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Interaction of hepatitis C virus with lipid and glucose metabolism

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Hepatitis C virus (HCV) infection induces modifications of the glucose and lipid metabolism that includes insulin resistance and hypobetalipoproteinemia and that is a direct consequence of virus replication. These modifications tend to increase the triglyceride content of the liver, likely favoring the assembly and secretion of the viral particles associated with apolipoprotein B (apoB) forming the lipo-viral-particles (LVP). HCV seems to maintain these metabolic changes through redundant mechanisms that includes interaction of viral proteins with key enzymes of the central carbon metabolism and nuclear receptor, like the farnesoid X receptor (FXR), regulating expression of these genes. It was shown that modulation of FXR regulate the replication of the HCV genome in Huh-7 cells with variable efficiency depending on the HCV genotype. The project is structured in three related parts with growing scope from the detailed analysis of the replication steps regulated by FXR to the understanding of the mechanisms of this regulation and, finally, to the putative extension of these observations to other viruses.

The first part will study the replication steps regulated by FXR, starting by testing several HCV full length replicons and cell lines that would allow to monitor the effect of FXR activation or inhibition on the genome replication and assembly, secretion and nature of viral particles produced by the cells.

Second, mechanisms of effective FXR activation and mechanisms of FXR activity. The role of co-activators as well as post translational modification of FXR on HCV replication will be studied, in particular the phosphorylation of FXR by PKC or the recruitment of PGC-1alpha. This goal will be achieved with the replicon system previously used for demonstrating the role of FXR on HCV genome replication and the use of activators or inhibitors of kinases. Transfection of PGC-1, native or constitutively active in HCV replication competent cell, concomitantly to activation of FXR by specific ligands will permit to analyze the relative contribution of these two factors. We previously showed that HCV NS5A protein interact with FXR. The interaction of FXR and NS5A domains synthesized in vitro will be analyzed by BiaCore and structural NMR to precisely define the domains involved in this interaction. These observations will be completed by comparing the transcriptome of cells under these conditions and upon FXR activation. These approaches should identify the metabolic pathways modify by HCV and critical for its replication. In addition genome wide screening of viral protein-cellular protein interactions in yeast two hybrid, the I-map program, indicated that HCV targets several key enzymes in the central carbon metabolism. To complete the transcriptome and interaction mapping, metabolic fluxes will be modelised by carbon 13 metabolic NMR.

Finally, these observations could likely be extended to other viruses since many viruses also target enzymes of the central carbon metabolism. Similar modeling of metabolic fluxes will be planned to further extend the pertinence of observation obtained with hepatitis virus.