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The role of microRNAs in metabolic interactions between viruses and their hosts

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Productive viral infection requires changes to the cellular metabolic landscape in order to obtain the building blocks and create the microenvironments necessary for the viral life cycle. In mammals, these alterations of metabolic pathways have been shown to be mediated in part by host and virus-encoded microRNAs. To counteract virally-induced changes in the cellular metabolic profile, the interferon-regulated antiviral response restricts viral access to key metabolites by altering cellular metabolism, mediated through induction of specific microRNAs regulating key lipid biosynthetic processes. In this review, we examine recent studies demonstrating the important role of microRNAs in the regulation of metabolic flux during viral infection.

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Introduction

As obligate intracellular parasites, viruses hijack the host metabolic processes in order to facilitate a productive infection. Metabolic reprogramming of infected cells enables the virus to achieve the necessary energy levels and biosynthetic precursors essential for viral processes. Consistent with these changes, metabolomics studies have identified significant fluctuations in biosynthetic intermediates during the course of a viral infection [1–8]. Viruses manipulate metabolic pathways to create specific microenvironments required for various stages of their life cycles (reviewed in [9]). Since there is a broad dependence on metabolic pathways to facilitate viral pathogenesis, it is not surprising that the mammalian innate immune responses strategically reconfigure the host metabolic gene network to restrict viral propagation.

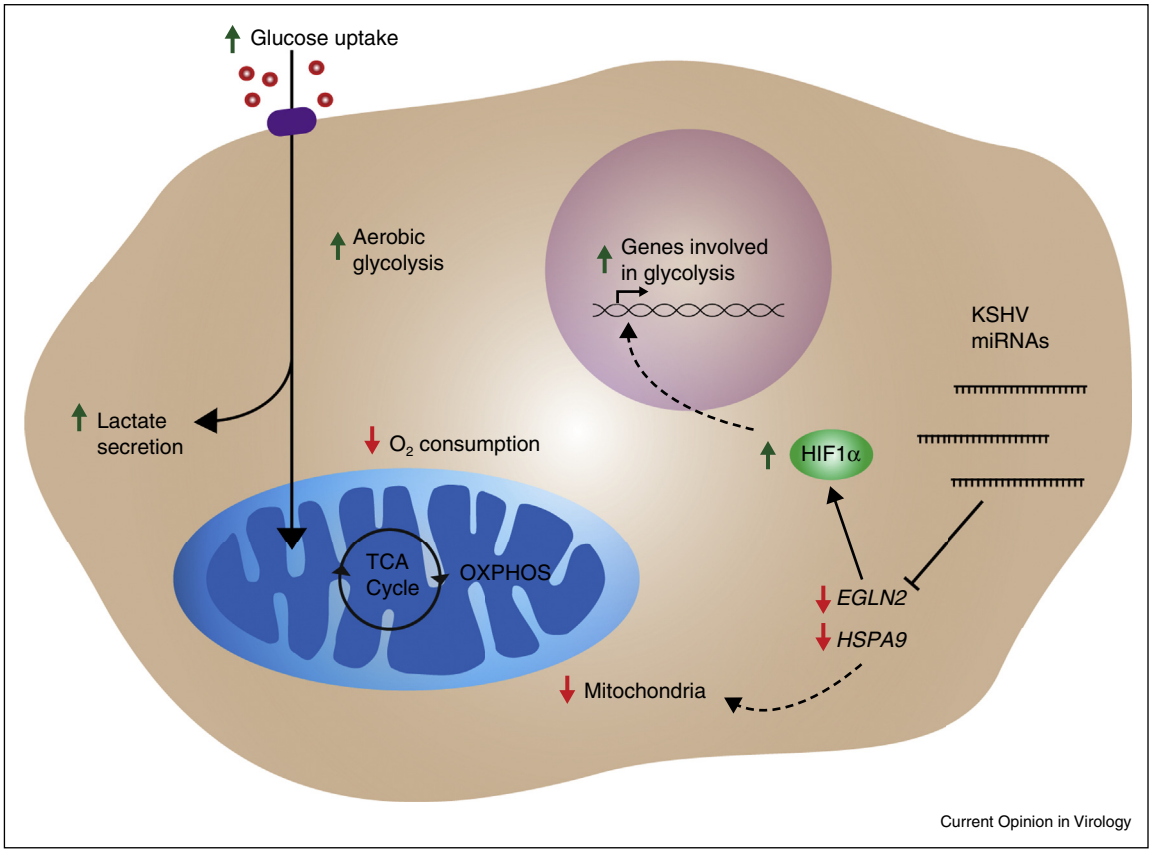
One approach invoked to modulate these pathways is the use of microRNAs (miRNAs). These small, non-coding RNAs, in association with the RNA induced silencing complex, bind partially complementary sequences in host mRNA transcripts. This results in repression of gene expression through a combination of translational repression and transcript destabilization [10]. The role of human miRNAs in the regulation of metabolism is well established, with dysregulation of miRNAs proposed to be an important factor in the development of metabolic disorders [11,12]. Additionally, virus-encoded miRNAs also have the potential to influence cellular metabolism through regulation of host transcripts [13]. In this review, we examine the role of virus-derived and mammalian miRNAs in regulating host metabolic alterations critical to viral pathogenesis and the innate antiviral responses to infection.

MicroRNA-mediated modulation of metabolic pathways in viral infection

Many viruses, including oncogenic viruses in particular, rely on metabolic reprogramming of cells to meet the demand for increased energy and the metabolic building blocks that can also serve as a basis for oncogenic transformation. miRNAs have been implicated in the reconfiguration of host metabolism during infection. For example, the metabolic changes required for viral latency in Kaposi's sarcoma-associated herpesvirus (KSHV) infection have recently been shown to be regulated in part by a virally-encoded miRNA cluster (Figure 1). During latent infection, the miRNA cluster induces a metabolic transformation from oxidative phosphorylation (OXPHOS) to aerobic glycolysis. This process occurs through miRNA-mediated downregulation of the HIF prolyl hydroxylase EGLN2 and the heat shock protein HSPA9. Downregulation of these proteins results in the activation of HIF1-α, a protein mediating the switch from OXPHOS to glycolysis, and decreased mitochondrial biogenesis [14••].

miRNAs are also implicated in metabolic reprogramming during adenovirus infection. Viral infection of the breast epithelial cell line MCF-10A by adenovirus 5 increases

Figure 1



Kaposi sarcoma-associated herpesvirus encoded miRNA cluster induces metabolic reprogramming. Expression of KSHV miRNAs results in a shift toward aerobic glycolysis, with increased glucose uptake, decreased oxygen consumption, increased lactate secretion and a decreased mitochondrial biogenesis. Mechanistically, this occurs in part through KSHV miRNA-mediated downregulation of the HIF prolyl hydroxylase EGLN2, resulting in stabilization of the HIF1α transcription factor which is involved in the switch from OXPHOS to aerobic glycolysis. Targeting of HSPA9 results in a reduction in the number of mitochondria.

glycolytic metabolism through expression of the E4ORF-1 gene product, which enhances MYC-dependent transcription and increases expression of glycolytic enzymes [15]. Activation of MYC leads to increased nucleotide biosynthesis from glucose intermediates, which benefits viral replication. Adenovirus 5 infection also promotes increased glutamine uptake in a MYC-dependent manner, which is required for synthesis and import of essential and non-essential amino acids. Mechanistically, MYC transcriptionally represses miR-23a-3p and miR-23b-3p, leading to increased expression of mitochondrial glutaminase and increased glutamine catabolism [16•,17]. Metabolic reprogramming is also a hallmark of other viruses, including hepatitis C virus (HCV), human cytomegalovirus (HCMV), human immunodeficiency virus and hepatitis B virus (HBV), although a role for miRNAs in the transition toward aerobic glycolysis has yet to be established [7,18–20].

Viruses also display a strong dependence on cellular lipid pathways to facilitate their life cycle [21]. Positive-sense RNA viruses, for example, induce significant lipid remodeling of cellular membranes to compartmentalize viral replication [22], while other viruses utilize lipid droplets as a platform for assembly or as a source of energy [23]. In addition, the lipid composition of cellular membranes and virion envelopes is crucial to facilitate membrane fusion for entry [24]. Virus-induced modulations in host miRNA expression can mediate these pro-viral manipulations of lipid pathways. HCV displays an intimate reliance on hepatic lipid metabolism for every stage of its life cycle [25]. These metabolic alterations can have pathological consequences, as observed by the increased rate of metabolic liver disease in patients chronically infected with HCV [26].

It is becoming clear that miRNAs can mediate viral manipulations of host metabolic pathways. Hepatic miR-27 expression was shown to be upregulated in the context of HCV infection, both in cell culture and mouse models [27••] as well as in HCV-infected patients [28•,29•]. We have recently demonstrated that miR-27b-3p promotes