Reviewer's report

Title: Smoking Status Impacts microRNA Mediated Prognosis and Lung Adenocarcinoma Biology

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Reviewer: Jeremias Wohlschlaeger

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Review Vucic EA et al.: Smoking Status Impacts microRNA Mediated Prognosis and Lung Adenocarcinoma Biology

Vucic and her co-workers report on a study in which they study miRNA expression in fresh frozen tissue from pulmonary adenocarcinoma and in non-tumorous tissue by whole transcriptome sequencing in three different groups: current (CS) and former (FS) as well as never smokers (NS). Their data reveal that miRNAs are differentially expressed in non-malignant vs carcinoma, and even more interesting, that miRNA expression patterns are irreversibly altered in former smokers. Since the role of disrupted miRNA expression in the pathogenesis has been well described in the past, this offers an explanation for the occurrence of lung carcinoma in individuals many years after cessation of smoking. In addition, they authors were able to define sets of miRNA specific for the given smoking status. Finally, the authors show how smoking status specific disrupted miRNA expression affects genes relevant in the pathogenesis of pulmonary adenocarcinoma. miRNAs were also found to be associated with the clinical outcome.

This study brings interesting and possibly clinically relevant information regarding the miRNA expression in the pathogenesis of pulmonary adenocarcinoma taking into account the smoking status of a given patient; in my opinion this a novel approach that not only increases the understanding of the role of miRNA biology in cancer, but also might offer new therapeutic approaches and, even more appealing, a potential screening method to monitor the individual risk of current and former smokers.

The abstract is a clear summary of the manuscript; the introduction is focused; the methodology is sound and well explained; the results are clearly presented and illustrated; the discussion is appropriate; the bibliography is adequate.

I have only some minor comments/discretionary revisions:

1. The number of cases studies is relatively small; however, this has already been stated in the manuscript as a limitation of the study.

2. I would like the authors to speculate more about the possible future role of miRNAs concerning screening methods or therapeutic approaches in the discussion. Could these tests also been done from blood samples or
bronchopulmonary washings?

3. Only adenocarcinoma has been studied so far. This is clearly the most important and prevalent subtype of lung cancer, but similar studies could be performed in squamous as well as small (SCLC) and large cell carcinomas (LCNEC).

After the authors made some complements in the discussion on the comments I can clearly recommend this manuscript for publication.

**Level of interest:** An article of outstanding merit and interest in its field

**Quality of written English:** Acceptable

**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.