

Peer Review File

Article information: <https://dx.doi.org/10.21037/atm-23-1806>

Reviewer A

In the manuscript titled “Potential role of short-chain fatty acids in the pathogenesis and management of acute lymphocytic leukemia”, Dr Song and Gyarmati reviewed the current literature about the role of microbiota and their metabolite in the HDAC function in the context of ALL.

The authors nicely and effectively toned the background and raised the subject issue. However, when they just entered the main subject of the manuscript i.e role of short chain fatty acid in the pathogenesis and management of ALL, authors ended the manuscript. By seeing the title, readers would expect details of literature, interpretation, hypothesis, and new perspectives with few or more illustrations about how short chains fatty acid are/might be involved in pathogenesis and management of ALL. It is disappointing that the nicely built manuscript was abruptly ended without discussing the main topics thoroughly.

I suggest first completing the story with few illustrations according to the title.

Reply: It is indeed a valid point, and it is partly due to the novelty of the issue and the lack of available data. However, we added an explanatory figure (Figure 1) to better visualize the subject of the review (Lines 384-395). We also added an additional paragraph to extend upon the clinical use of SCFAs in hematological malignancies (Lines 219-226).

Reviewer B

A review article of Peter Gyarmati and Yajing Song, discusses the effects of short-chain fatty acids on acute lymphocytic leukemia.

The topic of the paper is interesting; however the presented content is quite generic, and also the manuscript does not meet the formula of the review paper very well.

Comments to be considered:

Figures and tables should be added to better visualize the presented information.

Reply: We have added a figure (Figure 1) to better visualize and explain the topic of the review (lines 384-395).

The authors did not focus on clinical trials.

Reply: We added a paragraph (lines 219-226) to describe the available clinical trials in hematological malignancies using SCFAs.

Sometimes the authors just cite the articles without presenting their content in the text, or they do it minimally e.g. paragraph “HDAC studies in ALL – last sentence 39-43 (please correct, very generic information).

Reply: Citations 39-43 refer to the methodological challenges described in the paragraph. The authors thought it was important to emphasize that while we are describing studies and comparing results, there can be considerable differences in the methodology applied in the various works. In accordance with this statement, we tried to highlight the major characteristics of each study (e.g., while both can provide valuable findings, a whole genome RNA-seq will result in a different set of interpretable data than a 2-probe microarray).

Presenting epigenetic agents the authors can support with: 10.1177/20406207231173485, doi: 10.1016/j.drudis.2011.05.012, doi: doi: 10.3389/fonc.2022.874645, doi: 10.3390/cells9122721, and others.

Reply: While lymphomas and AML have a broader literature available regarding epigenetic modifications, our goal was to focus on ALL and the potential applications of epidrugs in this disease.

Part of the information given in text (the characteristic of HDACs) can be moved to the table. It would allow to show the inhibitors specificity.

Reply: A line has been added to direct the readers to a comprehensive review on receptor specificity of HDACs (lines 78-79). Our aim was to provide an ALL-specific view of HDAC inhibitors.