CellPress

Review

Stealing the Keys to the Kitchen: Viral Manipulation of the Host Cell Metabolic Network

Christopher M. Goodwin,[1] Shihao Xu,[1] and Joshua Munger[1,*]

Host cells possess the metabolic assets required for viral infection. Recent studies indicate that control of the host's metabolic resources is a core host–pathogen interaction. Viruses have evolved mechanisms to usurp the host's metabolic resources, funneling them towards the production of virion components as well as the organization of specialized compartments for replication, maturation, and dissemination. Consequently, hosts have developed a variety of metabolic countermeasures to sense and resist these viral changes. The complex interplay between virus and host over metabolic control has only just begun to be deconvoluted. However, it is clear that virally induced metabolic reprogramming can substantially impact infectious outcomes, highlighting the promise of targeting these processes for antiviral therapeutic development.

Trends

Numerous viruses modulate host-cell metabolic processes to ensure successful infection.

The host-cell metabolic network contributes the energy, precursors, and specialized components necessary to produce infectious virions.

Viruses deploy host-cell metabolic activities to organize viral maturation compartments.

Metabolic control is a host–pathogen interaction that can sway the outcome of viral infection.

The Host Metabolic Network: Multifaceted Contributions to Viral Infection

Viruses are obligate parasites that depend on the host cell to provide the energy and molecular precursors necessary for successful infection. A wide variety of evolutionarily divergent viruses have evolved mechanisms that target the host cell metabolic network as part of their infectious programs, and virally induced metabolic activities are commonly exploited for therapeutic intervention. For example, numerous different nucleotide metabolic activities are targeted by a variety of pharmaceuticals to treat viral infections, including hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), human cytomegalovirus (HCMV), varicella-zoster Virus (VZV), and herpes simplex virus (HSV) (Table 1) [1–5]. In recent years, the number of metabolic activities that have been found to be important for viral infection has expanded. Further, our understanding of the viral mechanisms through which viruses usurp cellular metabolic resources has increased. Many of these viral mechanisms stimulate nutrient uptake and catabolism to support the production of viral progeny. In addition to providing the energy and biomass necessary for turning cells into productive 'virus factories', new metabolic contributions to infection have emerged. These include small-molecule enzymatic activities that organize viral maturation compartments, synthesize specialized virion components, or regulate the immunological environment (Figure 1). Such virally induced metabolic changes do not go unnoticed by the host, but rather represent a major host–pathogen interaction that can sway infectious outcomes. Collectively, recent findings have made it clear that the landscape for metabolically targeted therapeutic intervention has expanded.

Viral Targeting of Core Metabolic Pathways

A wide variety of viruses activate glycolysis, which drives the production of energy in the form of ATP, NADH, and NADPH (Figure 2). Activated glycolysis also supplies the carbon necessary for

[1]Department of Biochemistry and Biophysics, University of Rochester Medical Center, Rochester, NY 14642, USA

*Correspondence: josh.munger@rochester.edu (J. Munger).

Table 1. Nucleoside/Nucleotide-Based Therapeutics[a]

Virus	Nucleoside/Nucleotide Analogs
HIV	Tenovovir; Emtricitabine; Zidovudine; Abacavir; Lamivudine
HBV	Tenovovir; Lamivudine; Entecavir; Telbivudine
HCV	Sofosbuvir; Ribavirin
HCMV	Ganciclovir; Cidofovir
HSV	Acyclovir; Valacyclovir
VZV	Acyclovir; Valacyclovir

[a]HIV, human immunodeficiency virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HCMV, human cytomegalovirus; HSV, herpes simplex virus; VZV, varicella-zoster virus.

the synthesis of numerous core biomolecules, including nucleotides, lipids, amino acids and carbohydrates (Figure 2). A number of DNA viruses induce glycolysis, including Kaposi's sarcoma-associated herpesvirus (KSHV) [6], HCMV [7], adenovirus [8], human papillomavirus (HPV) and Epstein–Barr virus (EBV) [9]. Multiple RNA viruses also activate glycolytic flux, including dengue [10], hepatitis C (HCV), [11] and influenza A [12]. Although there are some notable exceptions, such as herpes simplex virus-1 (HSV-1) and vaccinia virus [13,14], both the number and evolutionary diversity of viruses that target glycolysis speak to the broad importance of this pathway for viral infection.

Recently, the specific viral mechanisms targeting glycolysis have begun to be elucidated. For instance, the HCV NS5A protein has been shown to bind and activate hexose kinase, a rate-controlling glycolytic enzyme [15]. KSHV employs specific viral microRNAs targeting known regulators of glucose metabolism and mitochondrial biogenesis to induce glycolytic activity [6]. HCMV has been shown to induce the activity of the AMP-activated kinase (AMPK) [16], which regulates numerous glycolytic activities [17]. HCMV-mediated activation of AMPK was found to

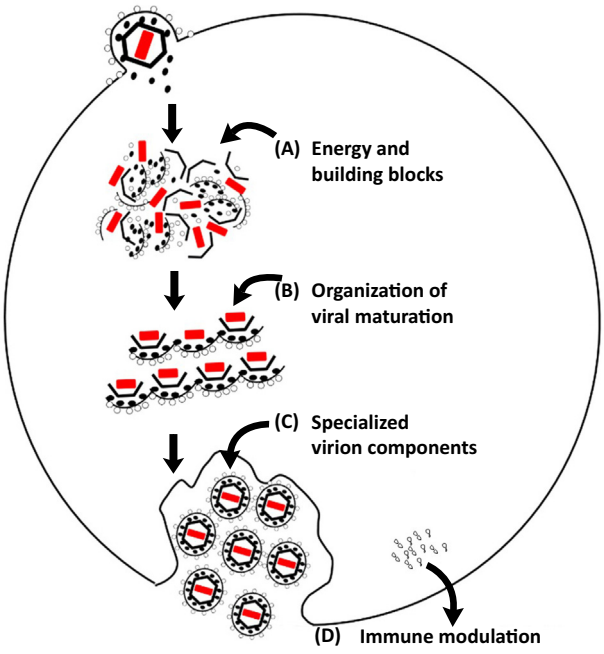

Figure 1. Small–Molecule Metabolic Contributions to Viral Infection. Production of infectious virions requires energy and biomolecular building blocks derived from the host cell metabolic network (A). A diverse set of host metabolic activities drives the mass production of viral nucleic acids (red), structural proteins (black octagons), non-structural proteins and phospholipid envelopes (both in black circles), and glycosylated proteins (white circles). Additionally, organization of viral maturation compartments has increasingly been found to be dependent on lipid-modifying enzymes (B). Viral infection has also been found to induce specific metabolic activities to form specialized virion components that are important to infection (C). Lastly, the evidence supporting the importance of small-molecule metabolism for immune regulation is increasing, as are the findings that these processes are targeted by viral infection (D).