# Old foes and new enemies

Better understanding of the biology of infectious agents and of the mechanisms of efficient immune responses advances strategies to achieve protection against infectious diseases.

Infectious diseases caused by old foes, such as tuberculosis and malaria, or those caused by emerging pathogens, such as Ebola, Zika and HIV, impose a high health and socioeconomic burden on endemic regions and a tangible threat of pandemics in today's interconnected world. Despite great efforts in basic and clinical research, vaccination or therapy approaches against some of these pathogens are lacking, inefficient or incomplete, and biomarkers of progression or protection from disease are needed. In this issue of *Nature Immunology*, five specially commissioned Reviews and Perspectives (https://www.nature.com/collections/infectious-diseases/) discuss the biology of these infectious agents, the characteristics of the immune response and the current strategies to achieve protection.

Approximately one in four people worldwide has been infected by *Mycobacterium tuberculosis*. Although most infected people generate an effective immune response that eliminates or controls the infection and thus remain asymptomatic, a small proportion develop active tuberculosis at some stage during their lifetime. Progression from latent infection to active disease can be clinically subtle, and the events that determine whether an exposed person will control the infection or develop disease are unknown. In a Perspective, O'Garra and colleagues describe how blood transcriptomics can provide information on the temporal changes in host immunity associated with an evolving infection and on how transcriptomics can be used for diagnosis and identification of asymptomatic people at risk of developing disease. Genes encoding molecules involved in type I and II interferon signaling and in the complement cascade produce a transcriptional signature that can be observed up to 18 months before diagnosis in people who ultimately develop microbiologically confirmed disease. As noted by the authors, transcriptomic approaches also show promise for the development of biomarkers for monitoring drug-treatment efficacy.

Saphire and colleagues discuss another modern approach to treat infectious diseases. The remarkable specificity, low toxicity and rapid discovery process of immunotherapies make them particularly attractive for treating emerging infectious diseases. Starting from observations made in a comprehensive study of a large number of antibodies to Ebola virus, the Perspective discusses the therapeutic potential of antibodies that confer protection through Fc-mediated effector mechanisms. In contrast to initial assumptions, NK cell activity and total antibody binding have been found to be strong correlates of protection, along with neutralization ability. Capitalizing on Fc-mediated protection is challenging, because Fc-receptor-mediated mechanisms vary among species, are difficult to estimate in vitro and may not readily translate in vivo. However, this type of functional activity can be maximized by engineering of the glycan modifications and FcR affinity of antibodies. Attachment of an engineered Fc to a potently neutralizing Fab may further improve the in vivo performance for immunotherapy.

No antibody responses have been as extensively studied as those to HIV. In their Review, Sok and Burton present an overview of the newest broadly neutralizing antibodies (antibodies able to neutralize diverse isolates of HIV) in terms of targeted epitopes, neutralization potential and attractiveness for vaccine design. The authors also discuss how the generation of chimeric simian–human immunodeficiency viruses (SHIVs) from HIV envelope sequences of different clades is beginning to recapitulate the diversity of global HIV isolates in controlled in vivo models. These improved models can be used to test new antibody structures, such as trispecific antibodies, or various challenge scenarios, such as the transmission of cell-free versus cell-associated viruses. The authors note that the field critically needs data on what concentration of neutralizing antibodies is needed to afford protection against HIV in humans in vivo. Two phase IIb multinational clinical trials launched by the US National Institute of Allergy and Infectious Diseases should provide this information for the first time and aid in vaccine design, prophylaxis and therapy.

Two Review articles discuss the immunological mechanisms of protection against major human pathogens transmitted by ticks and mosquitos: flaviviruses and malaria parasites. In their Review, Screaton and colleagues note that although the antiviral immune response is crucial for the control, clearance and prevention of infection with dengue and Zika viruses, it is commonly associated with immunopathology. In addition, the high degree of homology among flaviviruses can cause the responses to a particular virus to be dominated by mobilized low-avidity memory clones generated during a previous exposure to a different flavivirus. This so-called 'original antigenic sin' and the generation of cross-reactive antibodies may aggravate symptoms in people previously exposed to another flavivirus—such as in the recent Zika virus outbreak in areas with high dengue virus exposure—and has consequences for vaccine design.

Cockburn and Seder posit that vaccine design for malaria is more complex than that for most viral and bacterial infections, owing to the multiple stages of infection by the plasmodium parasites. The current focus is on sporozoite vaccines, which should induce protection at the preerythrocytic, asymptomatic liver stage, to either prevent or decrease the symptomatic erythrocyte stage. Major hurdles for inducing protective immunity are the lack of immunological correlates of protection easily detectable in the blood after immunization, enhancement of the antigenic breadth of sporozoite vaccines to achieve protection in conditions of prior and ongoing exposure to heterogeneous malaria parasites, and suboptimal and impaired B cell responses to malaria. Owing to these limitations, none of the current protection strategies mediate durable immunity.

These articles provide insight into the constant struggle to understand antibody- and cell-mediated immunity to these pathogens and to define the thresholds that translate into durable protection. Although the challenges posed by complex pathogens such as HIV, *M. tuberculosis*, *Plasmodium* or dengue and Ebola viruses are daunting, the successes and failures thus far provide important scientific and clinical insights and will drive future vaccine design and treatment strategies. ❐

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