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: Karlheinz Friedrich

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General

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

Susanne Klein-Scory et al.

Smad4 is a constituent of signaling pathways triggered by the TGF-ß receptor. It is consistent with the antiproliferative function of TGF-ß that Smad4 deficiency has been found associated with various cancers of the gastrointestinal and reproductive tract. Hence, the general interpretation of these findings was that loss of Smad4 causes TGF-ß resistance and consequently hyperplasia. The authors of this report and others, however, accumulated evidence that TGF-ß resistance and absence of Smad4 are not necessarily connected causally. They showed in particular that heterologous re-expression of Smad4 in Smd4-deficient cancer cell lines could reduce tumor growth in vivo, but did not revert TGF-ß resistance.

In this paper, the authors go one step further and generate cervical and pancreatic cancer cell lines that express Smad 4 in a regulatable fashion. They show that Smad4 mediates tumor suppression in vivo, and dose-dependently controls the TGF-ß-induced expression of genes associated with the extracellular matrix. Importantly, TGF-# target genes connected to cell cycle regulation such as c-myc, p21 and p15 were not affected by the experimental manipulation of Smad4. The authors draw the conclusion that tumor suppression by Smad4 occurs independently of a restoration of growth inhibitory TGF-ß effects responses.

This is an interesting and well performed study. I have no principal concerns with regard to the scientific contents, the design of the work, the presentation and the interpretation of the results.

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)
The manuscript could use some formal improvement:

1. The contents of the manuscript sections should be more focused: The introduction contains an extensive description of results which should be removed. The Introduction is too long in any case (as is the Discussion).

The figure legends should not contain interpretations of the data shown, they should rather be restricted to a description of what has been done and how it was carried out.

The text occasionally contains some awkward English and incorrect punctuation. I suggest to have it read by a native speaker upon final editing.

Fig. 2c: How often was this experiment performed? Since ratios are shown, the Fig. should include error bars.
Fig. 2d: significance of differences should be indicated

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

The Material and Methods section should contain a small paragraph on the statistical treatment of the results.

What next?: Accept after minor essential revisions

Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being published

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