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miR-122, *IL28B* genotype and the response to interferon in chronic hepatitis C virus infection

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In a recent article (25 years of interferon-based treatment of chronic hepatitis C: an epoch coming to an end. *Nature Rev. Immunol.* **13**, 535–542 (2013))[1], Markus Heim reviewed the 25-year history of therapies for hepatitis C virus (HCV) infection and introduced some new pharmaceutical agents that target cellular proteins and the microRNA miR-122. The author also described an association between a polymorphism in interleukin-28B (*IL28B*; also known as *IFNL3*) and the response to interferon-α (IFNα) treatment, but he did not review the molecular mechanisms that link genetic variation in the *IL28B* gene locus to the response to IFNα[1]. We would like to highlight a possible link between miR-122, the *IL28B* gene polymorphism and the response to IFNα treatment.

Janssen *et al.*[2] recently reported a Phase IIa clinical study of miR-122-targeted therapy (miravirsen), which showed that the use of miravirsen in patients with chronic HCV genotype 1 infection leads to a prolonged dose-dependent reduction in HCV RNA levels and no signs of viral resistance. miR-122 is a highly abundant microRNA that is expressed in the liver and is essential for the stability and propagation of HCV RNA[3]. Recently, a report has shown that pretreatment levels of miR-122 are predictive of the response to IFN and that miR-122 levels might be related to the *IL28B* genotype[4]. Su *et al.*[4] reported that serum levels of miR-122 can be used as a surrogate marker of hepatic levels of miR-122 and that serum levels of miR-122 positively correlated with hepatic necroinflammation. Patients who showed a complete early and sustained response to treatment had significantly higher serum levels of miR-122 before treatment compared with patients who had no response; in particular, a strong response to treatment was shown by patients who were infected with HCV genotype 2 and had the *IL28B* rs8099917 TT genotype. Su *et al.*[4] also showed that patients with the *IL28B* TT genotype had significantly better treatment responses and higher serum levels of miR-122 before treatment compared with those with the *IL28B* GT or GG genotypes[4].

Therefore, the *IL28B* genotype-dependent variation in levels of miR-122 in serum could be one of the molecular mechanisms that links genotype to the response to IFNα[5]. This might be through a recently discovered mechanism by which IFNα-induced cytosolic 5′ nucleotidase 3 (*NT5C3*) mRNA reduces miR-122 levels by sequestration, a process that is reversible by transduction with small interfering RNA that targets *NT5C3*. This mechanism links genotypes associated with an activated endogenous IFN system to a poor response to IFNα treatment[6]. Furthermore, the *IL28B* TT genotype is associated with the upregulation of expression of the IFNα receptor α-chain, and it is possible that the increased action of endogenous IFNα might also enhance the degradation of the anti-HCV microRNA let-7b through the same NT5C3 mRNA-dependent mechanism. This reduction in let-7b levels could compromise the action of exogenous IFNα, which is known to act synergistically with let-7b[7]. Therefore, in this context, it is possible that miR-122 levels are just a correlate of let-7b levels and that the regulation of let7b, and not miR-122, determines the response to exogenous IFNα. Because miR-122 acts as a tumour suppressor for hepatocellular carcinoma[8], attention needs to be paid to the long-term outcome of treatment with suppressors of miR-122.

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Competing interests statement
The authors declare no competing interests.