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# Editorial overview: Viral pathogenesis: dealing with complexity in virus-induced disease

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**Mark T Heise** is an Associate Professor of Genetics, with a joint appointment in the Department of Microbiology and Immunology at the University of North Carolina. He has studied viral pathogenesis since 1992, with an emphasis on understanding how viral interactions with the host innate and adaptive immune system shape virus-induced disease processes.

The term 'viral pathogenesis' describes the complex process by which a virus interacts with the host to cause disease. By definition, there are two sides to this coin, with both the virus and the host playing essential roles in determining whether infection results in disease, and if so, how severe that disease turns out to be. Therefore, the severity of a virus-induced disease depends upon qualities that are intrinsic to the virus, as well as host specific factors. Viruses must successfully execute a number of functions, including: binding and entry into appropriate target cells, replication, assembly, egress and dissemination. Viruses that are inefficient in any of these processes are likely to be attenuated, and at the very least, such defective viruses should be less effective at spreading within populations. Furthermore, most, if not all, pathogenic viruses employ mechanisms to avoid or suppress the host antiviral response. Viruses that are either ineffective or inefficient in these processes are likely to elicit potent antiviral responses, again resulting in viral attenuation. Likewise, the host is not a passive player in the infection process, and the kinetics, quality, and magnitude of the host immune response plays a major role in determining disease outcome. Individuals with severe immune deficiencies clearly have enhanced susceptibilities to viral pathogens. However, the range of variation in the population can be more subtle than this, in that individuals that mount weak antiviral responses may have enhanced susceptibility to developing severe acute disease or progressing to chronic viral infection, while individuals who mount extremely strong immune responses may be at risk for developing immune-pathology. This means that a virus that inefficiently interacts with its target receptor or lacks the ability to effectively antagonize the host antiviral response is likely to be attenuated in most hosts, however, this same virus may be capable of causing disease in immune compromised individuals. Therefore, the study of viral pathogenesis involves trying to define the viral and host factors that together contribute to the virus-induced disease process and then disentangle how interactions between these factors shape disease outcomes.

Given the complexity of virus/host interactions, it should come as no surprise that much of the progress in understanding the pathogenesis of specific viruses has come from studies that have focused on specific aspects of the viral lifecycle or the host response using reductionist approaches. For example, detailed analysis of how viruses interact with cellular receptors can provide significant insights into multiple aspects of the virus-induced disease process, including the impact of receptor usage on viral evolution, host range, and tissue tropism. These factors can then have downstream impact on the virus-induced disease process. Likewise, by dissecting the

role that individual host genes or pathways play in either limiting viral infection or exacerbating virus-induced disease, the field has gained significant insight into the important role that specific host pathways, such as the type I interferon system, or even specific interferon stimulated genes (ISGs), play in virus-induced disease processes.

Given the complexity of the pathogenic process for any virus, in order to better understand the virus-induced disease process, it is necessary to employ methods that attempt to integrate these complex interactions to build models that better represent the disease process. These 'systems biology' approaches use large sets of host response data, such as transcription profiles following viral infection, to build models that explain how interactions between multiple host pathways or signaling networks drive disease outcomes. Then, using combinations of cell culture, animal models, or even in silico systems, the investigator can perturb a specific component of the system to make predictions and test the relative importance of a specific viral factor (e.g. a virulence determinant) or host pathway in determining the outcome of the disease process. Though still relatively new, these systems biology based approaches promise to provide a more comprehensive picture of the complex processes that regulate virus-induced disease, while also providing avenues for identifying and testing the relative contribution of specific viral or host factors in the disease process.

The reviews in this issue, as well as an accompanying commentary by Dr. Matthew Frieman, illustrate the power of reductionist approaches for studying key aspects of viral pathogenesis, such as virus/receptor interactions and type I interferon mediated control of viral infection, while also introducing the reader to the emerging fields of Systems Biology and Systems Genetics, and their application to the study of viral pathogenesis. Though each of these reviews is focused on a specific pathway (e.g. type I IFN) or class of viruses (e.g. influenza A virus), many of the concepts and scientific approaches discussed in these reviews are likely to have broad application to the study of a wide range of virus-induced disease states.

Virus receptor interactions represent a key early step in the viral lifecycle that can impact not only viral host range and tissue tropism, but may also affect downstream virus induced disease. The interactions between coronaviruses, which include emerging pathogens such as SARS-CoV and MERS-CoV, and their receptors, illustrate how virus/receptor interactions can impact multiple aspects of the virus-induced disease process. Berend Bosch, Saskia Smits, and Bart Haagmans discuss how interactions between four human coronaviruses, SARS-CoV, MERS-CoV, HCoV-229E, and HCoV-NL63 and the membrane ectopeptidases that act as their entry receptors, impact coronavirus pathogenesis. In addition to playing a key role in determining viral host range, some host ectopeptidases, such as the SARS-CoV/HCoV-NL63 receptor, angiotensin converting enzyme 2 (ACE2), regulate key host processes, and the authors discuss how virus-induced alterations in these receptors can perturb the host to induce disease.

The type I interferon system plays an essential role in the antiviral immune response, both through direct antiviral effects of interferon stimulated genes (ISGs) and modulation of other components of the innate and adaptive immune system. Much of our understanding of the antiviral activity of specific ISGs has come from cell culture based studies, where individual ISGs are tested for their ability to inhibit specific viruses. However to fully understand what role a given ISG plays in the pathogenesis of a viral agent, it is important to extend this analysis in vivo using model organisms and/or patient populations. Therefore, John Schoggins reviews how animal models have advanced our understanding of the role that specific ISGs play in controlling viral infections, and how these findings relate to humans. Furthermore, given the large number of ISGs, he discusses the need for systematic approaches that will evaluate how interaction between different ISGs shape the host antiviral response.

The final three reviews in this issue discuss the application of systems biology and systems genetics approaches to the study of West Nile virus (WNV), influenza A virus (IAV), and human coronaviruses. Mehul Suthar and Bali Pulendran first discuss the field's current understanding of WNV pathogenesis, which has in large part come from WNV infection of knockout mice lacking specific components of the host innate and adaptive immune system. They then go on to review recent applications of systems based approaches to identify host factors regulating WNV tropism, as well as the use of high throughput screens to identify host factors that act in either a pro-viral or anti-viral manner. The final two reviews focus on two major types of human respiratory pathogens, IAV and emerging human coronaviruses. Heike Kollmus, Ester Wilk, and Klaus Schughart discuss the application of systems biology approaches toward characterizing the host response to IAV infection, while Alexandra Schafer, Ralph Baric, and Martin Ferris discuss recent advances in coronavirus pathogenesis that have arisen from Systems Biology based studies. Both of these reviews also introduce the concept of systems genetics, which involves the use of genetically diverse model systems, such as the Collaborative Cross mouse genetic reference population, to identify host factors that contribute to complex traits, (e.g. the host response to viral infection). Though relatively new, these types of approaches have the potential to provide important

new insights into the complex host processes that shape an individual's response to viral infection. Importantly, all of these reviews emphasize the point that by carefully combining classical experimental approaches with systems biology and/or systems genetics methodologies, it should be possible to significantly advance the field's understanding of the complex processes that contribute to the pathogenesis of many significant human pathogens.

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