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Review

Viral activation of cellular metabolism

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ABSTRACT

To ensure optimal environments for their replication and spread, viruses have evolved to alter many host cell pathways. In the last decade, metabolomic studies have shown that eukaryotic viruses induce large-scale alterations in host cellular metabolism. Most viruses examined to date induce aerobic glycolysis also known as the Warburg effect. Many viruses tested also induce fatty acid synthesis as well as glutaminolysis. These modifications of carbon source utilization by infected cells can increase available energy for virus replication and virion production, provide specific cellular substrates for virus particles and create viral replication niches while increasing infected cell survival. Each virus species also likely requires unique metabolic changes for successful spread and recent research has identified additional virus-specific metabolic changes induced by many virus species. A better understanding of the metabolic alterations required for the replication of each virus may lead to novel therapeutic approaches through targeted inhibition of specific cellular metabolic pathways.

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Introduction

Viruses are non-living entities and as such do not inherently have their own metabolism. However, within the last decade, it has become clear that viruses dramatically modify cellular metabolism upon entry into a cell. Viruses have likely evolved to induce metabolic pathways for multiple ends. Virus-induced metabolism may provide increased pools of free nucleotides necessary for rapid viral genome replication as well as increased amino acid production for rapid virion assembly. For enveloped viruses, increased lipid material may be needed to provide additional membrane material for envelopment of the viral particles. Alteration of cellular metabolism by viruses could also be necessary to provide specific substrates that are uniquely required at high levels for virion production, for example increased glycoproteins for viral envelopes. In addition to providing direct substrates for virion production, adjustments to metabolic pathways may be required to provide ATP in a rapid fashion for the high energy costs of genome replication and packaging. Altered cellular metabolism may aid in the survival of infected cells during the stress of viral infection. Identification of how viruses alter cellular metabolism and where in the virus life cycle these metabolic changes are necessary will provide a deeper understanding of virus replication needs and potentially provide cellular targets for inhibition of viruses.

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Table 1

Virus	Essential carbon source/ important metabolic pathway	Major publications
Poliovirus	Glucose	Eagle and Habel (1956)
	Glutamine	Darnell and Eagle (1958)
	Fatty acid synthesis	Nchoutmboube et al. (2013)
HCMV	Fatty acid synthesis	Munger et al. (2006)
	Glucose and glycolysis	Munger et al. (2008)
	Glutamine and glutaminolysis	Chambers et al. (2010)
		Vastag et al. (2011)
DENV	Fatty acid synthesis	Heaton et al., 2010
	Glycolysis	Perera et al. (2012)
		Fontaine et al. (2014)
HCV	Fatty acid synthesis	Kapadia and Chisari (2005)
	Glycolysis	Ripoli et al. (2010)
		Diamond et al. (2010)
		Ramiere et al. (2014)
VACV	Glutaminolysis	Fontaine et al. (2014)
	Fatty Acid Synthesis	Greseth and Traktman (2014)
HSV-1	Glucose and Glycolysis?	Lewis and Scott (1962)
		Courtney et al. (1973)
		McArdle et al. (2011)
		Vastag et al. (2011)
Ad5	Glycolysis	Thai et al. (2014)
KSHV (latency)	Glycolysis	Delgado et al. (2012)
	Fatty acid synthesis	Bhatt et al. (2012)
	Glutamine and glutaminolysis	Delgado et al. (2012)
		Yogev et al. (2014)

While there were clear indications from studies in the 1950s and 1960s that virus infection require specific metabolic pathways for replication, identification of virus induced metabolic pathways has been facilitated by recent technological advances. Advanced mass spectrometry techniques can concurrently measure the levels of many metabolites and measure carbon flux through the metabolic system. The term metabolomics was coined to describe experiments where large numbers of cellular metabolite levels are measured concurrently. These studies yield a broader comparison of mock- and virus-infected cell metabolite levels and can identify large-scale changes induced by a virus. Additionally, technological advances have led to the ability to measure carbon flux by following isotope labeled carbon that, while difficult to perform, have allowed a better understanding of the fate of extracellular carbon sources.

In 2006, the first eukaryotic virus-infected cell metabolomics study led the resurgence of the virus-induced metabolism field. The study analyzed over 60 metabolites during human cytomegalovirus infection (HCMV) (Munger et al., 2006). The metabolomics study was followed up with a carbon flux analysis that provided a clearer picture of the flow of carbon from labeled glucose and glutamine following CMV infection, further showing how carbon is utilized in the infected cell (Munger et al., 2008). Since these first studies, a number of viruses have been shown to alter multiple major metabolic pathways and have expanded the number of metabolites measured (Birungi et al., 2010; Delgado et al., 2012; Diamond et al., 2010; Fontaine et al., 2014; Fontaine et al., 2015; Hollenbaugh et al., 2011; Lin et al., 2010; Ritter et al., 2010; Roe et al., 2011; Vastag et al., 2011). A number of core cellular metabolic pathways, including glycolysis, fatty acid synthesis and glutaminolysis, are significantly altered by multiple virus families (Table 1). These core pathways are often similarly activated in many cancer cells. Therefore, it is important that, when possible, metabolomics studies are done in primary or minimally immortalized cells. While information can still be gleaned from studies in transformed cells, many pathways are masked by metabolic switches that are triggered during oncogenesis and in some cases cell lines are immortalized by oncogenic viruses or viral proteins that could contribute to the metabolic profile observed. The importance of glycolysis, fatty acid synthesis and glutaminolysis to viral infections is discussed below.

Glycolysis

Primary mammalian cells under standard growth conditions predominantly utilize glucose for oxidative phosphorylation in the mitochondria. Glucose is metabolized to pyruvate through multiple steps. Pyruvate is then translocated to the mitochondria, where it enters the TCA cycle and ultimately drives the electron transport chain, in a process that requires oxygen. In anaerobic conditions, glucose is primarily utilized for glycolysis where it is metabolized to pyruvate and then is converted to lactate and pumped out of the cell. In most cancer cells glucose is primarily utilized for the production of lactic acid even in the presence of abundant oxygen, a process often referred to as aerobic glycolysis or the Warburg effect. While oxidative phosphorylation provides significantly more ATP per glucose, glycolysis is a much faster process providing ATP rapidly. However, utilizing glycolysis as the main metabolic pathway for glucose requires increased uptake of extracellular glucose to match the increased metabolic rate. While cancer cells utilize aerobic glycolysis, it is not clear if the switch is needed for faster production of ATP or if the production of lactate and higher levels of glycolytic intermediates are advantageous as a source of biomass.

Early hints that glycolysis was required for viral replication came from viral infection studies in the 1950s and 1960s. In 1956, it was shown that the propagation of poliovirus in Hela cells was blocked in minimal media but the addition of glucose recovered a significant portion of the viral titer (Eagle and Habel, 1956). This finding was subsequently confirmed in primary monkey kidney cells where an increase in lactate in the media during the first two hours of infection was also shown (Baron and Levy, 1956; Levy and Baron, 1957). In 1962, it was shown that HSV-1 passage in Hela cells was dependent on the presence of glucose but not glutamine in the media (Lewis and Scott, 1962). In the absence of glucose, HSV-1 penetrated cells equally but did not produce infectious progeny. It was subsequently shown that HSV-1 virion production did not decrease significantly in the presence of 2-deoxyglucose (2-DG), a competitive inhibitor of glucose for hexokinase-2, HK2 (Courtney et al., 1973). However, the production of infectious particles was severely impaired in the presence of 2-DG, possibly due to alterations in the viral glycoproteins. Similar studies with pseudorabies, another alphaherpesvirus, found that viral nucleic acid replication did not require glycolysis and viral proteins were produced in the presence of 2-DG but there was a significant decrease in the production of infectious virus (Ludwig and Rott, 1975). These data show that virus production requires glycolysis for a later step in replication, possibly late gene synthesis, virion assembly or egress, and is not due to the simple explanation that cell integrity is compromised by the lack of glucose. Through the 1980s and 1990s studies of glycolysis and metabolism in virus-infected cells were mostly limited to transforming retroviruses where the effect was clouded by the transformation of the cells by the virus. However, there were studies showing that some viruses, including HCMV and HSV, induced glucose uptake (Landini, 1984; Saito and Price, 1984).

The first eukaryotic virus-infected cell metabolomics study found that glycolytic intermediates were induced following HCMV infection (Munger et al., 2006). This study measured over 60 metabolites following HCMV infection of primary human foreskin fibroblasts (HFF) cells. A number of glycolytic intermediates were significantly increased following infection. Flux analysis demonstrated an increased flux of glucose carbon through glycolysis