Reviewer’s report

Title: Hepatic microRNA expression is associated with the response to interferon treatment of chronic hepatitis C

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Reviewer: Patrice Morin

Reviewer’s report:

In this manuscript, Murakami study miRNA expression in liver biopsy specimens from patients with chronic hepatitis C and examine the possibility that miRNA patterns may be associated with the response to standard therapy (pegylated interferon and ribavirin). They use a miRNA microarray to identify several miRNAs that are associated with different therapeutic outcome. For example, they identify 9 miRNAs that are significantly different between patients that exhibit sustained virological response compared to the non-responders. They also examine miRNA that are associated with rapid or early response to therapy. The patterns of 3 miRNAs are validated by RT-PCR. Using a Monte Carlo cross validation approach they identify a set of prognostic miRNAs that may be able to predict drug response. They identify sets of miRNAs that can predict sustained viral response with specificity and sensitivity of 63% and 77%, respectively. The authors conclude that their method may be used for predicting drug response before the administration of therapy thereby reducing ineffective treatment.

This is an interesting manuscript, although somewhat preliminary due to the number of patients and relatively low number of miRNAs profiled (as compared to current databases). The miRNAs identified may be functionally relevant to the molecular mechanisms associated with the drug response of patients with chronic hepatitis C. It is unclear however whether the proposed miRNA-based predictive test can be of practical value.

*Major Compulsory Revisions

1) The authors mention that they chose to analyze miRNAs that were expressed in at least 70% of the samples. The rationale behind this cutoff is not explained. Would they have different candidates if a different cutoff had been chosen?

2) The RT-PCR validation is extremely limited. The authors mention that the miRNAs with the smallest fold difference were investigated. The authors should investigate additional miRNAs by RT-PCR to more convincingly validate the array results.

3) The authors conclude that the Monte Carlo cross validation suggests a prediction algorithm for therapy outcome and that they may be useful clinically. However, there is very little discussion of this and it is unclear how the prediction may be useful. First of all the relatively low specificity and sensitivity would lead to an unacceptable number of patients misclassified. In addition, even if the
outcome could be predicted accurately, what are the alternatives to current therapy that may work better in non-responders?

*Minor Essential Revisions

4) The abbreviations in Figure 1 are not explained in the legend.

5) The array used only contained 470 miRNAs. There are 940 human miRNAs in the current version of miRBase (release 15), exactly half of what the authors investigated. They should specify the exact microarray they used and discussed the fact that they may be missing important targets.

6) The English needs to be proofread and corrected.

*Discretionary Revisions

7) Figure 2 shows miRNAs that have been identified as differentially expressed. It might have been useful to show a heatmap that shows the clustered data for all the miRNAs (as a supplementary figure, perhaps?)

8) To prove the idea that the miRNAs affect many targets involved in immune regulation (as suggested in supp tables), it may have been useful to investigate these targets by immunoblotting.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests