Reviewer’s report

Title: Host-Derived RANKL is Responsible for Osteolysis in C4-2 Human Prostate Cancer Xenograft Model of Experimental Bone Metastases

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Reviewer: Françoise REDINI

Reviewer’s report:

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

The data presented in this paper relate to the relative contribution of tumor- vs host-derived RANKL in prostate associated osteolysis. To address this question, the authors used a neutralizing anti-huRANKL antibody in a model of human prostate C4-2 tumor cells inoculated in SCID mice. Increasing number of data are reported on the involvement of the microenvironment in tumor progression, including prostate cancer in which a vicious cycle is established between tumor cell proliferation and bone resorption. However, the specific mechanisms involved in the stimulation of osteolysis by tumor cells are not fully understood. This study provides an elegant model to discern the relative contribution of RANKL derived from tumor cells vs host cells in the microenvironment. However, the results presented are somehow indirect and not relevant enough to demonstrate the direct involvement of host cells.

Major points:
To clearly establish the direct involvement of murine host cells in bone metastases associated osteolysis, the authors should have completed their work by using muRANKL MAb which targets (host) murine osteoblasts to show the decrease of osteolysis. A study by immuno-histochemistry using MAb against RANKL from both origins should also be useful to compare the proportion of RANKL synthesized by host (murine) cells and that synthesized by tumor (human) cells.
To confirm the author’s hypothesis, co-cultures of human tumor cells with murine osteoblasts should also provide informations about the factors synthesized by human prostate cells to induce RANKL expression by murine osteoblasts.
The authors must address these points before affirming that RANKL involved in prostate cancer associated osteolysis is from host origin.
I am not convinced by the effectiveness of huRANKL MAb in vivo: why huRANKL is still detected by immuno-histochemistry in C4-2 tumors even after prevention or curative treatment by huRANKL MAb (Fig. 2A) ?

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article of importance in its field

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'below.