Reviewer's report

Title: High-level inducible Smad4-reexpression is associated with gene expression profiles that predict a preferential role of Smad4 in extracellular matrix composition

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Reviewer: Gertjan Fleuren

Reviewer's report:

General

The manuscript of Klein-Scory et al. describes the effects of inducible expression of Smad4 in Smad4-transfected clones of the C4-II cervical cancer cell line.

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

The article has been well written. However, the authors do not address the question they pose in the abstract: Are loss of growth inhibition by TGF-β and loss of Smad4 independent events in carcinogenesis. Instead the authors address the following question: What is the mRNA expression profile of Smad4 deficient C4-II after (inducible) re-expression of Smad4.

This study has been performed on only one cervical cancer cell line. It is unclear whether the inability to block cell growth after re-expression of Smad4 is related to additional (epi)genetic changes in this particular cervical cancer cell line or to a fundamental biological mechanism that occurs in all/the majority of the Smad4-deficient cervical cancer cell lines. For this reason it is important to expand the study with at least two other (Smad4 deficient) cervical cancer cell lines.

Because both the results and the discussion are focused on the C4-II cervical cancer cell line, the transfection with Smad4 of two Smad4-negative pancreatic carcinoma cell lines (at the end of the study) does not strengthen the message of the paper (Fig.6 and Fig.7).

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

The authors should discuss their observation of decreased cell growth in vitro and in vivo (Fig.2) after transfection with Smad4 and their finding that transfection with Smad4 had no effect (on the mRNA level) on repression of c-myc and induction of p15 and p21.

The introduction is rather lengthy and should be shortened. Furthermore a clear aim of the study should be stated at the end of the introduction.

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 of importance in its field

Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.