Reviewer's report

Title: Genomic Pathway Analysis Reveals that EZH2 and HDAC4 Represent Mutually Exclusive Epigenetic Pathways Across Human Cancers

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Reviewer: Patrick Tan

Reviewer's report:

This study by Cohen and colleagues reports an analysis of epigenetic gene signatures in numerous tumor types. The authors report the creation of gene signatures associated with EZH2, HDAC1, HDAC4, SIRT1 and DNMT2 activity, and tumor types/subtypes that show different pathway activities. They find that EZH2 and HDAC4 activities are exclusive to one another.

Major Comments:

1) What is the rationale for the 18 hour timepoint for harvesting cells post retrovirus infection? It would be good to provide some statement that this is appropriate for capturing early gene expression changes.

2) It would be interesting to find out the extent to which the HMEC-derived signatures are preserved in tumor types of other organs, eg GBMs. Was there a stronger overlap of the HMEC signatures in the breast cancers compared to other tumor types?

3) Were tumors exhibiting high levels of EZH2 or HDAC4 activity associated with differences in clinical prognosis?

Level of interest: An article of outstanding merit and interest 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:

No competing interests