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: Elke Schneider

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In this paper Fang et al. report that histamine H4R activation inhibits proliferation of colorectal cancer by blocking the cell cycle in G0/G1. However, the expression of this receptor is downregulated in these tumor cells, which is the reason why the H4R gene has to be transfected to see this growth-inhibiting effect. This is why the work is of minor interest in terms of therapeutic potential, even though technically speaking it is quite well performed.

Major Compulsory Revisions:
1. The authors ascribe the downregulation of H4R expression to increased histamine production associated with cancerogenesis, but instead of proving this statement in their model they refer only to the literature. Histamine production or HDC activity should be measured in these cells. Would an inhibitor of HDC like #-FMH increase H4R expression in CRC samples?
2. If histamine is actually produced and secreted by these cells, how do the authors explain the effect of exogenous histamine? Is histamine production diminished after transfection of the H4R gene?

Minor Essential Revisions:
1. 10 mg/ml of 5-FU seems a very high dose for so little effect on apoptosis, especially for a drug that is currently used for this type of cancer. Is this a spelling error?
2. Figure legends are not very clear, especially fig. 4 panel C (Fig. 4B instead of 5A?) and Fig. 5 B and C (3 instead of C).
2. The designation of the proliferation assay is not homogenous (colonogenic or colony-forming assay)?
3. There are a number of spelling errors like "whose characteristics of which" on page 5 and "more lower" on page 12.
4. The discussion is not really to the point.

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

Quality of written English: Needs some language corrections before being published
**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.