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Editorial overview: Antiviral strategies

Michael Gale Jr. and Curt M Horvath

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Michael Gale Jr.
Department of Immunology, Center for Innate Immunity and Immune Disease, University of Washington School of Medicine, Seattle, WA, USA
e-mail: mgale@uw.edu

Michael Gale, Jr., PhD, is a Professor in the Department of Immunology at The University of Washington, School of Medicine. He is Director of the Center for Innate Immunity and Immune Disease, where his laboratory studies innate immunity and RNA virus infection.

Curt M Horvath
Weinberg College of Arts and Sciences, Medicine-Hematology/Oncology and Microbiology-Immunology, Nortwestern University, 2200 Campus Drive, Evanston IL 60208, USA
e-mail: horvath@northwestern.edu

Curt M. Horvath is a Professor of Molecular Biosciences at Northwestern University. His research program has examined cytokine and interferon signal transduction and gene regulation in innate immunity and cancer. The Horvath lab has uncovered diverse molecular mechanisms of antiviral innate immunity, defined numerous virus innate immune evasion systems aimed at RLR and JAK-STAT pathways, and has used contemporary methods to examine genome-wide transcription responses during virus infection and in cancer. Current research on signal transduction and gene regulation includes investigation of virus–host interactions, protein–RNA interactions, and the molecular mechanisms underlying interferon production and cellular antiviral responses.

This issue of *Current Opinion in Virology* is focused on reviewing virus/host interactions of immune control, including innate antiviral immunity and inflammation, and interactions at the interface of innate-to-adaptive immunity, with discussion of viral evasion strategies directed by a range of pathogenic viruses.

Ma and Suthar [1] present a timely overview of innate immune interaction and evasion strategies used by emerging RNA viruses of public health concern. The authors walk us through specific innate immune signaling networks, including how RNA viruses are recognized as nonself to trigger innate immunity through RIG-I-like receptors (RLRs), RIG-I and MDA5, of host cells of infection. They show us where and how innate immune signaling factors and effector genes are targeted for control or direct suppression by Ebola virus, SARS coronavirus, West Nile virus and related flaviviruses, as well as Chikungunya virus, and Middle Eastern respiratory virus, and others. A common theme emerges from this presentation in that disease is linked to viral disruption of host innate immune response programs.

As illustrated by the autoimmune and inflammatory diseases caused by MDA5 hyperactivity, it is essential to regulate RLR signal transduction to prevent inappropriate signal transduction. Chan and Gack [2] describe a variety of mechanisms for RLR regulation, including direct RLR post-translational modification by phosphorylation and ubiquitin, post-transcriptional regulation of RLR and other antiviral mRNAs by microRNAs, and redistribution of RLR proteins to stress granules, peroxisomes, and autophagosomes for attenuation. Many of these regulatory processes have been exploited or targeted by viral immune evasion mechanisms, fueling the evolutionary battle between host and pathogen.

Initially described as a regulator of tumor differentiation and apoptosis, the RLR known as MDA5 is a key sensor of long cytosolic dsRNAs that is essential for antiviral responses recognition of cytosolic poly I:C and picornavirus infections. Del Toro Duany *et al.* [3] review the unique structural and biochemical properties of MDA5 in dsRNA recognition and cooperative assembly into filaments. The unique mode of dynamic MDA5 dsRNA assembly and disassembly allows for RNA length discrimination as a basis of non-self RNA sensing. The dsRNA filament assembly results in organization of the MDA5 CARD domains into a signaling-competent oligomer that in turn stimulate MAVS aggregation and antiviral signal transduction. Though MDA5 activity usually protects the organism from virus infections, these same mechanistic insights are also relevant to the pathogenic actions

of disregulated MDA5, as found in several autoimmune and inflammatory diseases.

Type 1 and type 3 interferons play major roles in induction and effector action of the innate antiviral response induced by acute virus infection. In the best scenario the interferons get induced during acute virus infection and drive the expression of overlapping sets of hundreds of interferon stimulated genes (ISGs) that encode proteins with a range of functions including antiviral, proinflammatory, and immune modulatory actions that limit virus replication and spread. Odendall and Kagan [4] present an overview to first compare type 1 and type 3 (now formally called interferon-lambda) interferons in virus infection and immunity. Interferon-lambda biology is then featured in depth to tell us how it signals host defense through production from specific cells types and novel signaling programs, as well as how tissue restriction of the interferon-lambda receptor defines a specific niche for innate immune effector actions of this interferon type.

Interferon-lambda genotype is predictive of infection outcome in patients exposed to hepatitis C virus (HCV). Schwerk *et al.* [5] present an overview of how post-transcriptional regulation of interferon-lambda imparts HCV infection dynamics. The authors first summarize the role of interferon-lambda in HCV infection and immunity. They present an overview of the interferon-lambda genetics in which specific polymorphisms in interferon-lambda genes are linked with the outcome of HCV infection and type-1 interferon-based antiviral therapy. Remarkably, mRNA from the interferon-lambda gene 3 is subject to targeted regulation by specific microRNA (miRNA)s. The authors review the mechanisms by which these miRNAs target interferon-lambda mRNA for post-transcriptional control of gene expression and show us how infection outcome-associated polymorphisms serve to evade miRNA control for likely effector actions that can limit HCV replication. Beyond miRNAs other post-transcriptional control processes of IFN-lambda gene expression are operating to impact innate immune defenses against HCV, thus explaining new concepts in our understanding of how chronic HCV infection develops from initial acute infection.

HCV infects nearly 200 million people, with new incidence of infection occurring daily among high-risk groups. While effective therapeutic for HCV infection are now in the clinic, they are incredibly expensive and therefore not available to the broad HCV-infected population nor do these new therapeutics protect from or prevent re-infection. Thus, there remains a huge need for effective HCV vaccine strategies that can confer protection from infection. Such strategies will require means to induce potent therapeutic or ideally a fully protective antibody response directed to the HCV surface glycoproteins, E1 and E2. These proteins problematically harbor hypervariable regions that drift away from inhibitory antibodies, while overall the unique structure of E1 and E2 present hurdles for effective antibody targeting and viral neutralization. Marcotrigiano *et al.* [6] present a review of the current understanding of E1 and E2 structure, with a focus on dissecting the structural information gained from recent protein crystallization efforts. Consideration is given as to how we can leverage structural information to build effective HCV vaccines.

OAS1 is among the better known ISGs, and along with OAS2 and OAS3 plays an essential role in activation the antiviral state through the synthesis of 1′-5′ oligoadenylic acid. Zhu *et al.* [7] consider the larger OAS family of proteins and provide an overview of the OASL proteins, recently demonstrated to be a participant in antiviral innate immunity. Mammalian OASL proteins have evolved to function independent of OAS catalytic activity to potentiate antiviral responses. The ability of OASL to directly activate RIG-I signal transduction highlights one of the ways this protein functions independent of enzymatic activity.

One of the first RNA virus proteins recognized to antagonize or dismantle innate antiviral responses is the NS1 protein of influenza A viruses. There can be little doubt that most influenza A viruses use NS1 to evade host innate responses, but while many explanations for the NS1-mediated antiviral suppression have been described, it is difficult to discern a general mechanistic basis for NS1 interferon antagonist activities. After examining the experimental data and mechanistic conclusions regarding NS1 action, Krug [8] finds that it is impossible to generalize NS1 actions, as they differ on a strain-by-strain basis. Early reliance on laboratory-generated strains may have missed biological activities that are more pronounced in circulating influenza viruses.

As virus infection progresses, products of virus replication and the host response to infection can both trigger the inflammatory response by engaging various inflammasomes of the host cell and tissues to induce the production of interleukin 1-beta (IL-1beta) and related cytokine family members. Inflammasomes are multi protein complexes that activate caspase-1 to cause maturation and release of IL-1beta. They are named by the nature of the known initiator protein for each. Recent advances have identified a variety of inflammasome initiator proteins whose actions respond to virus infection. Lupfer *et al.* [9] present a state of the art review of inflammasome actions in virus infection and disease. The authors present concepts to consider for leveraging specific inflammasome pathways for vaccine and therapy design to control virus infection and immunity.

Together, these articles describe in detail only a small representative sample of the diversity and complexity of

mammalian antiviral innate immune responses, underscoring the importance of virus–host interactions in driving human health and welfare. The coordinated evolution of viruses and human immune systems continues throughout the world, and enables both novel and established viruses take hold in the global community. Continued fundamental mechanistic research into antiviral immunity, and translation of these discoveries into novel diagnostic and therapeutic modalities are essential for maintaining public health.

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