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EDITORIAL

Anti-commensal Ig—from enormous diversity to clear function

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In this issue of Mucosal Immunology there are two reviews of recent research on the role of antibodies in host microbial mutualism and disease.[1,2] Sterlin and colleagues summarize the antibody response with a specific focus on anti-commensal IgG antibodies, whereas Pabst and Slack focus their attention around the binding mode and induction of microbiota-binding Ig. Both works provide exceptionally interesting perspectives on the induction and function of antibodies in intestinal immunity from early life, based on their own substantial contributions to the field and a spate of new results heralding recent important advances by others.[3–10]

The function of antibodies in containing host–microbial interactions has classically been studied in the context of pathogens. The capacity of antibodies to opsonize, to provide Fc-dependent signals to engage cellular immunity, or directly neutralize by obstructing cytopathic invasiveness, were clear measures for the pivotal role of humoral immunity in infection. There are numerous studies providing excellent in vivo functional assays that combine passive immunization with in vivo experimental pathogen exposure that establish antibody-dependent boundaries for pathogenicity or promotion of pathogen clearance.

However, without the advantage of the dramatic alterations in the host that accompany pathogen challenge, the role of humoral immunity in symbiotic and nonpathogenic situations, such as the mutual host relationship to the microbiota with its exquisite dependence on hygiene status and environmental conditions, are much more difficult to address. Both sides possess dynamic flexibility and may constantly adapt to challenges that are posed by the opposite side—likely not solely dependent on humoral intestinal immunity.[11]

First, Pabst and Slack provide helpful clarity with explicit definitions for "natural" antibodies and provide experimental criteria for the general term "cross-species reactivity" to describe the phenomenon of a single monoclonal antibody binding to more than one microbial species. This term encompasses cross-specific, cross-reactive, and natural polyreactive antibody binding: terms that have been used with overlap by different laboratories.[12,13] We strongly support adopting these definitions and terms to bring uniformity to the field.

Secondly, it has become clear that luminal and serum antibodies can coat members of the microbiota. This may occur by different binding modes, either specifically, through cross-species reactivity or by binding to bacterial superantigens.[14] Pabst and Slack carefully point out that all these binding modes can be possibly carried out Fab-dependent or Fc-dependent and involve protein–protein, protein–glycan, and glycan–glycan interactions—with glycan interactions being important but understudied in the field. Furthermore, only few microbial antigens targeted by antibodies are known, and Sterlin et al. point the reader toward interesting additional isotype-differences that can be observed in fractions of anti-commensal Ig. Seminal reports by Peterson et al. deal directly with antigen specificity but show the problems involved in generalization: of two monoclonal antibodies targeting different glycans of *B. thetaiotaomicron*, one modulates bacterial target expression (and limits mucosal innate immune activation), whereas the other is without such an effect.[15,16] Even antibodies that target the same antigen, but different epitopes, can show tremendous differences in effector function, as exemplified in antiviral and antiparasite antibody responses.[17,18]

Overall, the binding diversity on the one hand and high interindividual species diversity within the microbiota on the other, make it challenging for everyone in the field to design single conclusive experiments when working at polyclonal level with a complex microbiota. Large panels of well-defined monoclonal antibodies and microbial diversity reduction by using moderately complex defined floras or mono-associated animals can overcome these challenges, but they need to be more scalable to obtain comprehensive insights into the multidimensionality of host microbial mutualism.

Despite excellent models such as oral immunization in B-cell receptor transgenic animals to study IgA induction and fate decision, we completely agree with the authors that an important unmet need for progress is well-defined in vivo functional models.[19] The field is being transformed by the energy and scholarship of very talented scientists across the world. All learning is an approximation to the truth and there are inevitably some controversies. Good consistent functional models for mutualists, that can be used by different laboratories, will be far more demanding to develop than those for the study of pathogens. The overall challenge is to understand the function of Ig targeting mutualistic microbes with respect to diet and metabolism, colonization resistance, microbial community robustness, autoimmunity, and cancer.

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ADDITIONAL INFORMATION

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