Probing hepatic lipid pathways for novel host-pathogen interactions and therapeutic targets against the hepatitis C virus.

The hepatitis C virus (HCV) induces alterations in its host cells and hijacks host enzymes and pathways to facilitate its life cycle. We have developed a number of tools for the discovery and characterization of host-pathogen interactions including new methods in activity-based protein profiling and imaging, tools for studying microRNA function, and small molecule probes for investigating lipid metabolism and membrane alterations. In this talk I will describe how these tools have been used to shed new light on HCV host-virus interactions. This includes the identification of changes in enzyme activities during HCV infection in cell culture and in a mouse model for infection. Application of activity-based probes enabled identification of differential enzymatic activity along with the pinpointing of the subcellular localization where these changes are occurring. Additionally, the impact of non-coding RNAs through their regulation of hepatic metabolic pathways in the HCV life cycle will be discussed. We have identified miRNAs modulated by HCV to aid in the virus' hijacking of hepatic lipid metabolism. Lastly, we have discovered a small molecule inhibitor of lipid desaturation that reverses membrane alterations that are induced by HCV and can act as an antiviral agent. Collectively, these studies illustrate how our new methods can be used to uncover the molecular details driving HCV appropriation of hepatic cell systems, and to facilitate the discovery of new biomarkers and potential targets for therapeutic intervention.