Department of Oncology and Pathology
Cancer Center Karolinska
Karolinska University Hospital
2017-12-07

Dear Editor,

With this letter we would like to submit our manuscript entitled "An antisense RNA capable of modulating the expression of the tumor suppressor microRNA-34a" for consideration for publication in eLife as a Research Article within the topic of Cancer Biology. The manuscript has been previously submitted to bioRxiv with the MS ID# BIORXIV/2017/234310.

The micro-RNA34a (miR34a) is a well-known tumor suppressor that is a direct downstream target of TP53 and is often dysregulated in human cancers. Nevertheless, little is known concerning additional factors regulating this locus. In this manuscript we demonstrate the ability of an antisense long non-coding RNA to positively regulate miR34a expression in both a TP53 wild type and deficient background. In addition, we find that antisense-mediated up-regulation of miR34a is sufficient to cause miR34a induction and, thus, a decrease in oncogenic phenotypes in response to several types of cellular stress stimuli. Finally, this study provides a rare example of an antisense RNA capable of regulating a cancer-associated micro-RNA thus expanding the repertoire of regulatory targets for long non-coding RNAs in cancer. With this study we have chosen to forfeit a detailed investigation of the mechanism by which this antisense RNA operates in favor of being able to elucidate its function from a more in-depth and broader perspective. We believe these findings to be of equally high interest to members of the scientific community studying the underlying regulatory mechanisms of oncogenic phenotypes and cellular stress response, as well as those interested in the regulatory roles of long non-coding RNAs in cancer.

One of the reasons for choosing to first submit this manuscript to eLife is due to the journals commitment towards transparency and reproducibility, as we believe these attributes to be of the utmost importance to the integrity of scientific research. In addition, eLife has previously published the only other report involving characterization of an antisense RNA originating from the miR34a locus (Wang et al., 2016). We therefore believe that the journal may be pleased to continue reporting concerning this evolving story.

To facilitate the transparency and reproducibility of the data and analysis associated with this article we provide a supplementary R package, hosted on Github, that allows users to a) gain access to all utilized underlying data, b) easily replicate the package versions and environment in which the analysis was performed, c) regenerate all figures from the manuscript in real time starting from the raw data, and d) easily review all code used for each analysis.

In summary, we believe the information included in this work to be essential to the further understanding of mechanisms underlying the regulation of the tumor suppressor miR34a with significant insight concerning situations where a loss of TP53 has occurred.

Sincerely,
Jason Serviss, Felix Richter, Jimmy Van Den Eynden, Nathanael Andrews, Miranda Houtman, Laura Schwarzmuller, Per Johnsson, Erik Larsson, Dan Grandér, and Katja Pokrovskaia Tamm