Defining the Role of SREBPs in HIV/HCV Co-Infection

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Nearly 1 million people in the US (31 million worldwide) are infected with Human Immunodeficiency Virus (HIV). One quarter of HIV infected individuals in the US are co-infected with Hepatitis C Virus (HCV). Due to advances in HIV treatment, particularly HAART, the lifespan of HIV infected individuals has significantly increased; however, due to increased lifespan, HCV-induced diseases are more likely to progress in co-infected individuals. Chronic HCV infection can result in end-stage liver disease such as liver cirrhosis or cancer, and co-infection with HIV significantly accelerates progression of HCV-associated liver disease. No vaccine for HCV exists, and standard of care therapies can be costly. Moreover, these therapies can be ineffective for most of the common genotypes of HCV found within the US. Treatment of co-infected HIV/HCV individuals can be problematic due to the high costs of therapies and apparent adverse drug interactions between individual treatments. As such, novel therapeutic approaches are required to treat individuals harboring co-infections. HCV and HIV are enveloped viruses that have been associated with changes in host lipid metabolism. The SREBP transcription factors are the master regulators of the lipid homeostatic programs. Thus, we hypothesize that SREBPs would play a critical role in supporting HCV and HIV infection. In support of this notion, we find that genetic loss-of-SREBP activity dramatically attenuates HCV infection. Moreover, SREBP activation appears to be a critical determinant of HIV replication in macrophage cell lines. The studies proposed herein are designed to elucidate the molecular mechanisms by which SREBP activity influences HIV, HCV and HIV/HCV co-infection, and to determine if pharmacologic inhibition of SREBP activity can act as a novel therapeutic target to inhibit HIV, HCV or HIV/HCV co-infection. Furthermore, we will determine if inhibition of SREBP activation can synergize with current treatment modalities for both HIV and HCV to effectively lower the dose required to inhibit disease progression or viral clearance.