Reviewer's report

Title: B-Raf specific antibody responses in melanoma patients

Version: 1 Date: 21 July 2004

Reviewer: Dirk Strumberg

Reviewer's report:

General

-Fensterle and coworker analyzed almost 400 sera of stage IV melanoma patients and non-melanoma patients for B-raf, B-raf V599E, and C-raf specific antibodies using ELISA. Sera were screened for specific total Ig and for IgG. Sera with titers of 1:300 or higher were defined as positive and groups were statistically compared using standard tests.

The results demonstrate the presence of raf specific antibodies in 8.9% of advanced stage melanoma patients and in 2.5% of the control group. However, the antibodies did not discriminate between the wild-type and the V599E-form of B-raf. Furthermore, raf specific IgG was detected only in a few patients at very low levels. The antibody responses did not correlate with clinical parameters and emerged in some patients during disease progression.

The authors conclude that B-raf might serve as a potential target for immunotherapy.

Comments:

Technically this study is sound and the statistics o.k.

This study clearly shows that B-raf is immunogenic in a subgroup of melanoma patients under certain conditions, i.e. with a large tumor burden and/or during disease progression. I agree with the authors' hypothesis that the B-raf antibody response might be due to enhanced turnover of tumor cells in these patients. Specifically, enhanced necrosis or apoptosis of large tumor masses upon hypoxic conditions likely allow the presentation of intracellular proteins like B-raf generating an immunological response.

Beside these clear findings, I do not see the rationale for B-raf (neither wild-type not the V599E-form) being a potential target for immunotherapy.

For instance, B-raf specific antibody response was rather associated with late stage melanoma and disease progression than indicating any protection.

Furthermore, and the authors also made this statement in the text, it is very questionable whether humoral responses against intracellular proteins like raf will have any antitumor effect. Besides, recent raf-directed approaches using BAY 43-9006 (inhibits both mutated and WT-raf) failed as monotherapy in advanced stage melanoma patients (ASCO 2004). These clinical data might support rather B-raf being relevant for melanoma-initiation than driving advanced stage disease progression. Based on these clinical data, the authors should discuss the rationale for an immunological based B-raf directed approach.

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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)

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