



Abstract

A Moonlighting microRNA: Mechanism(s) of miR-122-Mediated Viral RNA Accumulation [†]

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Abstract: 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 analysis and assays for viral replication in cell culture to understand the interactions between the human Argonaute 2 (hAgo2):miR-122 complex and the HCV genome. In addition, we have analyzed several resistance-associated variants which were isolated from patients who underwent miR-122 inhibitor-based therapy in order to shed light on 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 and allows the viral internal ribosomal entry site (IRES) to form; (2) miR-122 binding to the 5' terminus protects the genome from the activity of cellular pyrophosphatases (DOM3Z and DUSP11) and subsequent exonuclease-mediated decay; and (3) the Argonaute (Ago) protein at Site 2 makes direct contact with the HCV IRES, enhancing viral translation. In addition, analyses of several resistance-associated variants that were isolated from patients that underwent miR-122 inhibitor-based therapy suggests that mutations in the 5' terminus alter the structure of the 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 insight into the mechanism(s) of miR-122-mediated viral RNA accumulation and suggest new mechanisms of antiviral resistance which are mediated by changes in RNA structure.

Keywords: Hepatitis C virus; Argonaute; miR-122; microRNA; Internal Ribosomal Entry Site; pyrophosphatase



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