Reviewer’s report

Title: Analysis of the Effects of Exposure to Acute Hypoxia on Oxidative Lesions and Tumour Progression in a Transgenic Mouse Breast Cancer Model

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Reviewer: Anton Berns

Reviewer’s report:

In this manuscript the authors use the MMTV-Middle-T Polyoma (MMTV-MT-Py) model to study the effects of oxidative stress on tumorigenesis. To achieve this they expose the mice to various treatment modalities: i. exposure to hypoxic conditions, ii. exposure of the mice to the lipid peroxydation product malondialdehyde (MDA), and treatment with methoxyamine (MX) to impair base-excision repair. MDA exposure mimics in lipid peroxidation and exposes mice to the oxidative compound, resulting in an increased level of 8-oxo-dG. While this effect was significant for MDA treatment as compared to control, the acute hypoxia exposure showed a trend of augmented 8-oxo-dG levels. It is hard to understand why in this study the 8-oxo-dG levels are increased whereas a reduction was found in the accompanying paper by the same authors in a slightly different MMTV-Neu model. As in the MMTV-Neu model no correlation was found between 8-oxo-dG levels and tumor latency and progression. However, in contrast to the MMTV-Neu model in the PyMT model a difference was found between the infiltration of macrophages, that were found to be higher in the hypoxia treated cells. Vascular densities of hypoxia or MDA exposed animals were, surprisingly, lower than controls. All these factors had no influence on the tumorigenic process, arguing that either these readouts are not relevant for tumorigenesis, or that the model system is simply not suitable to reveal a correlation.

Therefore, no firm conclusions can be drawn, neither about the suitability of the model nor about the correlations between oxidative stress and tumorigenesis. If the data of the polyoma MT and Neu models are compared one is left with the impression that these systems are influenced by factors that are hard to control. One actually wonders whether repeating the same experiment would give the same results or that other factors that differ from experiment to experiment influence the outcome, thereby making the results very difficult to interpret. The lack of correlation between 8-oxo-dG and tumorigenesis, even under conditions in which high levels of 8-oxo-dG are induced (e.g. by MDA) seems to indicate that 8-oxo-dG is likely not a causative agent, at least in this system. This raises the question whether the correlation does not exist (in other systems 8-oxo-dG might act as a marker rather than a causative lesion) or whether this system/approach is not suitable to answer this question. It is questionable whether these observations are of value for the scientific community. I have my doubts.
What next?: Reject because too small an advance to publish

Level of interest: An article of insufficient interest to warrant publication in a scientific/medical journal

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