"The molecular mechanisms of hepatitis C virus-associated predisposition to diabetes mellitus"

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Abstract
Chronic hepatitis C virus (HCV) infection often predisposes the host to type 2 diabetes through increased insulin resistance. However, the precise mechanism underlying the HCV-mediated insulin resistance is still unclear. Increased gluconeogenesis in the liver is one of the major characteristics of type 2 diabetes. The hepatic gluconeogenesis is regulated by the two rate-limiting enzymes, phosphoenolpyruvate carboxykinase (PEPCK) and glucose 6-phosphatase (G6Pase), which are transcriptionally upregulated by the transcription factor forkhead box O1 (FoxO1). The phosphorylated form of FoxO1 is transported from the nucleus to the cytoplasm so that the transcriptional activity of FoxO1 is downregulated. The FoxO1 phosphorylation is regulated by Akt/protein kinase B (PKB) through the insulin signaling pathway. It is also known that c-Jun N-terminal kinase (JNK) activates FoxO through the suppression of its phosphorylation. Production of reactive oxygen species (ROS) induces JNK activation and is known to be involved in insulin resistance. Does HCV promote hepatic gluconeogenesis even in a fed condition? If so, how? Glucose transporter 2 (GLUT2), the major GLUT on the liver cell, facilitates glucose influx into, and efflux from hepatocytes. Downregulation of GLUT2 may affect the glucose level in the cell, altering cellular microenvironments. AMP kinase (AMPK) senses cellular energy levels to maintain the balance between ATP production and consumption. What would happen to HCV replication if the glucose level decreases or if AMPK is activated in the cells? In my presentation, I will talk about viral strategies as to what (and how) HCV does in the host cell, with special reference to cellular gluconeogenesis and glucose homeostasis.

Selected Publications