Reviewer’s report

Title: Immunohistochemical Analysis of Oxidative Stress and DNA Repair Proteins in Normal Mammary Tissue and Breast Cancer Tumors

Version: 1 Date: 11 August 2009

Reviewer: Tadahide Izumi

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This report analyzed normal and cancer (benign to invasive) human tissues to determine their expression profiles of redox regulators and DNA repair proteins. It was concluded that most proteins characterized were dysregulated in cancer cells for their level and cytosol/nuclear distribution patterns. They argued that such an irregular expression may have increased the risk of carcinogenesis in the breast. The conclusion is reasonable and consistent to those of many others and thus these results are significant for cancer prevention and therapeutic medicine. However, the description of the DNA repair pathway for oxidative DNA damage is somewhat misleading and insufficient. Accordingly, the a large body of text and fig. 1 as well as some of data interpretation need to be revised.

-------- Major points ---------------

- The Fig 1 needs to be revised to reflect others' studies more accurately.

1. NM23-H1 (ref 55, 56) was found as a non-specific DNase, and the cited articles described its role in degrading DNA to cell death (apoptosis), not repair. Granzyme A keeps the enzyme from its active mode in normal condition. Therefore, one might argue that NM23 dysregulation affects cellular response to apoptosis rather than to the resistance to DNA damage. The authors should thus modify the scheme 1 (has coordination of NM23 with Ape1 been described?) and their interpretation of NM23 data to reflect the past studies, or should explain its role for DNA repair with additional references which this reviewer must have missed.

2. Although MPG is a DNA glycosylase that leaves abasic sites after its reaction, other DNA glycosylases cleave damaged DNA strands through their beta- or beta/delta-elimination. In fact, this type of reaction is more common in oxidative DNA base repair carried out by OGG1, NTH1, and NEIL1/2. Furthermore, the main function of MPG is to remove alkylated bases such as 3meG; ROS-damaged bases are weak substrates for MPG, if any. The figure 1 should be thus revised and include these DNA glycosylases. Indeed, since the work deals with oxidative stress and cancer development, it would have been more significant to determine the level of the other DNA glycosylases in the normal/cancer tissues.

It is interesting that MPG decreases as cancer becomes more advanced, representing a good contrast to other proteins tested including Ape1 and NM23. Their insight or comment on this matter and on significance to chemotherapy
using alkylating reagents would be an improvement.

--------------- Minor points ------------------
- In the graphical representation of relative intensity, their logarithmic values should be shown because some values are actually below 1.0, which might not be equally represented in the current format.

- In Conclusion:

"Our studies suggest that oxidative stress and DNA repair proteins not only protect normal cells from the damaging effects of ROS, but also promote survival of mammary tumor cells and foster tumor progression."

This might be a reasonable interpretation for DNA repair proteins and detoxification factors including Trx/R. However, whether increased levels of NM23 leads to cellular resistance has not been tested.

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

**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.