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Editorial overview: 2022 "Virus–Host Interaction" section of *Current Opinion in Virology*

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Viruses are equipped with effective strategies to turn infected host cells into factories of virus production. To achieve this, viruses interact with a myriad of mammalian host-cell components, including several host proteins or enzymes, as well as lipid components and cellular RNA or DNA. These virus–host interactions serve two principal purposes: they help to 1) directly facilitate specific steps of the virus lifecycle, including viral entry, intracellular trafficking, genome replication, gene expression, and viral egress; or 2) antagonize or evade cell-intrinsic or innate immune defenses such as type-I interferon (IFN)-mediated antiviral responses or cell death pathways. As many viruses, including coronaviruses, flaviviruses, and influenza viruses can infect several different species (i.e. insects, birds, and a variety of mammals), it is not surprising that these pathogens have evolved unique virus–host interactions in each host species. On the flip side, differences in antiviral host responses and species-specific roles of antiviral restriction factors determine disease outcome in the respective host.

The articles of this year's "Virus–Host Interaction" section of *Current Opinion in Virology* summarize and discuss recent advances on viral interactions with host factors that play a pivotal role in innate immune surveillance and IFN-stimulated gene (ISG) responses, cell death pathways, intracellular organelle organization, and epigenetic gene regulation. Whereas the primary focus of this section is on viral interactions with human factors, several details about virus–host interactions in other animal species are also being discussed. Finally, novel methodologies are being highlighted that allow for identifying novel virus–host interactions and for elucidating their impact on viral replication and pathogenesis.

Madden and Diamond [1] highlight the mechanisms by which sensors of the innate immune system — RIG-I-like receptors, toll-like receptors, NOD-like receptors, and cGAS — detect the recently emerged severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by recognizing nucleic acid or protein components. They also discuss the strategies that SARS-CoV-2 has evolved to dysregulate or evade innate immune signaling in order to suppress early IFN responses.

Z-DNA-binding protein 1 (ZBP1) is another nucleic acid sensor that mediates host defense against a variety of viruses by inducing necroptosis and inflammatory responses. Balachandran and Mocarski [2] highlight recent findings that elucidated the role of ZBP1 in orthomyxovirus and

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poxvirus (i.e. vaccinia virus) infection, as well as the mechanisms of Z-RNA ligand sensing in the nucleus or cytoplasm. Further, they discuss in detail how Z-RNA is formed in infected cells and whether perhaps modifications of Z-RNA or cofactors specific to viruses may impact Z-RNA formation during infection.

Studies on IFN-dependent and ISG-dependent antiviral immune defense mechanisms have traditionally focused on their roles in humans or animal model species, however, many of the ISG products are expressed in a variety of animal species, some of which are important reservoirs for zoonotic viruses. Schoggins and co-authors [3] summarize and discuss evolutionary aspects of the antiviral IFN response and the species-specific roles that ISGs (e.g. TRIM5α, IFIT1, and Mx 1 and 2) can have, which may play an important role in determining species-specific antiviral phenotypes.

Major zoonotic viral pathogens that cause millions of infections in humans every year are the flaviviruses such as dengue, West Nile, and Zika viruses. Schneider and Hoffmann [4] provide an overview of innovative low-biased methods that allow for the identification of novel flaviviral interactions with human components (protein–RNA, protein–protein, or genetic interactions). They also highlight recent work on the ER-resident host protein, TMEM41B, which is an important proviral factor for diverse flaviviruses and also coronaviruses.

A major human oncogenic virus is Kaposi's sarcoma-associated herpesvirus (KSHV), which displays a characteristic lifecycle of active lytic replication and latent infection where only a subset set of viral genes is expressed. Sandhu and Damania [5] summarize the host-cell factors and processes (e.g. innate immune signaling, RNA decay pathways, and DNA damage response) that regulate the latent-to-lytic switch of the KSHV lifecycle.

Guo and Gewurz [6] provide an overview of our current understanding of epigenetic control of the γ-herpesvirus Epstein–Barr virus (EBV) gene expression during the lytic and latent phase of infection. In particular, they highlight recent developments on the roles that higher order DNA structures, DNA methylation, histone chaperones, nonsense-mediated RNA decay, and m6A modifications play in EBV gene regulation and latency maintenance.

Cristea and co-authors [7] summarize the interactions of human cytomegalovirus (HCMV) with human host-cell factors that facilitate different steps in the HCMV lifecycle, in particular viral entry and gene expression, genome replication, virion assembly, and viral modulation of innate immune responses and metabolic pathways. Moreover, they discuss cutting-edge techniques such as novel proteomics approaches and thermal-proximity coaggregation profiling that will be instrumental in identifying new virus–host interactions and in investigating the virus' ability to modulate cellular events.

Dharan and Campbell [8] provide an overview of recent findings on spatiotemporal staging of HIV-1 nuclear entry, some of which challenged textbook understanding of the post-entry steps in the HIV-1 lifecycle. Different models for nuclear import and core disassembly are being discussed, as well as novel technical approaches (e.g. super-resolution imaging and inducible nuclear pore complex blockade assay) are highlighted that enabled to study these intricate processes in greater detail than before.

Investigating virus–host interactions that may limit the emergence of viruses from endemic reservoirs into humans is essential for preventing future pandemics. Peiris and Perlman [9] review the biology and epidemiology of Middle East respiratory syndrome coronavirus, notably the lack of correlation between areas of endemic camel infection and human zoonotic disease. Understanding this disparity may lead to measures to better control coronaviruses with pandemic potential.

Balakrishna Pillai and co-authors [10] review aspects of flavivirus interactions with platelets, and describe how these interactions may lead to platelet activation, thrombocytopenia, and vascular endothelial leakage. They describe the potential use of platelet-derived factors as biomarkers that may predict disease outcome after dengue virus infection.

Hepatitis-C virus (HCV) has evolved multiple mechanisms to disrupt host innate immune signaling pathways and to usurp cellular factors that facilitate virus replication. Lee and Ou [11] review how HCV manipulates mitochondrial dynamics, host autophagic response and metabolism, and disruption of IFN signaling pathways to allow for successful replication and persistence in the host.

The cGAS-STING signaling pathway is critical for responding to DNA virus infection. Webb and Fernandez-Sesma [12] provide an overview of how viruses interact with the cGAS-STING sensor system and review recent data highlighting how RNA viruses may activate this host surveillance pathway. Elucidating how viruses interact with the cGAS-STING pathway broadens our understanding of host restriction of virus infection and the mechanisms viruses use to antagonize this pathway.

Kirchhoff and co-authors [13] review evidence of how innate immunity factors may exert either pro- or antiviral effects, depending on the specific viral pathogen and on the level of expression of the host factor in the cell. They describe how host factors such as IFITMs, LY6E, Tetherin, APOBEC3, and MARCH8 can have opposing roles during virus infection and that assessment of each specific virus infection is essential for elucidating virus–host interactions.

The review by Hale [14] describes how RNA-Seq and bioinformatics analyses revealed that virus infections can reactivate transcription of transposable elements (TEs) that may activate inflammatory responses that contribute to viral pathogenesis. This review describes how viruses can both induce and counteract TE-based antiviral immunity.

The close interaction between influenza virus and host proteins suggests that host-directed molecular targets may provide an opportunity for new therapeutics. Trimarco and Heaton [15] review host factors identified by knockout/knockdown or overexpression screens, and describe how targeting of these host factors using RNA delivery vectors and transient CRISPR-mediated gene editing may provide novel mechanisms for countermeasures to block influenza virus and other viral infections.

Bats serve as the natural reservoir for many viruses, including Hendra and Nipah viruses that are highly pathogenic in humans. Why are not these viruses pathogenic in bats? Horvat and co-authors [16] review recent studies suggesting that bats have evolved systems that promote equilibrium between virus replication and antiviral defenses that allows viruses to propagate without triggering an excessive inflammatory response. Understanding the mechanisms used by bats to control these infections may provide new therapeutic approaches for treating these infections in humans.

In summary, the reviews compiled in this section of *Current Opinion in Virology* highlight the rapid recent progress made in understanding how viruses target or block specific host factors or commandeer fundamental cellular processes, and how these interactions aid in virus replication and dissemination. The articles also summarized cutting-edge technologies that allow for the identification and characterization of novel host–virus interactions or viral manipulation of host responses. Many questions however remain in this field, and continuous efforts to improve our molecular understanding of virus–host interactions and potential targeting thereof by using chemical inhibitors or other intervention technologies, will be important for the design of the next generation of antiviral therapies.

Conflict of interest statement

None.

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