Reviewer's report

Title: Antioxidants-mediated upregulation of OGG1 via NRF2 induction is associated with prevention of oxidative DNA damage in estrogen-induced breast cancer

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Reviewer: Filippo Acconcia

Reviewer's report:

In this paper Singh and co-workers identify a novel pathway that is responsible for the E2-induced DNA damage. Moreover, the Authors provide evidence that antioxidants prevents E2-induced toxicity through targeting the OGG/NRF2 pathway.

The experiments performed are sound and the resulting figures are of high quality. The manuscript is well written an the data support the conclusion.

However, I have some major concerns.

Major Compulsory Revision:

1. The ability of a physiological hormone to induce DNA damage in cells, thus inducing cancer, is to me odd.

This derives mainly by the fact that there is some degree of confusion in the manuscript regarding the concentration of E2 used.

What is the actual concentration rats are exposed to for 240 days?

Is this constant?

Did the authors take into consideration the physiological states of the female rats treated (i.e., pre-menopause/post-menopause)?

This point must be clarified because the effects the Authors find on OGG is observed in all tissues, thus suggesting a possible aspecific effect due to the treatment itself.

2. In line with the above questions, cells are treated with 50nM (0.05 #M), that is a quite high E2 concentration. Moreover, in figure 3 D CHIP is performed in 10nM E2 stimulation. Why did the Authors change the E2 treatment? The Author should explain this point or eventually perform a dose-curve 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.