

SÉMINAIRES ET CONFÉRENCES



Selena M. Sagan

Departments of Microbiology & Immunology and Biochemistry, McGill University

« A moonlighting microRNA: human miR-122-mediated viral RNA accumulation»

Hepatitis C virus (HCV) is a positive-sense RNA virus that interacts with a human liver specific microRNA, termed miR-122. miR-122 binds to two sites in the 5' untranslated region (UTR) of the viral genome and this interaction *promotes* HCV RNA accumulation. This interaction is important for viral RNA accumulation in cell culture, and miR-122 inhibitors have been demonstrated to be efficacious in reducing HCV titers in chronic HCV-infected patients. However, the precise mechanism(s) of miR-122-mediated viral RNA accumulation have remained elusive. We have used biophysical analyses, computational modeling, and assays for viral replication in cell culture to understand interactions between the human Argonaute 2 (hAgo2):miR-122 complex and the HCV genome. In addition, we have analyzed several resistance-associated variants isolated from patients who underwent miR-122 inhibitor-based therapy to shed light onto novel mechanisms of antiviral resistance. Our results provide a new model for miR-122:HCV RNA interactions and demonstrate that miR-122 plays at least three roles in the HCV life cycle: 1) miR-122 acts as an RNA chaperone to suppress an energetically favorable secondary structure (termed SLII^{alt}) and allow the viral internal ribosomal entry site (IRES) to form; 2) miR-122 binding to the 5' terminus protects the 5' triphosphate of the genome from the activity of cellular pyrophosphatases (DOM3Z and DUSP11) and subsequent exonuclease-mediated decay; and 3) the Argonaute (Ago) protein:miR-122 complex at Site 2 appears to make direct contact with the HCV IRES, enhancing viral translation. In addition, analyses of several resistance-associated variants isolated from patients that underwent miR-122 inhibitor-based therapy suggests that mutations in the 5' terminus alter the structure of the HCV 5' UTR in a manner that promotes RNA chaperone activity or viral genome stability, even in the absence of miR-122. Taken together, these findings provide novel insights into the mechanisms of miR-122-mediated viral RNA accumulation. Our analysis of resistance-associated variants suggests several new mechanisms of antiviral resistance mediated by changes in RNA structure. This work thus has implications for the mechanisms of action of miRNAs, and also provides insight into novel mechanisms of resistance to miRNA-based inhibitors that are increasingly entering into the clinic.



Boehringer
Ingelheim



Faculté de médecine
Département de biochimie
et médecine moléculaire



Le lundi 4 novembre 2019, 11h30

Pavillon Roger-Gaudry

Salle : G-415

Pascale Legault

Tél : (514) 343-6372 courriel pascale.legault@umontreal.ca