Reviewer's report

Title: Dissecting the signaling pathways associated with the oncogenic activity of MLK3 P252H mutation

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Reviewer: Tamara Tanos

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“Dissecting the signaling pathways associated with the oncogenic activity of MLK3 P252H mutation”

In this article, after finding several gene regulation by microarray the authors do not go further to explore the functionality of their findings. However it could add to the oncological and signaling field by suggesting new candidates regulated by MLK3

There are few items I would like to see clarified before suggesting to accept the article

1-When the authors mention in the background:

“In particular, mutation P252H, located in the kinase domain, was found to have a strong transforming potential, and to promote the growth of highly invasive tumors when subcutaneously XXX injected in nude mice.”

What type of cells they are referring to?

2-regarding the assay, It is surprising to see that the authors use such a transformed cell line as HEK293 instead of gastrointestinal cell lines. Later on, they address this issue by claiming that MAPKs proteins are frequently mutated in gastric cancers.

Minor revision: However, How do they know that they are not in HEK 293 cells? Did they check for that? It is already known?

3-It would be interesting to observe the regulation of several of their candidate MLK3 regulated genes in a panel of gastrointestinal cell lines.

Major Compulsory Revision: It would be important to validate their findings in several gastric cell lines by qCPRs.

Minor revision: if possible, also to check protein levels.

Minor revision: if possible It would be very interesting to observe some functional assays (invasion assays for example) with cells transfected with their MLK3 constructs.

4-I do not agree with the comment from authors claiming that
“Our results showed that mutant MLK3 exerts its oncogenic effects by deregulating several important colorectal cancer- associated signaling pathways such as WNT, MAPK, NOTCH, TGF-β and P53.”

Major Compulsory Revision: The authors should rephrase it and stick to their results, this statement is very strong. It is not possible to get such a conclusion from the data that authors provide performed in HEK293 cells and with the lack of in vivo validation.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:

'I declare that I have no competing interests’