Reviewer's report

Title: Vav3 oncogene activates estrogen receptor and its overexpression may be involved in human breast cancer.

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Reviewer: N Ahmad

Reviewer's report:

In this manuscript, Lee et al. tested the hypothesis that Vav3 is implicated in the development of breast cancer via estrogen receptor signaling. They show that Vav3 is expressed in breast cancer specimens and the Mcf-7 and T47D cell lines as compared with normal breast tissues and the Mcf-10A immortalized cell line. Vav3 was shown to be involved in estrogen-mediated growth of Mcf-7 and T47D cells. Also, Vav3 was shown to enhance ER\(\text{I}\)\(\pm\) activity in HeLa cells via the DH functional domain. Further, Vav3 was found to enhance ER\(\text{I}\)\(\pm\) activation with PI3k that was blocked by dominant negative Akt in HeLa cells. Also, wortmannin was shown to block both estrogen and Vav3-mediated ER\(\text{I}\)\(\pm\) activation in T47D cells whereas EGF was shown to enhance Vav3-mediated ER\(\text{I}\)\(\pm\) activity in T47D cells.

The major concern of this reviewer is that much of the mechanistic work characterizing the effect of Vav3 on the estrogen receptor was in HeLa cells instead of the breast cancer cell lines. A complete examination of the relationship between estrogen-mediated effects of Vav3 particularly with respect to PI3k/Akt pathway should be carried out in both Mcf-7 and T47D cells.

A second major concern is the small number of normal tissues used to compare Vav3 expression. The examination of only 8 samples calls into question the scope of the findings.

Some minor concerns are as follows:

1. Vav3 does not appear from Figure 1 to decrease the proliferation rate of breast cancer cells, yet the authors maintain that it is involved in their growth; please explain.

2. If Vav3 is involved in both estrogen-dependent and independent growth of breast cancer cells, a clonogenic assay to assess long-term proliferation rates would be important to determine.

3. In Figure 3, tamoxifen appears to increase ER\(\text{I}\)\(\pm\) activity, please explain.

4. The GST pull-down data is not convincing as there appears to be no change in the presence of Mcf-7 cells.

What next?: Reject because scientifically unsound
**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

'I declare that I have no competing interests'