Reviewer’s report

Title: Indirubin inhibits Wnt/β-catenin signal pathway via promoter demethylation of WIF-1

Version: 4 Date: 01 Jul 2020

Reviewer’s report:

The authors very much improved the manuscript concerning indirubin that inhibits Wnt/beta-catenin signal pathway via promoter demethylation of WIF-1. However, there is still one problem concerning the HaCaT cell line. Balato A et al showed that in HaCaT cells, TNF-α was able to induce IL-6, MCP-1 and VEGF, and the addition of IL-33 reinforced these increases. TNF-α + IL-33 combination showed similar results in primary KCs and ex vivo skin organ culture. This means that after the stimulation HaCaT cells became a model for psoriasis like keratinocytes. However as the focus is no longer on psoriasis in the paper this point is not relevant anymore.

However, I have still the note that HaCaT cells cannot be ordered by ATCC. ATCC has only primary epidermal keratinocytes; Normal, Human, Adult (HEKa) (ATCC® PCS-200-011™). And Cell lines services (CLS) sell HaCaT cells (https://www.clsghmb.de/p800_HaCaT.html). I know that in some publications it is mentioned that the HaCaT cells are obtained from ATCC but this is nevertheless wrong. Therefore, it should be corrected.

It is also good to delete the sentence concerning the passage number of HaCaT cells, because the earliest passage of HaCaT cells that can be bought from CLS are passage 38.

Publons Reviewer Recognition. Springer Nature can send verification of this review directly to Publons (a subsidiary of Clarivate Analytics). If you would like to take advantage of this service, please click on the “Yes” option below. Your name, email address, title of the reviewed manuscript, name of the journal, and date of your review submission (the “Review Data”) will then be transmitted to Publons upon publication of the manuscript. If you have already registered at Publons, they will notify you of the receipt of this review and update your profile as per your settings and their policy. If you are not registered with Publons, you will receive an email from them asking you to register in order for them to be able to recognize your review on your new profile page. Publons may use the Review Data to generate derivative metadata for the benefit of Publons and you as a reviewer, carefully considering the sensitivity of such information. For example, Publons may verify your record as a reviewer by updating your profile published on its webservice if you have registered for such service or help editors to identify candidate reviewers. Please find the details of processing in Publons’ privacy policy https://publons.com/about/terms

No

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.
Yes

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Yes

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

Yes

**Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?**
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

**Quality of written English**
Please indicate the quality of language in the manuscript:

Acceptable

**Declaration of competing interests**
Please complete a declaration of competing interests, considering the following questions:

1. Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

2. Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

3. Do you hold or are you currently applying for any patents relating to the content of the manuscript?

4. Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript?

5. Do you have any other financial competing interests?

6. Do you have any non-financial competing interests in relation to this paper?

If you can answer no to all of the above, write 'I declare that I have no competing interests' below. If your reply is yes to any, please give details below.
'I declare that I have no competing interests'

**Reviewer Publication Consent.** I agree for my report to be made available under an Open Access Creative Commons CC-BY License (http://creativecommons.org/licenses/by/4.0) if this manuscript is accepted for publication. Any comments that I do not wish to be included in the published report have been included as confidential comments to the editor, which will not be published. If you are not happy for us to publish this report, please contact the editorial office before completing the review. If you wish, you can include your name in your published report. Please note you must decide whether to include your name at the start of the process and confirm this decision whenever prompted. If you change your decision later, we will not be able to publish your name.

I agree to the terms of the CC-BY 4.0 license; please **do not** publish my name with my report. (default)