Commentary

Simple polysaccharides and global responses in the era of vaccinomics

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In an original, truly intriguing and, for several aspects, also surprising paper, Cywes-Bentley and colleagues,¹ report that a polysaccharide compound consisting in the polymer β -1-6, poly-N-acetylglucosamine (PNAG) or closed derivative of it is present in a large number of pathogenic bacteria as well as in some medically relevant fungal and protozoal organisms such as *Candida albicans*, *Trichomonas vaginalis* and *Plasmodium falciparum*, hence constituting what could be defined as a truly panmicrobial antigen. More important, these authors also report that polyclonal sera raised by immunization with a de-acetylated form of this antigen (suitably conjugated with a classic protein carrier such as tetanus toxoid) or a mAb specific to PNAG are protective against experimental infections caused by PNAG-expressing pathogens. Protection is attributed to the capacity of the antibodies for opsonic killing through complement fixation.

Besides the obvious implications for a sort of a passive universal vaccination, the authors also prospect the idea of generating a vaccine for active immunization against the above pathogens. It should be remarked that some in vivo data should be considered as provisional or preliminary to more extensive investigations with more appropriate animal models (see, for instance, the case of *C. albicans*). In addition, the probability that a tool like the above one could be by itself the only component for an effective active or passive immunization against eukaryotic pathogens endowed with high capacity for immunoescape like the plasmodial organisms is low. This being said, the data presented in this paper point out the construction of one or more immunological tools potentially conferring the broadest spectrum of antimicrobial protection that has ever been generated by, and indeed could be expected of, a univalent immunological tool. At the same time, this report raises several issues about biological

consequences of a vaccination eliciting such kind of global responses, particularly concerning the potential consequences of antibody selective pressure in vivo, as well as the homeostasis and functions of human microbiota.

As presented in this and previously published papers by these authors,^{2,3} it would appear that PNAG and closely related molecules are very widespread in the microbial world. There is a suggestion they contribute to resistance to stress and biofilm formation. However, it is unclear if they are indispensable for virulence and growth in vivo: from the published data, I would assume it is not. If pathogens may equally grow efficiently in vivo and express their virulence by other non-PNAG accompanying factors, it is expected that selective pressure induced by vaccination or prolonged antibody usage in immunotherapy can select for microbe variants with no or low PNAG expression, yet possibly equally virulent and aggressive, and obviously escaping anti-PNAG antibodies. In this context, PNAG-based vaccines could be rather construed as components of multivalent conjugates, which can include microbe-specific, non-redundant virulence or growth-affecting antigens.

As discussed elsewhere, mostly in the context of universal vaccines against influenza and opportunistic fungal pathogens,⁴ the identification of highly conserved antigens capable to induce broad spectrum functional immune responses, particularly neutralizing and growth-inhibitory antibodies, has become important to address protection by universal vaccines. Since PNAG is a common constituent of microorganisms which stably colonize humans or to which humans are frequently exposed, it is of no surprise that anti-PNAG antibodies are naturally present in humans. Why don't these antibodies eliminate the target bacterial or fungal strains by their opsonizing capacity and killing? The authors explain this failure by the lack of sufficient complement-fixing power of natural antibodies as compared to those generated by vaccination. It appears that antibodies to an antigen expressed during colonization are much less effective functionally than those raised by immunization with the same or cross-reactive antigen. This is logical as these natural antibodies need to spare our microbial commensals. Interestingly, some of the microorganisms among those investigated by Cywes-Bentley and collaborators have quite efficacious ways to escape from complement activity.⁵

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As for all other polysaccharide universal vaccines,⁶ the capacity of the protective antibodies raised by immunization to affect composition and function of the microbiota, particularly the intestinal one, is a major issue that warrants consideration. The larger is the spectrum of affected microorganisms, the higher is the potential of disruptive changes antibodies or activated cellular effectors can inflict to human indigenous flora. These remarkably important aspects are finely discussed, with added experimental documentation, in a supportive text to the main paper. My opinion is that concerns have very low, if any, biological relevance for passive vaccination and limited (in number and dose) serum or mAbs treatments. However, they should be seriously considered in the case of active immunization with the vaccine that is obviously expected to provide persistently high levels of antibodies in order to protect against a disparate set of different pathogens. At least for some components of this bacterial flora, a damage is possible, and must be addressed in clinical trials, as anticipated by the authors.

Polysaccharide-based vaccines constitute a landmark of the present-day vaccines designed to protect

against various encapsulated bacteria. However they suffer from their exquisite antigen specificity, in the face of the numerous serotypes and antigenic variants expressed by these bacteria, particularly the pneumococci. It is quite remarkable that a sort of 'second-generation' glycoconjugate vaccines based on 'universal' polysaccharides (glucan, for instance, for panfungal vaccines) might reverse those limitations and be useful to address 'universal' protection. In this perspective, the work made by Cywes-Bentley and collaborators leading to identification and use of PNAG to generate protective pan-microbial antibodies is groundbreaking, potentially redirecting our ideas on how to fight a multitude of human aggressive pathogens by unique, new tools.

References

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