MICROBIOLOGIE, INFECTIOLOGIE ET IMMUNOLOGIE

CONFÉRENCE

Dr Selena M. Sagan

Assistant Professor
Department of Microbiology & Immunology
McGill University

Investigating mechanisms governing hepatitis C virus genome stability and viral RNA accumulation

Hepatitis C virus (HCV) is a rapidly increasing global health problem with ~3% of the world population infected. HCV-infected individuals typically develop a persistent infection that leads to chronic hepatitis, cirrhosis, and hepatocellular carcinoma. To date, there is no vaccine available and until recently the standard of care has been IFN-α and ribavirin, although many patients do not benefit from this treatment. It is widely expected that small molecule drugs that target specific viral proteins will replace IFN-based therapies in the future. The approval of two protease inhibitors (2011) and a polymerase inhibitor (2013) were significant milestones in this regard. Although drug discovery efforts have historically focused on viral targets, every stage of the viral life cycle is dependent on the host, which can be explored for antiviral targets. Targeting the host offers numerous potential advantages including a high barrier to resistance, pan-genotypic activity, and a wide range of druggable targets where viral targets are limiting. For HCV, this approach has convincingly been validated by recent successes of cyclophilin inhibitors, which block protein-protein interactions, and the antisense inhibitors miravirsen and RG-101, which block microRNA-viral RNA interactions, important to HCV infection.

In my lab, we study the RNA-RNA and protein-RNA interactions relevant to viral infection. Herein, I will discuss interactions between the highly-abundant, liver-specific microRNA, miR-122, with the HCV genome as well as the interaction between poly-rC binding proteins (PCBPs) and the HCV genome revealed by individual-nucleotide crosslinking immunoprecipitation (iCLIP) analysis. Both miR-122 and PCBP2 interact with the HCV genome and ***promote*** viral RNA accumulation; however, the detailed mechanism(s) remain elusive. We hypothesize that PCBP and miR-122 bind to the HCV genome and form a functional complex that facilitates RNA replication by circularizing the HCV genome. Preliminary mapping revealed six high-confidence PCBP binding sites in the HCV genome, four of which mapped to structural motifs in the genome with annotated roles in the HCV life cycle. We anticipate that mutational analyses combined with assays for viral translation, replication, genome circularization and particle production will reveal the role of PCBPs and/or miR-122 in the HCV life cycle.

Jeudi 11 décembre 2014 à 11h30
Pavillon Claire-McNicoll, Salle Z-210

Invité par Dr Hugo Soudeyns
Tél: (514) 343-6285
Courriel: hugo.soudeyns@umontreal.ca