Reviewer's report

Title: Differential effects of arsenic trioxide on chemosensitization in human hepatic tumor and stellate cell lines

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Reviewer: vishakha bhave

Reviewer's report:

In this manuscript the authors have looked at the role of arsenic trioxide on chemosensitization in human hepatic tumor and stellate cell line. Based on their data, the authors conclude that combining ATO with currently used chemotherapeutic agents could be a better treatment for patients with HCC.

Major comments:

1. Based on the thymidine synthase levels (Fig. 5), the authors conclude that ATO-induced modulation of TS levels, may in part, account for the enhanced apoptosis with the 5-FU combination. However, there is significant decrease in TS levels only at the 25 mM ATO concentration whereas the ATO concentration used for combination with 5-FU is only 5mM (no significant decrease in TS caused by this concentration of ATO alone). It appears that there might be mechanisms other than TS levels responsible for this sensitization.

2. Procaspase-9 is an initiator caspase and an indirect marker of apoptosis. Increased procaspase-9 levels correspond to decreased apoptosis and vice versa. A more direct indicator of apoptosis like cleaved caspase-3 (an effector caspase by Western blot) or TUNEL assay on cells should be utilized to assess the degree of apoptosis.

3. Authors have used MTT assay as an indicator of proliferation. However, MTT assay is a colorimetric assay that is based on active mitochondrial function. It is thus only an indirect indicator of cell number and does not directly measure the extent of proliferation. It should be noted that treatments that can affect mitochondrial activity can modulate MTT results irrespective of their proliferation status. Hence the MTT data should be corroborated with a more direct measure of proliferation like PCNA (by WB or IHC) or KI67.

Minor comments:

4. Fig. 6A: why does the loading control (GAPDH) have 9 lanes as opposed to 8 lanes in pMAPK and MAPK Western blot?

5. Fig. 7F Western blot is missing loading controls.

6. Fig. 7E is missing statistical analysis.

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