Reviewer’s report

Title: Attenuated expression of histamine receptor H4 in colorectal cancers: a potential correlation with histamine-mediated tumor growth

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Reviewer: Paul Bryce

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“Attenuated expression of histamine receptor H4 in colorectal cancers: a potential correlation with histamine-mediated tumor growth” by Fang et al. aims to explore the relationship between histamine effects, particularly via HRH4, and colorectal tumors.

They do this using initially simple screening of a fairly sizable cohort of biopsies from tumors in various grades but the quickly move into cell lines for subsequent mechanistic questions.

General Comments:

This work is largely supportive of some previous studies that have examined histamine and histamine receptors in tumor development and progression. The experiments in this manuscript are performed reasonably well but the manuscript suffers somewhat from a lack of direction and focus. The “aim” set out in the abstract (“to evaluate the clinical and molecular phenotypes of colorectal tumors with abnormal HRH4 expression”) is not really the bulk of this study and, instead it seems to be more focused on the regulation of cell lines by HRH4 and histamine. As such, extensive rewriting is needed to make this manuscript more balanced between what is being shown versus the conclusions.

Major Compulsory Revisions:

The title and abstract must be revised to reflect the fact that most of the data being presented is derived from overexpression systems and less from the colorectal cancer dataset. As it stands, I feel the title and abstract are somewhat misleading.

The previous work by Boer et al., showing decreased expression of HRH4 in colorectal tissues, also reported a reduction in HRH1. Is this true of this biopsy dataset?

While the protein is reduced by Western Blot on whole tissue extracts, it would be important to see immunohistochemistry to determine specific localization in the tissues. Since most colorectal tissue contains inflammatory and structural cells in or around the tumor tissue that will be extracted also during the biopsy, this could be an alternative source of the differences than the tumor cells themselves.
Overexpression of HRH4 could alter the expression of the other histamine receptors (including HRH3). This needs to be determined in order to determine the specificity of the effects of histamine and clozapine.

That the cAMP effects are not via PKA is somewhat surprising since this kinase has been previously described as important for mediating the effects of signals via HRH4. The only known alternative pathway would be via EPAC. Are changes in EPAC observed?

Minor Essential Revisions
None

Level of interest: An article whose findings are important to those with closely related research interests

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