Reviewer’s report

Title: Activation of the steroid and xenobiotic receptor, SXR, induces apoptosis in breast cancer cells.

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Reviewer: Rakesh K. K. Tyagi

Reviewer’s report:

Reviewer’s Comments

The present manuscript by Verma S et al focuses on an important area of active research on xenobiotic receptor SXR/PXR and cancer. With specific reference to breast cancer, authors have shown that ‘ligand-activated SXR’ is anti-proliferative in p53 (WT) breast cancer cells and induces cell cycle arrest and apoptosis. The findings suggest that in specific breast cancer types, SXR activators may serve as therapeutically effective and chemo-preventive agents. The sequence of events beginning from SXR activation to induction of iNOS expression, increase in NO levels, followed by enhanced expression of p53 and its target genes have been well traced and dissected. Based on the findings the authors have presented a model that establishes a link among activated SXR, wild type p53, cell cycle arrest and breast cancer cells.

The findings reported on the subject are novel. The experiments have been well designed, executed and analyzed. The manuscript is well composed citing adequate literature on this critical subject. Though, the authors have incorporated significant data in support of their claims some suggestions and points of concerns are being highlighted below that will help in strengthening the manuscript:

-Major compulsory revisions
No major compulsory revisions

-Minor essential revisions
1. Refer to Figure 4F: While pretreatment with iNOS inhibitors blocked the rifampicin-activated p53 up regulation, the effect of iNOS inhibitor 1400W on basal p53 levels is confusing. Apparently, when used alone, both 1400W and rifampicin are potent SXR activator as well as inducer of p53 level. But when used in combination (1400W + rifampicin) lead to down-regulation of rifampicin-activated p53 level. These results are not as would be expected, and therefore, need to be discussed in the text. Is it possible that as a ligand, rifampicin competes out 1400W for SXR binding?

2. Refer to Figure 5C: Though the Western blot results supports the claims of the authors when considering the SXR/GAPDH ratio, the amount of total protein loaded in lane SCR appears to be more than in lane UT that initially gives a contradictory/confusing impression. Also, lane SiRNA is a portion from other blot.
This figure, if replaced by a single composite blot with equal protein loading will be more convincing to your claims.

- Discretionary revisions

3. While the present manuscript is under review another article dealing with the role of SXR in ovarian cancer has been highlighted in the reference below. A reference to the study may be incorporated in the present manuscript.


**Level of interest:** An article of importance in its field

**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.