Reviewer's report

Title: Adenosine A2b Receptor Promotes Progression of Human Oral Cancer

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Reviewer: Carlos Caulin

Reviewer's report:

In this manuscript the authors address the potential role of ADORA2B in OSCC. They found increased expression of ADORA2B in OSCC cell lines and tumors compared to normal controls. In addition, suppression of ADORA2B slows cell growth. The expression of ADORA2B in OSCC is induced by hypoxia, as previously demonstrated in other cellular systems. The authors propose that HIF-1a is regulated by ADORA2B in what it may be a positive feedback loop, as it has been shown that HIF-1a can also induce ADORA2B. As this data has potential biological implications it would be important to address whether transcription of HIF-1a is regulated by ADORA2B or other mechanisms may be involved.

Additional comments:

1. Page 6, line 16. This sentence doesn’t seem to be correct: Adenosine A2b receptor (ADORA2B), classified into four subfamilies (ADORA1, 2A, 2B, 3).

2. Figure 1. How are the HNOKs cultures established? Are they primary cultures or established “normal” keratinocyte cell lines? Are they derived from normal tissue of cancer patients or from healthy donors? I would expect to see at least two independent samples of HNOKs for reproducibility of the data.

3. Figure 5. Is HIF-1a induced by hypoxia in OSCC cells?

4. The authors show nicely that hypoxia induces ADORA2B. Did they see an increase in proliferation as well?

5. Figure 6. Total Erk and Akt seem to be downregulated in HSC-3 cells after ADORA2B suppression. The westerns should be quantified and total Erk and Akt normalized with the loading control.

6. Figure 6. Is HIF-1a transcription regulated by ADORA2B?

7. Figure 6. Is the induction of HIF-1a by hypoxia prevented in ADORA2B-suppressed cells?

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