ANTIVIRALS

MicroRNA versus virus: uncovering new layers of complexity

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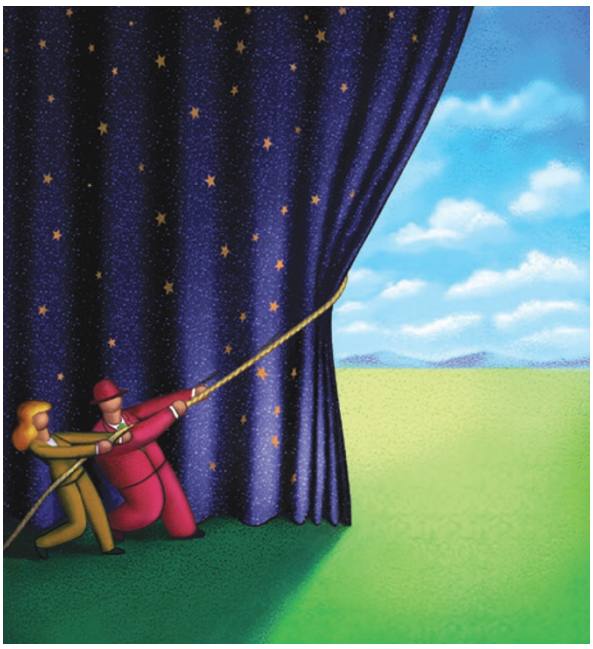
MicroRNAs (miRNAs) are a class of small non-coding RNAs that have been shown to play a role in the antiviral defence of plants and invertebrates. Now, two papers demonstrate that specific miRNAs also take part in the battle of the human immune system with two important viruses. Specific interferon (IFN)-induced miRNAs are highly active against hepatitis C virus (HCV), and the human immunodeficiency virus (HIV) is even one step ahead — using cellular miRNAs to maintain a reservoir of latently infected cells.

In mammals, over 500 different miRNAs have been identified. On the basis of homology, miRNAs can bind to mRNAs and either induce mRNA degradation or inhibit their translation (a process termed RNA interference). The role of antiviral miRNAs in lower organisms has been well described; however, in mammals, it was thought that the powerful IFN system may have displaced the miRNA-mediated mechanisms of RNA interference. Reporting in *Nature*, Pedersen and colleagues show that miRNAs can play a role in mammalian antiviral defence against HCV, and can in fact be induced by the IFN system.



The authors carried out microarray analysis of IFN-stimulated cells, and identified several miRNAs that were specifically upregulated or downregulated on IFN-α/β or IFN-γ exposure. By sequence complementarity analysis, the seed sequences of eight IFN-β-regulated miRNAs were found to have nearly perfect matches in the HCV RNA genome. Five of these were shown to actively inhibit HCV replication, and a corresponding mix of synthetic miRNA mimics downregulated viral mRNA levels by 80%. Conversely, transfection with corresponding antisense inhibitors attenuated the antiviral effect of IFN-β exposure to 75%. Furthermore, one miRNA (miR-122) that had previously been shown to play a positive role in HCV replication, was shown to be specifically downregulated by IFN-β. Adding a mimic of miR-122 to the mix of antisense inhibitors reduced the antiviral effect of IFN-β to 50%, showing that miRNAs have an important, albeit not exclusive, role in the antiviral effects of IFN-β. These findings add a new layer of complexity to mammalian host defence mechanisms, and add a new component to the arsenal used by IFNs.

Meanwhile, reporting in *Nature Medicine*, Huang and colleagues demonstrate that HIV uses miRNA-mediated downregulation of viral protein expression to its own advantage. 'Latently infected' resting $CD4^+$ T-cells, which have HIV stably integrated into their genome but do not produce any viral proteins, cannot be eliminated by the immune system or targeted by any existing anti-HIV drugs, but can rekindle the infection at any time. The authors show that a particular cluster of cellular miRNAs is enriched in resting $CD4^+$ T-cells, and that almost all spliced and unspliced HIV mRNAs contain the sequence targeted by these miRNAs. Inhibition of these miRNAs in resting T-cells, derived from HIV patients on highly active antiretroviral therapy, increased HIV protein expression, suggesting that HIV recruits the resting-cell-enriched miRNAs to control the translation of viral mRNA into protein. Therefore, strategies based on antisense miRNA constructs might purge the latent reservoir and perhaps transform HIV infection into a curable disease.

Although many obstacles remain (for example, the challenge of achieving 100% targeting of all latently infected cells in HIV infections), miRNA-mimics and miRNA antisense constructs could hold promise for the design of a new generation of antiviral drugs.

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ORIGINAL RESEARCH PAPERS Pedersen, I. *et al.* Interferon modulation of cellular microRNAs as an antiviral mechanism. *Nature* **449**, 919–922 (2007) | Huang, J. *et al.* Cellular microRNAs contribute to HIV-1 latency in resting primary $CD4^+$ T lymphocytes. *Nature Med.* **13**, 1241–1247 (2007)