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

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In their response to my Review 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], Jae Il Shin and Michael Eisenhut (miR-122, *IL28B* genotype and the response to interferon in chronic hepatitis C virus infection. *Nature Rev. Immunol.* http://dx.doi.org/nri3463-c1 (2013))[2] highlight a possible link between the microRNA miR-122, the interleukin-28B (*IL28B*; also known as *IFNL3*) genotype and the response to interferon-α (IFNα) treatment in patients with chronic hepatitis C virus infection.

Indeed, we previously reported the association between miR-122 expression and the response to treatment[3], which was recently confirmed by Su *et al.*[4]. Patients with normal miR-122 expression levels are significantly more likely to have a sustained virological response to treatment with pegylated IFNα and ribavirin, whereas low miR-122 expression levels are associated with no virological response[3]. As described in detail in the recent Review article[1], several groups have reported that patients with induced expression of IFN-stimulated genes (ISGs) in the liver, as measured in pretreatment biopsy samples, are poor responders to pegylated IFNα and ribavirin[5–7]. The link between high ISG expression and low miR-122 expression has been elusive, but the recent paper by Hao *et al.*[8] showing that miR-122 could be sequestered by binding to the 3′ untranslated region of the mRNA encoding cytosolic 5′ nucleotidase 3 (NT5C3), a classical ISG, indeed provides a potential explanation that should be explored more quantitatively in human liver biopsy samples.

Also, several groups have reported a significant association between the *IL28B* genotype and the expression of ISGs in liver biopsy samples taken before treatment[9–11]. However, the molecular mechanisms that are responsible for ISG induction in patients with minor alleles of the *IL28B* gene locus are unknown.

Taken together, the significant associations between *IL28B* genotype, hepatic ISG expression and hepatic miR-122 expression are now firmly established. However, the molecular mechanisms underlying these statistical associations remain to be uncovered, and they continue to be a central question and formidable challenge in this research field.

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Competing interests statement
The author declares no competing interests.