Viral infections and metabolism: a clue to antiviral therapy? Example of hepatitis B.

Viral replication requires both energy and elementary building blocks for the formation of intracellular replication complexes and assembly of virions. To this end viruses adjust the cell metabolism to provide the needed biomass and energy or replicate only in cells that already provide any specific metabolic pathway. System metabolism approaches of human cytomegalovirus (HCMV) or hepatitis C virus (HCV) infection showed major metabolism switches in the central carbon metabolism, including a Warburg-like effect. These studies also suggested that cells re-orient their metabolism in the context of the virus-induced changes with anti-viral consequences. The mechanisms underlying these metabolism modifications remain largely unknown even if the role of metabolic nuclear receptors seems central.

Hepatitis B virus (HBV) genome is expressed as an episomal covalently closed circular DNA (cccDNA) in the hepatocyte nucleus. Expression of the viral transcripts is mediated by cellular nuclear receptors and transcription factors PPARα, HFN1 and 4, FXR, RXR, and LRH1 the activity of which is controlled by coactivators or inhibitors, PGC-1α. These factors are key metabolic factors in adaptation to fed-fasted transition. Interestingly it has been proposed that HBV is a “metabolovirus” whose replication is enhanced by fasting and repressed by feeding. FXR, farnesoid X receptor, is a nuclear receptor activated by bile salts that regulates the cholesterol catabolism into bile acids, lipid synthesis and secretion. HBV enters hepatocytes through NTCP, the main bile acids transporter, in competition with bile salts. Chronic hepatitis B is associated with variation in the expression of FXR and of the genes under its control. HBV replication appears thus highly intertwined with the bile salts and lipid metabolism. Reciprocally, interfering with FXR ligands with this metabolism consistently modulates the replication of HBV with putative therapeutic development.