Reviewer's report

Title: Calcitriol restores antiestrogen responsiveness in estrogen receptor negative breast cancer cells: A potential new therapeutic approach

Version: 4  Date: 3 February 2014

Reviewer: Filippo Acconcia

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Major compulsory revision.

The manuscript presented by the Authors is improved after the revision. Nonetheless, I am still not convinced that the conclusion by which calcitriol determines ERalpha re-activation in negative breast and for this reason becomes targettable by anti-estrogen cancer is supported by the data:

Indeed, after calcitriol treatment
1- Estradiol does not lead to cell proliferation
2- Estradiol does not determine the activation of its classical target genes
3- Estradiol-dependent activation of Ser118 phosphorylation has not been performed.

In my opinion, the explanation given by the Authors are not satisfactory. Is it possible that the effects observed depend on calcitriol binding to ERalpha?

The explanation given by the Authors that ERalpha re-expression is a win-win strategy to combat negative breast cancer is to me still too preliminary. Indeed, Authors should also consider that it is now clear that aggressive breast tumours, including those classified as ERalpha negative on the basis of the presence in the nucleus of the ERalpha, are indeed ERalpha positive: as a matter of fact the same nuclear ERalpha associates with signalling intermediates in the cytoplasm of isolated breast cancer cells as well as in biopsy of breast cancer patients and association with these signalling molecules are detrimental in terms of disease-free survival (EMBO Mol Med. 2012 Nov;4(11):1200-13. doi: 10.1002/emmm.201201615).

Moreover, in the response the statement that ‘estrogens and their receptors protect against cancer cell invasiveness through distinct mechanisms’ is not convincing.

Indeed, there are overwhelming evidence that indicate how estradiol is a proliferative and a migratory hormone for ERalpha positive breast cancer (Please, see the work of Dr Tommaso Simoncini, Dr Ellis Levin, Dr Rakesh Kumar to mention only some important Authors in the field). Furthermore, estradiol is a complete mitogen for breast cancer cells (Please see all the work of Dr Auricchio) and therapies for breast cancer patients target estradiol synthesis (aromatase inhibitors) or estrogen receptor alpha expression (e.g., tamoxifen;
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.