Reviewer's report

Title: Wnt1 is epistatic to Id2 in modeling mammary gland development and in causing mammary tumors

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Reviewer: Gertraud Robinson

Reviewer's report:

General

The manuscript by Marino et al. investigates the functional relationship between Id2 and over expression of Wnt1 in mammary gland development and carcinogenesis. Id2 is a downstream target of canonical Wnt signaling in MEFs and colon cancer. To address the question whether Id2 also mediates Wnt signals in mammary epithelial cells the authors crossed a mouse line than over expresses Wnt1 in mammary epithelial cells with a line in which Id2 is deleted. Over expression of Wnt1 in mammary epithelial cells causes increased side branching in virgin mice and leads to the development of tumors. Id2 deficient mammary epithelial cells display reduced proliferation due to an induction of the CDK inhibitor p21 and fail to differentiate during pregnancy. The results reported here show that the effects of Wnt over expression also occur in Id2-/- animals, they present increased side branching in virgin mice and tumors develop at the same rate as in control mice. The entire analysis of the development of the gland consists of whole mount images, which is rather superficial - I would have been nice to show at least histological sections of the “rescued Wnt1 Tg/Id2-/- epithelia - but is sufficient to make the point that Wnt1 transgenics and Wnt1 transgenics on an Id2-/- background look similar and there is obviously no interaction in this system.

In summary, these experiments are based on sound scientific reasoning. Even though the analysis of the results is executed with minimal effort they should be published. However, the results should not be over interpreted and need to be discussed in more depth.

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

Although these data are in a sense “negative” data they should be published. However, the discussion is poorly written and needs substantial rewriting. For example the authors use different and rather vague formulations to interpret their findings:
“epistatic” in the title
“placing Wnt1 targets downstream of Id2” in the abstract
“independent of Id2” in the discussion

Since there is no evidence of an intersection of the genetic pathways to be gained from the data it seems appropriate to stick to "independent" and not to interpret the findings in genetic terms. It also cannot be excluded that in an artificial situation such as the over expression of a signaling molecule such as Wnt1, compensation through another member of the bHLH family could take place. These considerations need to be addressed in the discussion.

Furthermore, the terminology the authors use to describe mammary gland development is incorrect. “Remodeling” is conventionally used to describe the events occurring during involution not as is the case here for the process of side branching. Likewise “alveolar” development takes place during pregnancy, a phase that is not investigated in this study. The development that is observed here should be referred to as “side branching”.


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

It is not stated clearly how the “rate of tumorigenesis” was measured (last paragraph of Results). What was the endpoint? What sizes were the tumors?

The 2nd sentence of the Abstract is incomplete.

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: No

Declaration of competing interests:

None