Reviewer’s report

Title: Smad4-expression is decreased in Breast Cancer Tissues: a retrospective study

Version: 1 Date: 5 December 2005

Reviewer: ALFONSO DUENAS-GONZALEZ

Reviewer’s report:

General
Smad-4 expression is decreased in breast cancer tissues by Stuelten et al., describe the immunohistochemical expression of smad-4 protein in a cohort of primary breast cancer patients and correlated the finding with the prognosis of patients. In addition they interrogate the Smad-4 expression in a series of breast cancer cell lines exhibiting different degree of malignancy.

Overall, the work is well-done however, the authors must address some issues that may improve the manuscript.

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

Even though clinical and pathological characteristics are well described, the authors analyzed a cohort of 197 patients from almost 12 years which seem to represent a small number. This data may suggest that there was selection of patients, for instance, availability of archival material?, available data of follow-up?, etc. Authors should comment on this issue.

Patients registered as “unknown cause of death” were analyzed as death not due to cancer. Was it this proportion considerable? What could had happen if these were put into “death due to cancer”?

In all instances (results, discussion) authors should always add “trend” and avoid to use “longer, superior, better, distinctly higher, etc,” when refer to survival results that were not statistically significant as this means that random can solely explain the “longer survival”.

In line with these observations, the sound conclusions should be reconsidered. Authors did demonstrate lower expression in tumor tissues as compared to surrounding normal ones, however, DID NOT demonstrate that disruption of TGF-B- Smad-signaling because of loss of TGBRII or smad4 slows down metatatic disease and therefore improves 5-year survival in node positive breast cancer patients (the body of evidence by this and previous works point to this) but again in the present work this is not demonstrated.

As authors point out, Kang et al., (PNAS 2005, 102:13909-14) nicely demonstrate that activation of smad-pathway is required for bone metastases development. Based on this authors should consider to analyze in their study patients the existence of a correlation between smad-4 status and metastasis (specially bone) free-survival instead of only death. It is known that survival and metastasis is well-related however, the advances in the treatment of metastatic disease in breast cancer result in many patients living longer despite having bone metastasis, hence metastasis-free period could be a better endpoint for this study.

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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the
The main message from the manuscript is the loss of Smad-4 in tumor tissues and its trend (but no statistically significant) with better patient prognosis. As such, the tables are of no value. I suggest to condense all tables in one showing the associations between smad-4 status and TGBRs and their corresponding survival stratified by TGBRs status.

As authors correctly state “the role of TGF-B signaling is complex” accordingly, a simple study like this performing only IHC in primary tumors has severe limitations for dilucidating the issue and as such, this must be emphasized in the discussion.

Methods section. Pag 7, first paragraph. The scoring “1<IRS<12” is not clear.
Results. Pag 8, line 20 “known”.
Pag 13, first line “carinomas”.

Discretionary Revisions (which the author can choose to ignore)

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

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: Yes

Declaration of competing interests:
'I declare that I have no competing interests'