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# Editorial overview: Viruses and cell metabolism

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As obligate intracellular organisms, viruses require host cells for many functions to support replication, which includes provision of building blocks for viral nucleic acids and proteins, but also energy. Thus, although many viruses are seemingly simple, they have evolved extensive and complex mechanisms to exploit multiple host processes. Research for decades has delineated how viruses regulate and usurp macromolecular processes of DNA replication, transcription, translation; how they organize specialized structures and compartments for replication, assembly and virus release; and how they control the innate immune responses that seek to block virus replication. But all macromolecular processes of gene regulation in the cell are themselves linked to production of energy, metabolites, building blocks and components. As such, viruses also alter host cellular metabolism to meet the material and energy demands of their life cycles. As a consequence, it is not surprising that recent evidence suggests cells have evolved controls over metabolism that can limit virus replication, and that viruses have developed countermeasures to inhibit those cellular responses. And so the complex host response-virus countermeasure relationships are extended yet to a new level.

Energy metabolism is in many ways linked to stress through inverse relationships. Cell growth signaling, linked to high metabolism, is the antithesis of stress signaling, which is linked to restriction of metabolism and autophagy. As viruses promote cell stress and provoke the cascade of stress responses that restrict activities from the nucleus to the mitochondria, the coincident restriction in metabolism must be averted by successful viruses. Large shifts in energy metabolism are linked to stress responses in cell fate decisions that are prosurvival versus anti-survival (e.g. apoptosis activation). One could also ask: are metabolic responses another form of the innate immune response? The answer might be yes in consideration of known stress responses that are clearly tied to activation of innate immunity and responses against viruses.

Since viruses exploit the cell machinery at many levels, they can be good tools for “metabolic engineers” interested in understanding new ways to control cancer and to learn about mechanisms that link basic anabolism/catabolism decisions in the cell with stress

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events. The functions selected by viral evolution that differentially promote a subset of the cell catabolic processes versus anabolic processes promise to reveal much new information about metabolic regulation. New techniques to study host metabolism combined with use of selected viral systems offer promise to advance understanding of metabolic control of gene expression.

This special issue of Current Opinion in Virology seeks to bring together and highlight new information about how alterations in host metabolism may affect viral replication and pathogenesis. Though this is an emerging new field in virology, it is also a reemerging interest in cancer and cell biology and some reviews have been written on virologic aspects that can be consulted for more information on this exciting area of research [1-3]. The reviews herein focus on a variety of subtopics in different virus systems that are related to alteration of lipid metabolism and rearrangement of membrane architecture, control of cellular metabolism, immunometabolism and virus-driven microRNA fluxes that modulate metabolism. Many RNA viruses require specific novel membranes to support and organize RNA replication. Lipids are used for membranes and energy storage, and thus are closely tied to metabolic processes. These discussions paint a picture of an emerging field and foretell of future directions.

In many chapters the possibility that new antiviral therapeutics may inhibit metabolic steps is discussed. While some may target the virus itself, others may target cellular processes and potentially be less prone to emergence of drug-resistant viruses.

Three of the reviews describe how viruses coopt cellular lipid metabolic processes in the formation of novel membranous structures to support virus RNA replication and virion assembly.

In the case of rotavirus, reviewed by Sue Ellen Crawford and Ulrich Desselberger, virus proteins regulate certain long chain acyl-CoA synthetases that promote lipid droplets adjacent to viroplasm sites of replication. George Belov reviews how picornaviruses trigger biosynthesis of signaling lipids and structural lipids and reroute cholesterol trafficking pathways, in the process creating novel membrane microdomains that restrict innate immune PAMP recognition. Finally, Tristan Jordan and Glenn Randall detail how flaviviruses modulate carbon metabolism by stimulating the processes of glycolysis and lipid anabolic and catabolic pathways to enhance fatty acid synthesis near replication centers in the cytoplasm. Dengue virus also triggers lipid catabolism by promoting lipophagy, a type of selective autophagy.

The review by Michael Lagunoff discusses how latent Kaposi’s Sarcoma herpesvirus infection of endothelial cells alters metabolism, induces glycolysis and fatty acid synthesis, possibly to utilize specific metabolites to support latency and drive cancer.

Nicholas Matheson, Edward Greenwood and Paul Lehner review new evidence for a complex interplay between host restriction factors that exploit cellular metabolic dependencies to limit HIV replication. They also discuss HIV accessory proteins that manipulate nucleotides, glucose, amino acids and lipid metabolic pathways to optimize the intracellular environment for productive infection. Downregulation of cell surface

transporters to control nutrient supply and viral modulation of T cell amino acid metabolism are new concepts for immunometabolism.

Cesar Llave highlights how our current knowledge of primary metabolism is altered with viral infections in plants and how these changes modulate the outcome of viral infections related to stress acclimation and defense.

Finally, Megan Powdrill, Geneviève Desrochers, Ragunath Singaravelu and John Pezacki cover microRNAs that are modulated by different viruses to hijack host cell metabolism and elements of the innate immune response to counter these measures.

## Biography

Richard Lloyd is Professor in the Department of Molecular Virology and Microbiology at Baylor College of Medicine. His research encompasses aspects of enterovirus–host interactions and has focused on translation regulation and control of stress granules and P-bodies in cells.

Dr. Mary Estes holds the Cullen Endowed Chair of Human and Molecular Virology at Baylor College of Medicine. She directs a multidisciplinary research program to understand gastrointestinal virus–host interactions.

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