Reviewer's report

Title: Evolution of somatic mutations in mammary tumors in transgenic mice is influenced by the inherited genotype.

Version: 1 Date: 31 March 2004

Reviewer: Kent Hunter

Reviewer's report:

General
This article describes the analysis of the secondary mutation spectrums of the H-Ras gene in Wnt1 and Wnt1/p53-/-, Wnt1/Neu, Neu and Wnt1/Neu transgenic mice. Frequent mutations were observed the H-Ras gene in the Wnt1 tumors, as well as activating mutations in Neu in the Neu transgenics. No mutations were observed in Wnt1/Neu or Wnt1/p53-/- tumors. The authors interpret this data to suggest that the mutational spectrum that is required for tumorigenesis is dictated by the genetic background on which primary initiation events occur.

The methods and analysis of this paper is basically sound. However there are a number of minor points that I believe would strengthen the presentation.

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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)

1) In the methods, was the p53-/- bred onto the FVB background? It is not entirely clear as stated. If so, please indicate the number of generations of backcrossing. Since the potential for genetic background affects might significantly affect the results of this particular experiment it is helpful to know what the likelihood of these events might be.

2) Second page of methods. Did you use 50 micrograms (?g) of tumor powder for the extractions or 50 milligrams (mg)?

3) Sequencing. Did you only consider those sequencing reactions that showed potential mutations in both strands or only one? Please make clear. Also, due to the fact that it is not uncommon to get spurious heterozygous peaks resulting from secondary structures in sequencing reactions it would be helpful to show an example of your sequencing results. It would enable the readers to have greater confidence in your results if you show convincing sequence traces. Also, have you confirmed any of these potential mutations by some other method, ie SSCP? That also would add confidence to the results.

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Discretionary Revisions (which the author can choose to ignore)

4) page 3 paragraph 2, the author stated that “…those tumors induced by genes that activate the Ras signaling pathway (e.g. polyoma…) than to tumors induced by components of the Wnt signaling pathway…” However, the current study indicates that Wnt1 also activates the Ras signaling pathways. The conflict should be clarified. Also, “signaling” was misspelled as “signalling” in the text.
5) page 13, paragraph 2, the authors suggested that “...expression of a wild-type version of the Neu transgene is sufficient to provide the growth advantage that is apparently conferred by secondary somatic mutations of H-Ras in ...” Could this promotional effect due to epigenetic factors?

What next?: Accept after minor essential revisions

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No

Declaration of competing interests:

None