N-glycan-dependent pro-inflammatory effects of IgM in anti-MAG Neuropathy

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Introduction.

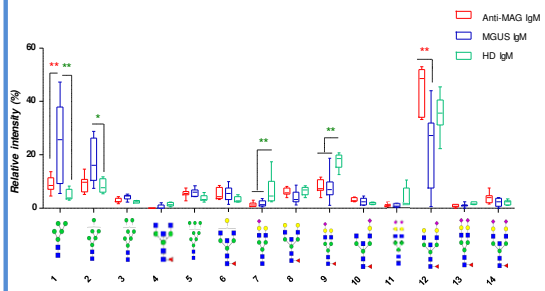
IgG glycosylation plays a key role in autoimmune diseases, but IgM glycosylation differs significantly and remains understudied.

This study investigates IgM N-glycosylation in anti-MAG neuropathy and its role in disease pathogenicity.

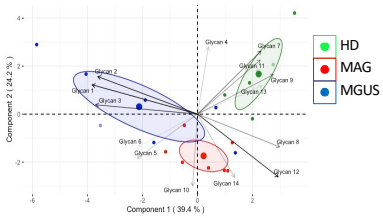
Methods:

IgM antibodies were isolated from patients with anti-MAG neuropathy (n=17), asymptomatic MGUS patients (n=8), and healthy donors (n=6) (HD). N-glycan analysis was performed using mass spectrometry. The binding of IgM to Fc receptors (Fcα/μ, DC-SIGN) and complement (C1q), was compared between anti-MAG, MGUS and HD IgM, using ELISA. The impact of IgM N-glycosylation on cytokine production by monocyte-derived macrophages was assessed before and after N-deglycosylation between both anti-MAG and MGUS IgMs.

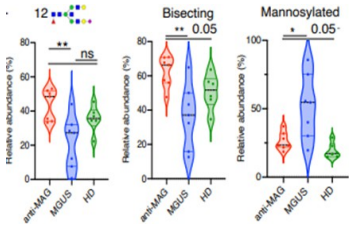
Anti-MAG IgM exhibit a distinctive N-glycan signature



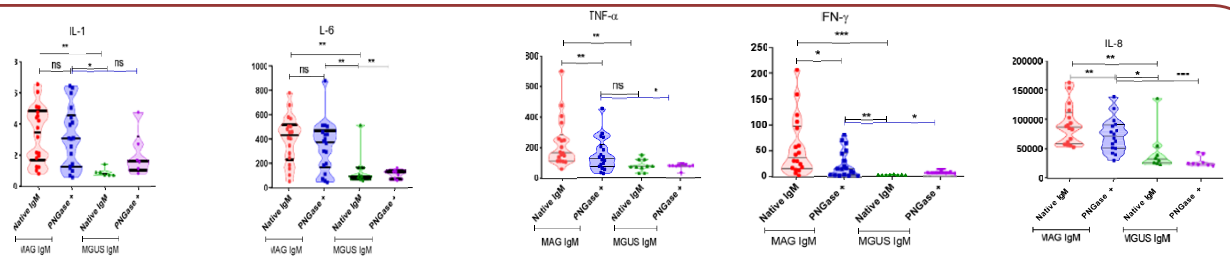
Comparisons of IgM N-glycoforms between anti-MAG, MGUS and HD IgM groups



Principal Component Analysis of the 14 major N-glycans measured in anti-MAG patients, MGUS and controls

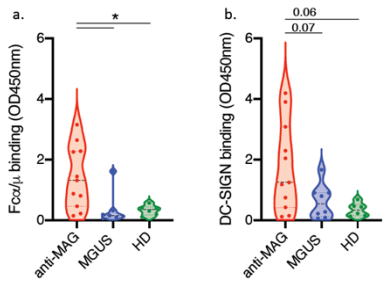


Relative abundances of N-glycan (peak 12), bisecting and mannosylated N-glycans in the three groups

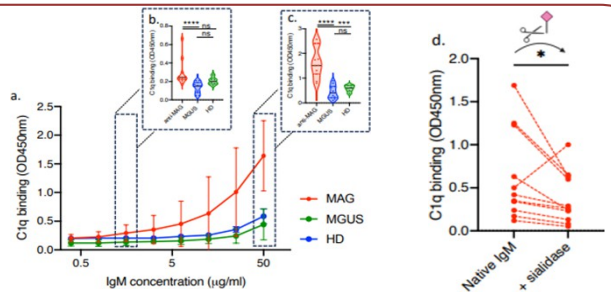


1. Anti-MAG IgM display unique pro-inflammatory properties

TNF-α, IFN-γ, and IL-8 expression being glycosylation-dependent and unrelated to the paraproteinemia, as MGUS IgM did not induce a similar effect. After deglycosylation, they maintain reduced pro-inflammatory activity, except TNF-α, while the IgM glycome enhances inflammation.



2. Anti-MAG IgM efficiently bind Fcα/μ and DC-SIGN receptors compared to MGUS IgM which could in turn trigger macrophage activation and cytokine production.



3. Anti-MAG IgM N-glycosylation enhances binding to C1q (a,b,c)

After desialylation (d), C1q binding decreases by 40.0±19%. Complement deposition increases with IgM sialylation[1]. The level of anti-MAG/C1q binding seems to correlate with the complement's myelinolytic activity[2]

Conclusion

- This study uncovered a unique N-glycosylation pattern of anti-MAG IgM, crucial for its interaction with Fc receptors and binding to C1q.
- Moreover, anti-MAG IgM increased the macrophage cytokine production, driven by their glycosylation. `
- The increased IL-8 expression and C1q binding suggest two potential therapeutic strategies: inhibiting IL-8 expression and/or targeting the complement pathway.
- Additionally, the C1q binding of anti-MAG IgM could serve as biomarkers for monitoring this neuropathy.

References:

1. Haslund-Gourley BS, Woloszczuk K, Hou J, et al. IgM N-glycosylation correlates with COVID-19 severity and rate of complement deposition. *Nat Commun.* 2024;15(1):404
2. Idusogie EE, Wong PY, Presta LG, et al. Engineered antibodies with increased activity to recruit complement. *J Immunol.* 2001;166(4):2571-2575.