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Translating Antibody Insights

VIRUSES THAT DEFEY HOST IMMUNE RESPONSES AND PERSIST OR RECUR TAKE A HUGE TOLL ON GLOBAL human health. Many of these, including HIV-1, influenza viruses, and several flaviviruses (such as dengue, hepatitis C, and West Nile virus) rapidly proliferate, frequently mutate, and evolve highly variable surface structures. The effectiveness of such immune escape mechanisms has thwarted multiple attempts to create long-lasting and broadly protective vaccines.

Nevertheless, these pathogens are not invulnerable. Key surface regions of the virus are constrained by requirements for precise interactions with the host cell that allow viral entry. These domains can contain antigenic determinants (epitopes) that elicit broadly neutralizing antibodies (bNAbs) from immune cells (B cells) in the infected host, even to highly variable viruses. Characterization of these bNAbs is accelerating because of improved approximations of the three-dimensional structure of antibody-binding sites on the virus surface, new tools for efficient detection of specific bNAbs from immune cells, and longitudinal studies of the evolution of antibody production by B cells during the immune response (B cell affinity maturation).

The ultimate goal is to identify antigens for “universal” vaccines that provoke long-lasting memory B cells that neutralize all relevant virus variants and provide protection from infection. Unfortunately, this is easier said than done. A major challenge is delineating the nature of the epitopes of interest. The important viral epitopes recognized by bNAbs to HIV-1 and influenza tend to be nonlinear, sequestered from the reach of most antibodies, a minor component of the total antibody response, and represent only a small portion of the conserved virus structures. Thus, it has been difficult to convert these epitopes into stable vaccine antigens that elicit the intended protective antibodies. In addition, mutations in these epitopes that escape recognition by bNAbs may eventually appear. Furthermore, bNAbs

usually develop later in chronic infections and often have complex atypical configurations in their variable regions. Strategies to induce and shape the B cell response to produce such unusual antibodies have not yet been developed. Another concern is that broad neutralization defined by studies in cultured cells may not translate into broad protection from infection in humans. Inducing cells to produce enough bNAbs to confer protection against primary infection may be essential. For at least some of the flaviviruses, epitope binding can result in either neutralization or more severe pathology, perhaps depending on the absolute number of occupied binding sites, creating a challenge to vaccine safety.

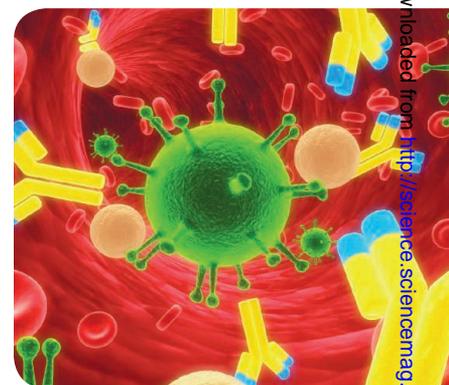
Experimental studies to explore treatments involving the injection of well-characterized bNAbs and that evaluate new vaccination strategies to elicit bNAbs for preventing infection can now build on the emerging science of bNAbs. Several animal studies indicate that infusions of a single bNAb, or combinations of such antibodies, can prevent or control certain viral infections. New technologies to expeditiously isolate specific human antibodies and manufacture them in large quantities have evolved to the point where passive immunization to prevent or treat infection is scalable and is a potentially effective approach to previously refractory infectious diseases or emergent outbreaks. Palivizumab, a licensed antibody product for preventing respiratory syncytial virus infection in high-risk infants, is proof of this concept. For now, the most exciting value of bNAbs may be their utility as probes into the complex host-pathogen interactions that underlie chronic and recurrent viral infections. High-resolution studies of how to shape the evolution of B cell response to elicit bNAbs after vaccination or natural infection will improve the rational design of future vaccine strategies. Ultimately, these efforts will contribute to the prevention and control of some of the most serious and intractable global infectious diseases.

– Julie Louise Gerberding

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