cell responses could be induced against C. jejuni LPS is unknown. Thus, the role of T cells in the production of cross-reactive antibodies against LPS and gangliosides in GBS has yet to be elucidated.

References

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The Journal of Infectious Diseases 1998;178:1548–9 © 1998 by the Infectious Diseases Society of America. All rights reserved. 0022-1899/98/7805-0048$02.00

0022-1899/98/7805-0048$02.00
Replies

To the Editor—Moran and Prendergast [1] speculated that high expression of the hyaluronic acid–like O chain is more important for the development of Guillain-Barré syndrome (GBS) than molecular mimicry between the ganglioside and the lipopolysaccharide (LPS) of Campylobacter jejuni. They analyzed only 4 isolates of C. jejuni O:19, but a much larger number of isolates is required to show that there is a statistically significant difference between the dosage of the hyaluronic acid–like O chain from GBS-associated isolates and that from enteritis-associated isolates.

As stated in my article [2], reports of the number of patients who developed GBS after being administered bovine brain ganglioside have mounted. The clinical fact of the existence of cases of GBS subsequent to ganglioside injection strongly suggests that ganglioside mimicry has a very important role in the development of GBS subsequent to C. jejuni enteritis. Although molecular mimicry is not restricted to O:19, this serotype has been isolated more frequently from GBS patients than the other serotypes [3, 4]. We therefore assume that the serotypic determinant (the hyaluronic acid–like O chain) functions in the induction of antibodies to the ganglioside-like structure in the LPS. The adjuvant activity of the hyaluronic acid–like O chain must be examined to test this assumption. Only a few patients who have had C. jejuni O:19 enteritis or a ganglioside injection develop GBS; the great majority do not. This suggests there is an immunogenetic predisposition of the host to develop GBS.

Moran and Prendergast [1] did not agree with our theory that T cells function in the production of cross-reactive antibodies against LPS and ganglioside in patients with GBS after C. jejuni enteritis. Carbohydrates generally are T cell–dependent antigens. IgG antibodies to bacterial polysaccharide generally are restricted to the IgG2 subclass. Earlier we investigated the subclasses of IgG antibody to the ganglioside-like LPS and showed that they are restricted to IgG1 and IgG3, characteristic of a T cell–dependent antibody response [5]. This finding has been confirmed by others [6, 7]. Moreover, in GBS contracted after an injection of ganglioside that does not carry protein, the predominant anti-ganglioside antibodies are IgG1 and IgG3 [8]. Furthermore, pokeweed mitogen (a T cell–dependent polyclonal B cell activator) stimulates the in vitro synthesis of anti-ganglioside antibody in GBS patients [9]. As this evidence is indirect, further studies are needed to confirm our theory.

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References

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