Reviewer's report

Title: Alterations in the Glycome after HDAC Inhibition Impact Oncogenic Potential in Epigenetically Plastic SW13 Cells

Version: 0 Date: 20 Aug 2018

Reviewer: Gwang Hyeon Eom

Reviewer's report:

Montgomery MR and Hull EE reported the novel findings though manuscript entitled "Alterations in the glycome after HDAC inhibition impact oncogenic potential in epigenetically plastic SW13 cells" The authors treated highly HDAC1-selective HDAC inhibitor, romidepsin, on SW13 cells. 1nM of romidepsin significantly induced the cells into invasive phenotype, which was well correlated with previous report by same group (Davis MR et al., 2016 BMC Cancer, PMID: 27188282). The authors screened the epigenetic changes in response to romidepsin in SW13 cells and the authors suggested an alteration of glycome profiles through high throughput array. The study was well organized and nicely structured. The findings were interesting and somewhat informative. Large parts of the study, however, are lack of scientific rationale. Furthermore, the authors have failed to clarify the detailed mechanism which target enzyme(s) is(are) associated with acquired-phenotypes in response to romidepsin. The reviewer has raised several fundamental questions to be answered.

Major points

1. Large part of the current study has overlapped with previous report (Davis MR et al., 2016 BMC Cancer, PMID: 27188282). The novelty of current version of study is only 'romidepsin-induced glycomes'.

2. Why the authors have focused on the alteration of glycome? Basically, romidepsin is selective HDAC1 inhibitor, which means that the primary and direct effect of romidepsin in not the alteration of glycome but acetylome.

3. Romidepsin affected transcription activity of certain promoter rather than directly induced acetylation of non-histone targets. This means that another HDAC inhibitors, such as apicidin (class I selective HDAC inhibitor), trichostatin A (pan-HDAC inhibitor), or valproic acid (pan-HDAC inhibitor), also showed similar effects. More specifically the authors should present HDAC1 knock-down (siRNA or shRNA) or knock-out effect, simultaneously.
4. The array data should be quantified. The authors failed to demonstrate constant result of lectin-binding study throughout Fig 3 to Fig 4.

5. Nonetheless, the authors should delineate specific mechanism for romidepsin-induced glycosylation. What is the master regulator of glycosylation? And which glycosyl-protein(s) play(s) crucial role in phenotypic switch?

6. In Fig 5, the authors suggested that pre-treatment of romidepsin allows resistant against paclitaxel. Throughout the manuscript, the reviewer could catch the message arisen from the authors. If the authors would like to conclude that the mechanism of chemotherapy-resistance by HDAC inhibition is due to glycosylation, prove it. Pick the candidate(s) suggested in the table 1 and table 2, and test knock-down effect one by one.

Minor points

1. Could the authors quantify the results in Fig 1B and Fig 1C? Cropped-images sometimes represent exaggeration.

2. Scale bars are missing in Fig 1.

3. In Fig 2, input control should be delineated in Y axis.

4. The description of figures would be alphabetical order. Why the authors explain Fig 3B earlier than Fig 3A in the main text?

5. FITC-conjugation experiments in Fig 4 failed to present detailed mechanism. Instead, quantification experiments allow more precise information.

6. The results from lectin binding array are very important among the whole study. However, descriptions are too minute. Detailed writing is required.

7. In lane 262 and 264, "Figure 3" should be "Figure 2".

8. In lane 272, "FKK28" should be "FK228".

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

No
**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.

No

**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

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