Reviewer’s report

Title: DNA damage response and DNA repair - dog as a model?

Version: 2  Date: 17 January 2014

Reviewer: Augusto Matos

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Upon suggestion by the editor, Grosse et al. presented a debate manuscript on the use of spontaneous dog cancer as a model for the study of DDR in human cancer. Although it is true that canine tumors have been previously proposed as human models, this reviewer believes that the specific focus on DDR may be regarded as novel or perhaps as a refinement of previous general arguments. While, as the authors concluded, the information is not abundant in the canine species, its potential therapeutic impact and the acceleration of the investigation processes that emerge from a more rapid evolution of canine cancer when compared to humans constitutes a plus-value and strengthens the suggestion of using such model of disease. The manuscript is well argued and the list of references, not being exhaustive due to its nature (discussion paper and not an exhaustive review), is suitable.

Overall the manuscript is well written. A few suggestions follow in order to further improve it.

There are a few points (minor essential revisions) that, in this reviewer opinion, deserve some attention:

1- Background: When the authors state “mouse xenograft tumors revealed a second wave of dsbs,… 2 days after the initial wave”, they should specify that they are referring to radiation-induced DNA break, if it is the case.

2- Background: Please define in the text the acronym “IR”. I believe that it was not previously done.

3- Background: The authors state “As the overall lifespan of dogs is shorter than that of humans, conclusions from clinical studies can be drawn faster”. It is true that the evolution of most cancers in dogs is often much faster than in humans, but that is a fact per se, not necessarily because their life span is shorter.

4- Discussion- question (1): The statement “Nonetheless, the canine gene products seem to be more closely related to their human homologs than those of mice.” would benefit if a couple of examples are provided.

5- Discussion- question (2): The authors state “throughout mammalian species, deregulated cell cycle check points and apoptosis mechanisms lead to: increased proliferation (…) by the continuously activated DDR.” It is debatable if the activated DDR increase proliferation per se. Considering that its activation succeeds a cycle arrest in order to determine cell viability, it could be hypothesized that it would reduce, not increase, proliferation. Of course that if DDR is deregulated, then the effect would be increased proliferation, but its
continuous activation by itself does not guarantee deregulation.

6- Discussion- question (3): Replace “Study addressing the capacity…” by “One study addressing the capacity…”

7- Discussion- question (3): The sentence “In normal vs. adenoma samples, BRCA2/1 and RAD51 expression was reduced” is misleading since it means that normal tissues have less expression than adenomas. In the reference, however, the opposite result is described: “The relative copy numbers of BRCA1 in adenomas of 6 of 10 dogs was reduced to <0.5-fold when compared with normal gland epithelium (Fig. 5). Similarly, expression levels of BRCA2 and RAD51 were also reduced in adenomas of 4 of 10 dogs” (sic ref 45)

8- Discussion- question (3): Please provide units in “Though dogs live shorter than humans (16.6 vs. 90, respectively)…”

9- Discussion- question (4), skin cancer: The authors state “In the two most common tumors of the skin, squamous cell carcinoma and melanoma…”. However this is not true. Many of the most frequent canine skin tumors are benign (lipomas, histiocytomas, perianal gland adenomas, etc.) and, amongst the malignant tumors, the most prevalent are mast cell tumors (Withrow & MacEwen’s Small Animal Clinical Oncology, 5th Ed., pp. 306).

10- Discussion- question (4), skin cancer: In the sentences “The p53 protein was shown to solely localize to the cytoplasm in many tumor cases” and “Therefore, misregulation of important tumor suppressor genes leads to genomic instability and progression of canine skin tumors” the authors should specify that they are referring to skin melanomas, since it hasn’t been demonstrated in other skin tumor types.

11- Discussion- question (4), skin cancer: The statement “Important cell cycle regulators are mutated in about 72% of the tumors” is, in this reviewer opinion, oversimplified. Without tumor specifications or references, the reader may be confused about which type(s) of tumor(s) are these results.

12- Discussion- question (4), skin cancer: In the sentence “…the high frequency of malignant lymphoma (7-24%) in dogs…” Please specify the percentage, i.e. 7-24% of all canine tumors, if it is the case (I presume it is).

13- Conclusions: Please write “in vivo” in italic.

14- Conclusions: Please replace “Integrating canine tumor models” by “Integrating spontaneous canine tumor models”.

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