STRAIN-LEVEL MICROBIOTA VARIATION SHAPES IMMUNE RESPONSES TO GLYCOCONJUGATE VACCINATION

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Glycoconjugate vaccines are widely used to induce protective immune responses, primarily against encapsulated bacteria. However, inter-individual variability in vaccine immunogenicity remains poorly understood. Growing evidence suggests that gut microbiota plays a critical role in shaping host immune responses [1,2], but the contribution of specific microbial taxa and strain-level variation remains underexplored. This study investigates how distinct microbiota compositions influence humoral and cellular responses to glycoconjugate vaccination.
We vaccinated 6-week-old Swiss Webster (SW) (outbred) and C57BL/6 (inbred) specific pathogen–free (SPF), antibiotic-treated, and germ-free (GF) mice with a panel of glycoconjugate antigens two times at a two-week interval using alum as an adjuvant. Serum antigen-specific IgG responses were measured by ELISA, and cellular immune responses were characterized via flow cytometry in draining lymph nodes and spleens. To identify microbial taxa linked to enhanced IgG responses, we performed 16S rRNA sequencing and applied differential abundance analysis (ANCOM). GF mice were selectively colonized with single bacterial strains or complex microbial communities via oral gavage.
Bioinformatics analysis identified microbiota compositional patterns associated with increased IgG responses to vaccination, which was further confirmed by targeted colonization experiments. Notably, strain-level variation within gut microbiota significantly influenced humoral immune responses, with specific strains enhancing IgG production. Additionally, microbiota composition influenced germinal center B cell responses and regulatory/inhibitory immune environments, shaping the overall immune landscape. Colonization experiments in both SW and C57BL/6 mice demonstrated that host genetic background modulates the immunogenic impact of microbiota, with outbred mice displaying greater sensitivity to microbiota-driven effects.
These findings underscore the importance of specific microbial taxa in modulating immune responses to glycoconjugate vaccines and highlight the interplay between host genetics, microbial strain diversity, and carbohydrate immunogenicity. Understanding how microbiota shape antibody responses to carbohydrate antigens could open new avenues for microbiota-targeted vaccine strategies and optimize the efficacy of glycan-based therapeutics.

References:

1. D. J. Lynn, S. C. Benson, M. A. Lynn, B. Pulendran, *Nat. Rev. Immunol.* **2022**, *22*, 33-46.
2. G. Stefanetti, D. L. Kasper, *Biochemistry* **2022**, *61*, 2849-2855.