Reviewer's report

Title: Metformin-mediated growth inhibition involves suppression of the IGF-I receptor signalling pathway in human pancreatic cancer cells

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Reviewer: Elisabeth Barton

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This study examines how the anti-proliferative actions of metformin on pancreatic cancer cells is affected by glucose levels. The authors propose that these actions can be blunted in the presence of high glucose, and so when using this drug for treating diabetes, the beneficial effects of the compound for cancer prevention may be lost if glucose levels are not controlled adequately.

Please number your comments and divide them into

- Major Compulsory Revisions
  1. The goals of the study need to be more clearly stated in the introduction. They are too descriptive.
  2. While many of the figures show compelling data in the form of immunoblots, there is no quantification or statistical analysis provided. Thus, the results in Figures 2-6 are anecdotal, and the bar graphs are only descriptive of 1 replicate. All of these results must be shown in terms of the multiple replicates performed, to ensure that the blots shown reflect the main conclusions.
  3. The dose of metformin seems higher than those used in other publications (1-5 mM appears in several culture studies). Is there a reason for such a high dose? Further, it is not clear what does was utilized for the experiments in figure 5 and 6 – 10 or 20 mM? Are there off-target effects associated with such high concentrations? For instance in Panels of Figure 1, B and C exhibit no dose dependence, whereas A shows some modest does differences between 10 and 20 mM. Where are these effects saturated?
  4. There are no descriptions of the statistical analyses other than proliferation. This is related to the 2nd point, where there are only blots with no quantification shown.
  5. For Figure 2, there was 1% serum added in this experiment, but the rationale is not clear.

- Minor Essential Revisions
  1. The data presentation in Figures would be improved if the cell lines used were notated on the panels.
2. Please define SFM (I assume it is serum free media) in the methods.

3. Page 4, line 6. Suggest replacing “up to” with “almost”.


5. A recent paper on this subject was published using the same cell lines, and glucose modulation (Sinnett-Smith et al, 2012, BBRC). While this might have not been available prior to the authors submission, it will be important to address the findings in this study with respect to this publication.

- Discretionary Revisions
  None noted

**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.