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VIRAL PATHOGENESIS

microRNA rides tandem

A recent study by Sarnow and colleagues showed that a liver-specific miRNA (miR-122) was able to interact with a target sequence in the 5′ noncoding region (NCR) of the hepatitis C virus (HCV) RNA genome and promote viral replication. Now, reporting in *Cell Host & Microbe*, Jopling, Schütz and Sarnow have extended their original findings by showing that miR-122 binds in tandem to two recognition sites. The position of these sites is important for gene expression and viral RNA replication.

MicroRNAs are short oligonucleotides that function by imperfect complementary base pairing to sequences in the 3′ NCR of target mRNAs to cause repression of mRNA expression. The mechanism of downregulation of gene expression remains controversial, but microRNAs are thought to affect both translation initiation and transcript stability.

To address whether the unusual 5′ position for the miR-122 binding site that was observed in the HCV RNA genome was important for stimulating replication, the authors inserted the region of the HCV RNA that contained the miR-122 binding site into either the 5′ or the 3′ NCR of a luciferase reporter that was expressed in liver cells. In a 3′ NCR position, the miR-122 site repressed gene expression, as shown by an increase in translation following miR-122 disruption, whereas in the 5′ NCR, the site had no effect, confirming that its function was position dependent. Surprisingly, mutation of the binding site did not completely knock out the sensitivity of the reporter to miR-122 disruption, which resulted in the identification of a second novel miR-122 site in the HCV RNA that was only 14 bp from the first identified miR-122 site.

Binding of miR-122 to both sites in the 5′ NCR of HCV was required to increase HCV genome replication. Interestingly, the sequence between the two miR-122 binding sites was conserved between different HCV genotypes and linker disruption also had a deleterious effect on HCV RNA replication, which indicated that the spacing of the miR-122 sites may be important. Therefore, unlike the general repressive role of miR-122 on liver target genes, miR-122 bound to 5′ NCR tandem sites stimulates genome replication in HCV. It will be interesting to see whether other organisms have adopted a similar position-dependent use of tandem microRNA binding sites.

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ORIGINAL RESEARCH PAPER Jopling, C. L., Schütz, S. & Sarnow, P. Position-dependent function for a tandem microRNA miR-122-binding site located in the hepatitis C virus RNA genome. *Cell Host Microbe* **4**, 77–85 (2008)
FURTHER READING Jopling, C. L. *et al.* Modulation of hepatitis C virus RNA abundance by a liver-specific microRNA. *Science* **309**, 1577–1581 (2005)