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Unravelling the importance of microRNAs during hepatitis C virus infection in the human liver ☆

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Decreased levels of microRNA miR-122 in individuals with hepatitis C responding poorly to interferon therapy. Sarasin-Filipowicz M, Krol J, Markiewicz I, Heim MH, Filipowicz W.

Several microRNAs (miRNAs), including liver-specific miR-122, have been implicated in the control of hepatitis C virus (HCV) RNA replication and its response to interferon (IFN) in human hepatoma cells. Our analysis of liver biopsies from subjects with chronic hepatitis C (CHC) undergoing IFN therapy revealed no correlation of miR-122 expression with viral load and markedly decreased pretreatment miR-122 levels in subjects who had no virological response during later IFN therapy; other investigated miRNAs showed only limited changes. These data have implications for the prospect of targeting miRNAs for CHC therapy.

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Antiviral defense was one of the first elucidated roles played by small non-coding RNAs during RNA silencing processes in plants. The genetic requirements of this response against viruses are now well defined in plants but also in insect organisms [1]. Hence, Dicer or Dicer-like enzymes will recognize the invading viral RNA, or its replication intermediate, to cleave it into small interfering (si) RNAs. These siRNAs are then loaded into the RNA-induced silencing complex (RISC), invariably containing a member of the Argonaute family, which in turn will target the viral genome for degradation. This mechanism does not seem to have been preserved as such in mammals [2], probably due to the development of a more robust innate immune response involving interferon and PKR. Some viruses even take advantage of the cellular machinery to express their own micro (mi) RNAs [3]. However, several studies have shown that miRNAs, an endogenous class of small non-coding RNAs, can to some extent recognize viral transcripts and regulate their expression. The biogenesis of miRNA shares some components of the RNAi machinery [4] (Fig. 1A). Similarly to siRNAs, miRNAs assemble into RISC complexes and guide them on target transcripts mostly by inhibiting translation after imperfect binding in their 3′ UTR. In 2005, a first report described that the primate foamy virus could be negatively regulated by the cellular miRNA miR-32 [5], although it was not clear whether this recognition was fortuitous or played a real role during infection. This initial observation has been confirmed for other viruses, and a definite proof of the antiviral role of cellular miRNAs during viral

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Abbreviations: CHC, chronic hepatitis C; cEVR, complete early virological responder; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IFN, interferon; miRNAs, microRNAs; PKR, protein kinase R; PNR, primary nonresponder; RISC, RNA induced silencing complex; UTR, untranslated region.

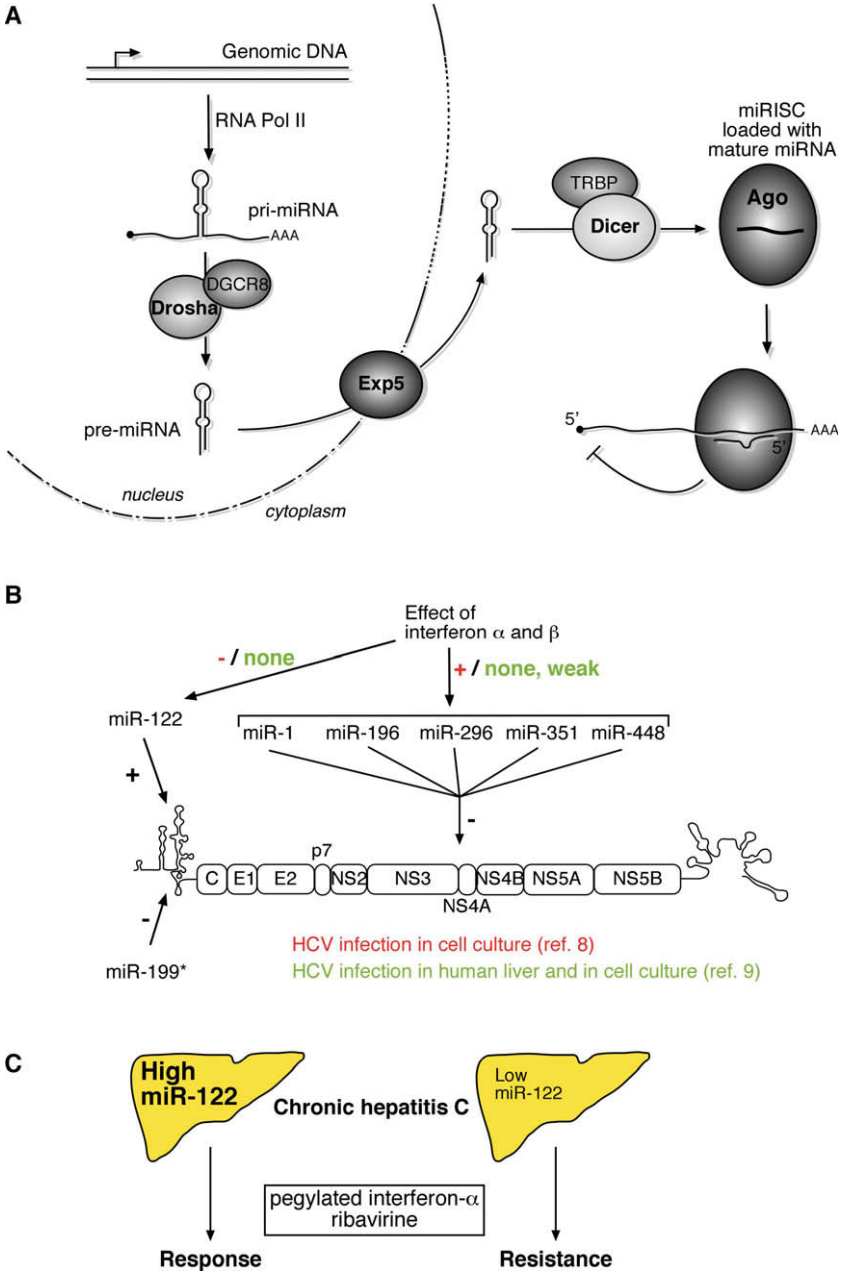

Fig. 1. (A) Simplified model of miRNA biogenesis in animals. Pol, Polymerase; DGCR8, DiGeorge Critical syndrome Region 8; Exp, Exportin; TRBP, Tat-Responsive element Binding Protein; Ago, Argonaute. (B) Summary of known interactions of miRNAs with HCV RNA and the effect of interferon on their expression *in vitro* and *in vivo*. The expression of miR-199* does not seem to be controlled by interferon and is not discussed in this manuscript. Effects of IFN-α and β on miRNAs expression in cell culture models and HCV infection *in vivo* are indicated. (C) Association of liver pretreatment miR-122 levels with outcome of treatment based on pegylated interferon-α and ribavirin in patients with chronic hepatitis C as shown by Sarasin-Filipowicz et al. [9].

infection was shown in a mouse model of vesicular stomatitis virus infection [6].

The relationship between hepatitis C virus (HCV) and the miRNA machinery is more complex. Hence, the first miRNA that was described to interact with HCV, the liver specific miR-122, exerts a positive effect on the virus replication in cell culture after imperfect binding in the viral 5′ UTR [7] (see Fig. 1B). This finding suggested that miR-122 is an important host factor for HCV replication and could at least partly explain why HCV replicates more efficiently in Huh 7 cells compared to other cell lines. Indeed, they are the only liver cell line that express a detectable amount of miR-122 [7]. Conversely, another study has shown that some miRNAs that were induced by interferon (IFN) β could inhibit HCV replication in cell culture [8] (Fig. 1B). In the same