Reviewer’s report

Title: ERBB2, but not EGFR, mutations in hepatocellular carcinoma may predict response to EGFR-targeted therapy

Version: 1 Date: 20 September 2006

Reviewer: Daphne Bell

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General
Bekaii-Saab et al., report a mutational analysis of exons 18-21 of both EGFR and ERBB2 among a series of 18 hepatocellular carcinomas and 22 biliary carcinomas. No mutations were detectable within EGFR in this series. As a positive control for EGFR mutation detection, 2 of 44 NSCLCs were shown to have an EGFR mutation. Mutations affecting ERBB2 were found in two cases of hepatocellular carcinoma. In each case the mutation substituted a tyrosine for histidine at position 878 (H878Y). At least in one tumor, the mutation was shown to be absent within matched control DNA. The authors conclude “mutations in the tyrosine kinase domain of ERBB2 in hepatoma may underlie responsiveness to agents that target ERBB2 and/or EGFR”.

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

(1) The conclusion of the text that “mutations in the tyrosine kinase domain of ERBB2 in hepatoma may underlie responsiveness to agents that target ERBB2 and/or EGFR”, as well as the title of the paper “ERRB2, but not EGFR, mutations in hepatocellular carcinoma may predict response to EGFR-targeted therapy”, are over-stated. This study analyzed tumors from unselected (untreated) cases. While it is reasonable to speculate that the single, recurrent ERBB2 mutation identified may be germane to response to EGFR-targeted therapies, it should not be presented so definitively.

(2) The abstract states that “11% of hepatomas … harbored novel mutations in the activating domain” of ERBB2. This is misleading as it implies that multiple novel mutations were found. The abstract should be changed to accurately summarize the findings that a single novel mutation (H878Y) was found within ERBB2, which was recurrent in nature, being observed in two of 18 cases (11%).

(3) The authors should state in the degree of tumor cellularity (as a %) of the analyzed cases within the materials and methods whether the tumors were reviewed for cellular heterogeneity. Were they enriched for tumor cell content by gross or laser-capture microdissection? This information is critical in indicating whether the findings reported here are likely to be an accurate reflection of the overall incidence of EGFR and ERBB2 mutations in these tumor types, or whether they are likely an underestimate of the true mutation frequency.

(4) The authors have not provided the nucleotide change that leads to the H878Y missense mutation within ERBB2. Was it the same nucleotide substitution in each case? This information should be added to the results as well as the figure legend. The protein change should be stated in the abstract.

(5) Were the two mutation-positive cases of hepatocellular carcinoma different from the mutation-negative cases in terms of their associated clinicopathological features?

(6) Was matched normal tissue genotyped for both cases? While this is implied in the abstract, it should be stated implicitly with both the Materials and Methods and the Results.

(7) The methodology provided is insufficient in detail to permit replication of the work. The authors should provide details of the primers and PCR conditions used for mutational analysis of ERBB2 in this study.

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 explicitly state that the mutational analysis of EGFR in a series of NSCLCs was conducted as a positive control for mutation detection, rather than simply a positive control.

The conclusion should be combined with the discussion

Discretionary Revisions (which the author can choose to ignore)

Can the authors provide data on the genotype of ERBB2 exons 18-21 in an expanded series of primary hepatocellular carcinomas or cell-lines derived from these tumors?

Do the authors have access to any cases of hepatocellular carcinoma that showed a response to EGFR-ERBB2-targeted therapies, for mutational analysis?

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:

I am an inventor on a patent application describing EGFR mutations and receive royalties resulting from the licensing of a genetic test for EGFR mutations.