oedema, such as that associated with fulminant hepatic failure.

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Ganglioside complexes in MFS

# Ganglioside complexes as targets for antibodies in Miller Fisher syndrome

**H J Willison**


## The specificity of Miller Fisher syndrome sera for ganglioside complexes may influence its pathogenesis

In the early 1990s, Kusunoki's group[1 2] showed, in two seminal papers, that antibodies directed against the ganglioside GQ1b were present in the acute-phase sera of patients with Miller Fisher syndrome (MFS). Since then, numerous studies have been published which show that anti-GQ1b antibodies and closely related anti-GT1a antibodies have a central role in MFS pathogenesis.[3] In the latest paper from Kusunoki's group by Kaida *et al*[4] ***(see page 1043)***, another fundamental issue surrounding anti-GQ1b antibodies has been uncovered, which confounds several issues and adds an intriguing layer of complexity to this highly charged subject.

Gangliosides are a large family of glycosphingolids that are concentrated in the nervous system. In Schwann cells and neuronal plasma membranes of peripheral nerves, gangliosides reside in clusters in specialised microdomains termed as lipid rafts. Here, their extracellular carbohydrate moieties are readily accessible to act as landing pads for circulating autoantibodies, which then mediate inflammatory injury to the membrane. Autoantibodies to around 20 individual ganglioside species have been reported in Guillain–Barré syndrome (GBS) and related disorders, and many studies attest to their clinical and pathological significance.[3]

In 2004, Kusunoki's group[5] observed that GBS-associated autoantibodies occasionally preferred to bind to mixtures of gangliosides rather than to a highly purified single-ganglioside species. By carrying out immunodetection studies in which gangliosides (GM1, GD1a, GD1b and GT1b) were admixed in varying proportions, they determined the optimum ratio of ganglioside mixtures to effect maximum binding for a range of different anti-ganglioside antibody-containing GBS sera. Most importantly, they identified some GBS sera that entirely failed to react with single-ganglioside species, but nevertheless reacted strongly with ganglioside complexes. In this study, they extended this approach to investigate a similar phenomenon in MFS sera. Thus, anti-antibody reactivity with GQ1b or GT1a can be enhanced by the presence of additional gangliosides, including GM1, GD1a and GT1b. Furthermore, they identified one MFS serum that failed to react with either GQ1b or GT1a, yet reacted strongly with GQ1b/GM1 and GT1a/GM1 complexes, thereby accounting for at least some of the occasional MFS cases that are apparently anti-GQ1b antibody negative. Although it is too early to draw firm conclusions from the small sample size in this study, the specificity of MFS sera for GQ1b, GT1a and their respective complexes may influence the pattern of clinical features seen in this already diverse spectrum of anti-GQ1b antibody-associated disorders.

Kusunoki's studies have to date concentrated on the identification of ganglioside complexes under artificial immunoassay conditions. One crucial pathophysiological issue is the extent to which these clusters exist in the natural membrane environment of the peripheral nerve and, if so, whether they can act as stable targets for autoantibodies. A second issue that requires study is the mechanism by which antibodies to ganglioside complexes are formed, as the prediction from Kusunoki's studies is that carbohydrate complexes should be present on the bacterial and viral surfaces that trigger GBS. Various models can be proposed to support this possibility.[6] These fascinating studies lead us towards new vistas in carbohydrate recognition by antibodies and other sugar-binding proteins (lectins), which will greatly enrich this field from both clinical and basic perspectives.

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