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Editorial overview: Viral immunology
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Opening remarks
Our immune system has evolved to protect us from the barrage of infections that we encounter throughout our lives. The articles in this section highlight the complexities and co-ordination of anti-viral immune responses, how they are tempered by the need to limit immunopathogenesis, and the impact of the breadth and cross-reactivity of the response on the efficacy of infection control and the durability of immunity. The immunological success story begins with innate defense mechanisms which sense the very first signs of an infection. This detection triggers further activation and launches adaptive cellular and humoral immunity. The responses can be overwhelming and capable of completely eradicating the viral pathogen. Ideally, as a consequence of this original infection we develop immunological memory and are now even better guarded against subsequent exposures. Anti-viral immune responses can also exhibit a degree of cross-reactivity. These expanded powers can confer a level of protection against both related viral variants as well as other unrelated pathogens. Understanding these immunological victories gives us a better appreciation of how these responses fail. Not all viruses elicit protective immunity leaving us vulnerable to further rounds of infection, and viral persistence can become established despite ongoing immune activation. Why is an immune response so powerful sometimes so inept at clearing the infection? Viruses have evolved mechanisms to circumvent, delay and subvert the host’s response. Thus, détente between the pathogen and the immune system may result, permitting a restrained infection while muting collateral damage. Shifting this balance may improve the control of the infection, but the price to pay may be more harmful to the host.

The contributions to this section outline the triumphs, limitations, and challenges of anti-viral immunity, and discuss potential strategies for harnessing these responses to improve viral control and human health.

Calibrating and re-calibrating the response
The first line of defense against viral infections is the induction of type I interferon (IFN-I). Inciting this response mobilizes other innate effector mechanisms and facilitates the development of adaptive anti-viral immune responses. Vijay and Perlman discuss how the tempo of this very early IFN-I response influences the virological, immunological, and clinical outcomes of infection with the coronaviruses that cause Severe Acute Respiratory Syndrome and Middle Eastern Respiratory Syndrome. These recently emerged infections use multiple strategies to delay and evade the IFN-I response, which hinders clearance of the virus, impairs cellular and humoral immunity, as well as ultimately contributes to dysregulated cytokine synthesis and pathogenesis. The success of anti-viral immunity centers on the ability to control the infection while limiting pathogenesis. Although the
Noroviruses are a significant cause of gastrointestinal disease and can establish persistent infections. Roth and Karst highlight the failure of norovirus infections to elicit lasting protective immunity and discuss emerging information regarding viral immune-modulatory mechanisms that potentially impede the induction of immune responses by obstructing the expression of anti-viral cytokines and chemokines and limiting antigen presentation.

Infections of the very young are especially challenging due to the physical and immunological immaturity of the infant. Ruckwardt et al. review how one of the first viral pathogens that may be encountered, respiratory syncytial virus (RSV), provokes distinct responses that may develop due to the immunological bias to establish tolerance during the earliest stages of life. They also discuss possible vaccination approaches to directly or indirectly protect the vulnerable infant population from RSV.

During chronic viral infections anti-viral T cells may succumb to exhaustion and display reduced portfolios of effector functions. While this dampening of the response compromises the ability to fully eradicate the infection it also limits immunopathogenesis. Zehn and colleagues explore the ongoing immunosurveillance functions of anti-viral T cells during persistent infections and their ability to keep chronic infections in check. They also discuss methods for augmenting these responses and how they may be impacted by the diversity of the virus-specific T cell population. In addition to their roles in containing chronic viral infections T cell responses also limit the reactivation of latent infections. In order to accomplish this it is critical that the anti-viral T cells are available locally at the sites of infection. Thom and Oxenius discuss the establishment of tissue resident CD4 and CD8 T cells during cytomegalovirus infections and overview how these non-recirculating subsets become deposited at the sites of viral persistence and operate to provide immediate immunological protection. They also outline potential vaccination strategies for generating tissue resident T cells to ensure that they are available at mucosal barriers to very rapidly combat the infectious first encounter.

The power and perils of cross-reactivity

Pre-existing infections and cross-reactive immunity can influence both the clinical outcome of current infections as well as the susceptibility to new unrelated infections. Cornberg and Wedemeyer discuss the potential mechanisms and benefits of cross-reactive immunity in the context of hepatitis C virus (HCV) infections. They discuss how existing responses may alter the pathogenesis of HCV infection and highlight the roles of cross-reactive HCV-specific T cells in conferring heterologous immunity to other infections as well as in safeguarding against superinfection with HCV.

Whereas Cornberg and colleagues focus on the benefits of cross-reactive immune responses Massilamany et al. focus on the association between picornavirus infections and the induction of damaging autoimmune responses. A deleterious outcome of several picornavirus infections can be the induction of autoimmune diseases such as diabetes, myocarditis, or neuroinflammatory diseases. The underlying processes which influence whether these pathological conditions develop following these often asymptomatic or mild infections are still being unraveled.

Massilamany and colleagues overview our current understanding of how the release of autoantigens from infected target cells, dysregulated cytokine production, the induction of cross-reactive T cell responses, and stimulation of T cells which express dual T cell receptors contribute the induction of pathogenic self-reactive cellular immune responses.

Although the off-target actions of the anti-viral immune response may be detrimental, as can be the case following picornavirus infections, cellular immune responses with expanded recognition capabilities may benefit the host by offering broader and more flexible immunological surveillance. The sustained immune-mediated containment of highly variable persistent viral infections such as HIV requires that the cellular immune response keeps pace with viral variation, resulting in bidirectional adaptation between the virus and the host’s T cell response. Appay and colleagues describe the links between the clonotypic composition of the anti-viral T cell pool, antigen-sensitivity and the ability of cross-reactive T cells to detect viral escape mutants. They also discuss how these factors influence the ability to maintain viral control.
The importance of cross-reactive CD8 T cells is further highlighted by Kedzierska and colleagues as they discuss T cell based strategies to combat influenza A virus (IAV). Notably, CD8 T cells can control IAV independently of neutralizing antibody responses and their cross-reactivity can confer heterosubtypic immunity. Immunization strategies designed to exploit these broadly reactive capabilities may lead to universal protection against IAV, alleviating the necessity for annual strain-specific vaccines. This article also overviews the utility of a T cell based vaccination approach for protecting highly susceptible populations such as the elderly.

Closing comments
Common themes emphasized in these articles include the balancing of the anti-viral immune response and how this can both restrict the infection as well as limit immune-mediated damage, and also how the breadth of the reaction to an original infection can shape the ability to recognize and respond to viral variants and heterologous infections. These aspects reflect our current appreciation of the tremendous diversity and complexity of anti-viral immunity. Nevertheless, it is clear that our knowledge of these processes remains limited and we need to continue advancing our understanding of why disparate responses develop and how they are exploited and directed by viral pathogens.

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