Reviewer's report

Title: Characterization of a novel PTEN mutation in MDA-MB-453 breast carcinoma cell line

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Reviewer: Michel Longy

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The paper by Singh et al. “Characterization of a novel PTEN mutation in MDA-MB-453 breast carcinoma cell line” reports the analysis of the biological effect of the PTEN E307K missense mutation found in the MDA-MB-453 cell line. The results indicate that this mutant protein retains its ability to dephosphorylate PIP3 and to suppress cell proliferation in PTEN null cells but is associated with the aberrant cellular distribution of Pten. More precisely, this mutant protein is preferentially located to the plasma membrane and is excluded from the nucleus. Aberrant ubiquitination induced by the lysine at position 307 is likely to be the cause of this nuclear exclusion. The relocation of Pten to the plasma membrane is associated with a paradoxal greater ability to suppress the PI3-K pathway. Conversely, the nuclear exclusion is associated with resistance to cisplatinum treatment in PTEN null cells whereas wild type PTEN restores sensitivity.

This is an interesting paper raising the question of the predominant role, nuclear or cytoplasmic, of PTEN in malignant transformation.

My main concern is that the authors don’t indicate that MDA-MB-453 is a cell line representative of a very peculiar kind of breast cancer, named “molecular apocrine”, androgen receptor positive and estrogen receptor negative (Doane, Oncogene 2006;25:3994 – Robinson, EMBO 2011;doi:101038). This characteristic should be discussed, particularly as molecular apocrine breast carcinoma is more frequent in patients with Cowden disease (Banneau, Breast cancer res. 2010;12:R63).

Minors points:

1/ In the “Background” section (page 4) it is not true that the location of PTEN mutations is different in Cowden disease and in Banayan Riley Ruvalcaba (Bonneau, Hum Mutat. 2000; 16:109).

2/ In the “Discussion” section (page 15) the hypothesis of a germline origin of the E307K mutation is attractive. Are medical records concerning the patient from whom the cell line was derived available? Clinical findings in favour of Cowden disease could support this hypothesis.

3/ In the “Discussion” section (page 16) if the main effect of the E307K mutation is the nuclear exclusion of Pten, it is difficult to conceive a dominant mechanism either positive or negative for this mutation. A gene dosage effect with haplo-insufficiency may be also implicated.
**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'