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Current Opinion in Virology

Editorial overview: Viral immunology: Generating immunity to diverse viral pathogens

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Current Opinion in Virology 2018, **28**:viii–x

For a complete overview see the Issue

http://dx.doi.org/10.1016/j.coviro.2018.02.003

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Acclaimed biologist E.O. Wilson once posited that " . . . the variety of genes on the planet in viruses exceeds, or is likely to exceed, that in all of the rest of life combined [1]." Indeed, the remarkable diversity of viruses poses a tremendous challenge for the immune system. Luckily for jawed vertebrates, the immune system has evolved into two major branches: the innate immune system — which utilizes germline-encoded pattern recognition receptors (PRRs) to rapidly trigger a cell autonomous antiviral response; and the adaptive immune system — which is characterized by a cell-mediated and humoral response that can clear viral infection and provide protection against re-infection. In particular, the RIG-I like receptors (RLRs) and Toll-like receptors (TLRs) recognize specific pathogen-associated molecular patterns (PAMPs) and rapidly trigger a potent antiviral response characterized by the production of type I interferon (IFN), pro-inflammatory cytokines and expression of hundreds of IFN-stimulated genes (ISGs). Within antigen-presenting cells (e.g. dendritic cells) these processes are essential for priming T cell responses, which ultimately function to clear viral infections and provide protection against re-infection. Understanding the virus–host interactions that regulate T and B cell responses is critical for combating emerging/re-emerging viruses.

This issue of Current Opinion in Virology features eight outstanding reviews summarizing new and exciting areas of research covering innate and adaptive immune responses to RNA and DNA virus infection. Reflecting the breadth of the topics under the 'viral immunology' umbrella, the authors take disparate approaches to cover this multifaceted topic. Four of the reviews highlight contemporary findings related to the immune mechanisms of protection against emerging/re-emerging viruses (Chikungunya virus (CHIKV), Ebola virus (EBOV), Influenza A virus (IAV), and Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) coronavirus (CoV)) and the ubiquitous pathogen cytomegalovirus (CMV). Another set of reviews focus on tissue-specific immunity, including the generation of protective immunity within the skin and central nervous system as well as the differentiation and generation of tissue-resident memory T cells during virus infection. The final set of reviews highlight two nascent areas of intense interest in viral immunology — imaging of antiviral immune responses and the impact of host metabolism on immunity during virus infection.

Alphaviruses are mosquito-borne pathogens that are found throughout the world and cause diseases ranging from polyarthralgia to fatal encephalitis in humans. Carpentier and Morrison highlight the critical role of RLR and TLRs in triggering type I IFN-mediated antiviral responses to alphavirus infection. In addition to IFNs, recent studies have also implicated

inflammasome signaling, which promotes the production of IL-1β, IL-18 and IL-33, in contributing to the increased severity of CHIKV-induced disease. Further, IL-1β has recently been identified as a biomarker for severe CHIKV disease in patients. Lastly, the authors highlight a role for C-type lectin receptors, which include DC-SIGN and L-SIGN, as alphavirus attachment receptors and their potential role in regulating inflammation during alphavirus infection.

Ebola virus (EBOV) is a pathogen of significant global health concern due to the high mortality rate in humans and the lack of antivirals or vaccines to block virus infection. EBOV causes an acute infection that can often lead to multi-system organ failure and hemorrhagic fever disease in humans. McElroy, Mühlberger and Muñoz-Fontela provide a detailed summary of the molecular and immunological mechanisms that regulate immunity to EBOV infection. EBOV potently blocks type I IFN signaling, which likely contributes to rapid virus replication and spread within the host. Due to the lack of a small animal model that faithfully recapitulates EBOV pathogenesis, the consequence of inhibiting PRR signaling on B and T cell responses are not well understood. Limited studies in non-human primates, mice and EBOV-infected patients have identified a potential role for antibodies in mediating protection against EBOV infection. As such, current vaccine efforts are focused on generating EBOV glycoprotein (GP)-specific antibody responses. As highlighted by these authors, there are currently no known immunological correlates of protection against EBOV, which will be critical for determining the overall vaccine efficacy against EBOV.

As with nearly all pathogenic viruses, there is an ongoing battle between the ability of the host to promote an antiviral immune response and the ability of a virus to block these responses. IAV and SARS/MERS-CoV are respiratory viruses with significant pandemic potential that continue to be major public health concerns throughout the world. Zheng and Perlman highlight recent research efforts to define the correlates of immune protection as well as understand the virus–host interactions that regulating immunity and infection outcome to these respiratory viruses. In general, the innate immune response, including PRRs, type I IFN, and ISGs, and the adaptive immune response, including humoral and cell-mediated immunity, are critical for thwarting IAV and SARS/MERS-CoV replication, tissue and cell-tropism and mediating viral clearance. These viruses also encode several immune evasion proteins, which can prevent PRR activation, block induction of type I IFN and impair DC responses. This can lead to the development of potentially pathogenic immune responses and ultimately more severe respiratory disease outcomes. Thus, these virus–host interactions are currently being explored as targets for development of novel antiviral therapeutics. Moreover, current vaccine efforts against IAV and SARS/MERS-CoV are focused on developing neutralizing antibodies, but also attempting to drive lung-resident memory T cell responses.

Many recent surprises in viral immunity in general have stemmed from the study of CMV. CMV is transmitted from mother to offspring (resulting in lifelong persistence in spite of a robust humoral and cell-mediated immune response), and is a leading cause of congenital birth defects. Hill highlights recent progress using CMV as a vaccine vector as well as the unorthodox adaptive immune response to this virus. Taking advantage of the overwhelming anti-CMV response combined with the failure to prevent re-infection, CMV-vectored vaccines have been developed and can be administered sequentially, allowing the development of responses to multiple neo-antigens delivered separately. Intriguingly, the rhesus CMV-vectored vaccine against simian immunodeficiency virus (SIV) generates immunodominant $CD8^+$ T cells specific for SIV-peptides presented by two unusual sets of proteins: MHC class II molecules (rather than MHC class I) or the rhesus ortholog of HLA-E (a non-classical MHC class I molecule thought to present a limited repertoire of peptides). Adding even more complexity, CMV immunomodulatory proteins serve to promote or inhibit the production of these unconventional virus-specific $CD8^+$ T cells. These fascinating aspects of CMV immunity are currently being explored in the hopes of both developing a vaccine against this important virus and generating novel vaccine vectors taking advantage of CMV's unique immunobiology.

Historically, antiviral T cells have been studied primarily after infection of and removal from secondary lymphoid organs such that T cell behavior and attributes in peripheral tissues have been less well understood. Hobbs, Osborn and Nolz review $CD8^+$ T cell activation and tissue migration after epicutaneous infection with vaccinia virus (VACV), a large DNA virus that served as the effective smallpox vaccine after introduction and replication in human skin. After infecting mice in the skin via a similar route (mimicking human vaccination), $CD8^+$ T cells can be activated in the draining lymph node through direct priming (infection of the antigen presenting cells and presentation of endogenously derived viral peptides on the cell surface). Although activation through direct priming has been previously demonstrated during VACV infection, the contribution of cross-priming has been harder to separate and less defined. Regardless of the mechanism of priming, activated, VACV-specific $CD8^+$ T cells traffic to the skin using a number of cell-surface ligands, and after infection, a subset of these cells transition into tissue resident memory cells. Importantly, VACV infection also induces circulating $CD8^+$ memory T cells, which traffic into the skin using core 2 O-glycans that bind to P-selectin and E-selectin. Both tissue

resident and circulating memory provide protection from subsequent VACV infection.

Tissue-resident memory (TRM) T cells are generated by a range of virus infections, can populate nearly all tissues (including the lung, skin, gut and genital tract) and may provide superior antiviral protection compared to circulating memory cells. Shin discusses factors mediating the formation of TRM cells in general, including the down-regulation of T-bet and Eomes and upregulation of Hobit, a transcription factor promoting tissue residency. A number of other environmental cues shape the formation of TRM, including key cytokines such as TGF-β and IFN-γ, though there are variations in requirements depending on the specific tissue and infection. Once TRM cells become re-activated by cognate antigen, they rapidly respond through the production of antiviral cytokines and can invoke a general anti-pathogen state in the tissue, thereby limiting the replication of both cognate and non-cognate viruses. Importantly, TRM cells afford protection to areas that are extremely sensitive to immunopathology, such as the lung or the central nervous system (CNS).

Manglani and McGavern extend the analysis of immunity to viral infection of the CNS, discussing the important contribution of innate cellular populations to eliminating infection while simultaneously limiting immunopathology, highlighting the important role of IFNs in driving the innate immune response and protection in the brain. While previously considered an isolated, immune-protected organ, recent studies have shown that the CNS is both immune competent and dynamic — constantly contacting the peripheral immune system through a newly discovered network of lymphatic drainage. As also detailed by Shin, memory $CD8^+$ T cells persist in brain after infection with vesicular stomatitis virus (VSV) or lymphocytic choriomeningitis virus (LCMV), and more studies, including intravital microscopy of the CNS, will uncover their precise behaviors and mechanisms of antiviral activity.

As the critical site for the initiation of adaptive immunity, the lymph node has been the subject of intense recent investigation, and in particular, the cellular composition of the node has been explored spatially during the developing immune response using advanced imaging techniques. De Giovanni and Iannacone detail recent advances in our understanding of antiviral immunity gained through the application of intravital microscopy (IVM), an imaging modality allowing visualization of immune effectors in real time in living animals. IVM imaging of the LCMV-infected lymph node revealed surprising B cell interactions with newly recruited inflammatory monocytes, leading to B cell apoptosis and diminished virus-specific antibody production. On the T cell side, several groups have recently demonstrated a crucial role for $XCR1^+$ dendritic cells in the generation of both antiviral $CD4^+$ and $CD8^+$ T cells against disparate viruses using IVM. Recent advances in molecular virology allowing the genetic manipulation of medically relevant viruses should allow the dissection of the spatial distribution and kinetics of viral replication in the tissue, expanding IVM analyses into the realm of viral pathogenesis.

Varanasi and Rouse conclude this special focus on viral immunology with a discussion of how host metabolism impacts the outcome of viral infection. While much excitement and effort has recently been focused on better understanding the metabolic requirements needed for the development of the cellular immune response in general, studies aimed at uncovering the role of nutrition and metabolism in both viral replication and pathogenesis have been lacking. Protein starvation, glucose deprivation, and inhibition of fatty acid uptake in the host all cause increased mortality or susceptibility to IAV infection. The authors speculate that host-directed therapies manipulating metabolism could serve as a broad new class of antiviral therapy that merits further examination.

Collectively, these works highlight the remarkable diversity in human viral pathogens as well as in the immune responses against them. With more years of life currently lost due to infection than any other disease process [2], there is a critical need to understand the unique and common features of antiviral immunity to each virus (or viral family) in order to respond to emerging viral threats as quickly and precisely as possible.

Acknowledgments

Heather Hickman is supported by the Division of Intramural Research, NIAID, NIH. Mehul Suthar is supported by National Institutes of Health Grants U19AI083019, R21AI113485, U01AI131566, 2U19AI100625, 5U19AI09965, 5U19AI109965, P51OD011132, Junior Faculty Focused Award, Children's Healthcare of Atlanta, Emory Vaccine Center, and The Georgia Research Alliance.

References

1. Wilson EO: *My Wish: Build the Encylopedia of Life*. TED Talks; 2007.

2. World Health Organization: *The Global Burden of Disease 2004. Part 4: Burden of Disease: DALYs*. 2004.