Reviewer's report

Title: High class I HDAC activity and expression are associated with RelA/p65 activation in pancreatic cancer in vitro and in vivo.

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Reviewer: Krishna P. Bhat

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The manuscript by Lehmann et al. titled "High Class..................in vivo" describes the observation that HDAC expression correlates with nuclear p65 expression in pancreatic cancer. Furthermore in pancreatic tumor cells treated with HDAC inhibitors, the nuclear p65 levels and activity were reduced. Although the data presented in this manuscript is interesting, it lacks mechanistic insights into HDAC regulation of RelA.

Major points:

1) Previous studies by Miyake et al. (Pancreas 2008) has shown HDAC1 as a prognostic marker in pancreatic cancer, but the authors fail to observe similar effect in their tissues.

2) The case for pursuing HDAC inhibition as a strategy because it inhibits NF-kappaB activity is not compelling. First, the authors claim that HDAC in addition to altering histones have been shown to deacetylate other non-histone proteins such as p53, NF-kB. Going by the literature, the acetylation of RelA is an important post-translational modification that marks it for phosphorylation and increased nuclear accumulation. If HDAC deactylates RelA, the assumption is that it leads to inactivation. Thus treating cells with HDAC inhibitor should augment RelA activity, rather the authors show the opposite. So, the effect that they observe is indirect.

3) VPA or SAHA both inhibit most forms of HDAC, then why is the effect of VPA not statistically significant whereas SAHA did? This clearly implies HDAC inhibition alone is insufficient to reverse RelA activity.

Minor points:

1) Page 3, line 6 change "aminoterminal" to "amino terminal"

2) Figure 2B, a bar graph comparing the %nuclear versus cytoplasmic RelA may be needed. As is, only three cells show cytoplasmic retention of RelA in VPA treated cells compared to majority that are in the nucleus. The authors should also consider adding a DAPI stain to clearly show nuclear staining.

Level of interest: An article of limited interest
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'