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## Virology meets Proteomics

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Recent years have witnessed the significant contribution of proteomics to understanding important concepts in virology. Viruses have co-evolved with their hosts, acquiring mechanisms to capture and manipulate host cellular processes for their replication and spread. Similarly, host cells respond by deploying defense mechanisms or by adapting to the infection environment. Proteomics has delivered powerful tools for characterizing this dynamic interaction between viruses and hosts. This success was driven by improvements in proteomic workflows and mass spectrometry instrumentation, as well as by the increased awareness of these valuable proteomic methods within the virology community. Indeed, in recent years, mass spectrometry (MS) has progressed from being a sparsely used technology, hidden in the supplementary material of some virology studies, to being a major contributor to fundamental discoveries in virology. For example, MS-based analyses have been used to characterize the composition of virions, define virus-host protein interactions, map global proteome or secretome changes following infection, determine the function of posttranslational modifications during infection, and define novel mechanisms of host defense against viruses.

Our Special Issue aims to celebrate and highlight the integration of these two fields of research, Proteomics and Virology, as well as to raise awareness in both communities of the opportunities present in Viral Proteomics research. The issue contains 15 manuscripts that reflect the impressive diversity of virology studies that benefit from the wide range of available proteomic-based approaches. The elegant merge of these two fields of research is illustrated by the fact that these manuscripts come from both virology and mass spectrometry laboratories. While, of course, not all of the leading laboratories were able to contribute to this issue, we are very pleased to say that, as detailed below, the investigators highlighted in this issue represent some of the major supporters of proteomics for virology studies. We have organized this issue using classical virology taxonomy by dividing the issue into two main sections communicating reports describing either DNA or RNA viruses and a third section on non-MS based proteomics.

Section 1, DNA viruses, begins with an informative review discussing the biological discoveries made possible by MS-based proteomics when studying alpha herpesviruses, a major family of human pathogens. This review comes from one of the world-leading virology groups in this area - the Enquist laboratory. Extending the theme of alpha

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herpesviruses, the two next research papers uncovered protein interactions during infection with herpes simplex virus 1 (HSV-1). First, from the laboratory of David Knipe, one of the first to use MS in protein interaction studies during infection. This study identified an important viral-viral protein interaction for the HSV-1 tegument protein VP16, and proposed an expanded role for VP16 in transactivation of viral gene expression. Second is a paper by Rowles *et al.* which highlights the value of immunoaffinity purification (IP) and MS for defining virus-host interactions, identifying the association of HSV-1 proteins with an important cellular epigenetic factor. This study adds to the growing interest in the scientific community in understanding the impact of viral infection on the epigenetic landscape of a cell, and comes from a group that was the first to use IP-MS, a now central tool in the field, to study temporal virus-host protein interactions during the progression of an infection. The next three manuscripts focus on the beta herpesvirus, human cytomegalovirus (HCMV). The Moorman lab elegantly demonstrates the importance of studying RNA-protein interactions, identifying a new mechanism through which a viral factor regulates translation during HCMV infection. The next two papers characterize changes in both the proteome and posttranslational modifications. The Terhune lab used metabolic labeling in conjunction with cellular fractionation to build a valuable repository of changes occurring in the nuclei of HCMV infected cells, discovering nuclear import factors that are required for effective HCMV replication. The final beta herpesvirus manuscript comes from the laboratory of Tom Shenk, a world-recognized expert in HCMV biology. Metabolic labeling and phosphopeptide enrichment approaches uncovered the impact of a viral kinase on the cellular phosphoproteome and a novel phosphorylation motif. Further emphasizing the broad contribution of proteomics to herpesvirus studies, the next paper focused on a human cancer virus, the gamma herpesvirus Kaposi's sarcoma-associated herpesvirus (KSHV). The Robertson group investigated cellular proteins that bind to the SUMO-interaction motif of the viral latent nuclear antigen (LANA), expanding the current understanding of the role of SUMOylation in KSHV infection and pathogenesis. This section concludes by transitioning from studies on large DNA viruses to small DNA viruses - papillomaviruses, which have been associated with cancer development. This study comes from a prominent papillomaviruses laboratory, the group of Alison McBride. The authors investigate virus-host protein interactions by studying eleven viral proteins from diverse phylogenetic groups of the *Papillomaviridae* family.

The section on RNA viruses begins with a review from the Ploss laboratory, a critical player in developing small animal models permissive to infection with Hepatitis C virus (HCV). This manuscript underscores the fact that improvements in proteomic technologies have occurred in parallel with developments of experimental models in virology, and reviews the current and expected contributions of proteomic methods to understanding HCV biology. Shifting to HIV Colquhoun *et al.* provide insights into the impact of viral infection on cellular acyl modifications – modifications that can alter cellular distribution of proteins. A novel bio-orthogonal labeling approach was used to isolate palmitoylated and myristoylated proteins and identify proteins differentially modified in HIV infection. This approach, involving “Click-Chemistry”, is applicable to other viral systems, in conjunction with both MS and imaging studies. Continuing the focus on HIV, the manuscript from the Karn lab used an array of methods, including MS, mutagenesis, and biochemistry approaches, to

investigate the impact of phosphorylation of a critical transcriptional regulatory protein, HEXIM1, on HIV replication. Continuing the theme of dynamic phosphorylations during infection, the next manuscript in this section discovered a wide range of changes in protein phosphorylation upon infection with Sendai virus (SeV). This elegant study from the laboratory of Tuula Nyman further shows that, similar to DNA viral infections, mTOR signaling is activated during SeV infection and required for viral protein synthesis. The Nyman group has a long history of integrating proteomics with virology studies. Beautifully illustrating the breath of virology studies benefiting from proteomics approaches, the next paper comes from the laboratory of Michelle Cilia, one of the few groups currently working on virus-host interactions during infections with plant viruses. This study of the potato leafroll virus (PLRV) characterized virus-host interactions that are virion readthrough protein (RTP)-dependent. Finally, as the anchor for this section, the last manuscript on RNA viruses comes from the Berard group, which used quantitative MS to compare global cellular responses following infections with two distinct subtypes of reovirus T3D that differ in their pathogenicity.

To highlight that viral proteomics extends beyond MS-based methods, the last section of our special issue presents an important proteomics resource for virology studies. The LaBaer group describes the generation and testing of protein arrays for studying interactions with numerous viral proteins from 25 different viruses, and demonstrates the applicability of these arrays for identifying antiviral antibodies. This still-evolving resource promises to provide a high-throughput mean for studying virus-host protein interactions for a wide variety of viruses.

In closing, we thank the authors for their valuable contributions and for supporting this important topic. We also thank the Editor-in-Chief, Prof. Michael J. Dunn, and the Managing Editor, Dr. Hans-Joachim Kraus, for all their help and for making this issue possible. As numerous highly-specialized, sensitive, and quantitative proteomic approaches are yet to be taken advantage of in virology studies, we hope that this issue will inspire future studies and further promote the integration of these two great fields of research.