Author's response to reviews

Title: Potential role and chronology of abnormal expression of the Deleted in Colon Cancer (DCC) and the p53 proteins in the development of gastric cancer.

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Graziano et al: Potential role and chronology of abnormal expression of the Deleted in Colon Cancer (DCC) and the p53 proteins in the development of gastric cancer.

The following points deal with the reviewers' comments and they indicate where new information has been provided and where changes have been made in the revised manuscript.

Dr N. Tanaka:

Point 1. We agree on data which found DCC to be involved in the axonal development rather than in tumorigenesis of mouse intestine, however, according to new findings, DCC may function as tumor suppressor gene controlling apoptosis. This issue has been debated and new sentences have been included. Also, three new references have been added.


Points 2. We agree that the histologic subtype of gastric carcinomas may influence the analysis of results. However, the limitation of LOH of DCC to a specific histotype, as observed by Wu et al was not confirmed by Fang et al. Also, we performed a preliminary analysis of DCC and p53 expression including cases of intestinal and diffuse gastric cancer, without detecting significant differences between histotypes. Thus, both intestinal and diffuse gastric carcinomas have been included in the final analysis. These issue have been discussed with new sentences and data.


Point 3. To our opinion, the growing evidence on the prognostic role of LOH of DCC as well as its protein abnormalities supports the role in the development of gastric cancer. Likely, after the early carcinogenetic steps, DCC abnormalities confer a more aggressive phenotype due to impaired apoptosis. This process may explain the phenomenon of a late DCC abolished function.

See modifications for point 1
Point 6. The title has been modified to be more informative on the study.
Dr. van der Burg

Point 1. Actually, we observed an ‘all or nothing’-like phenomenon for DCC expression too. Before performing the analysis we planned a 25% cut-off level for DCC expression which resulted unnecessary.
We agree that the original 25% cut-off level for p53 overexpression might jeopardize the reliability of results, especially when a small percentage of positive cells indicating loss of gene function may confer an aggressive phenotype to this disease. We have observed the same results after performing a new p53 analysis considering the 5% cut-off level.
These issues have been clarified and new sentences have been added in the revised text.
Materials and Methods, page 5, lines 21-22 and page 6, lines 2-4. Results, page 7, lines 5-15.

Point 2. Mention of results observed by Wu et al on the chronology of DCC/p53 abnormalities has been included in the Discussion.
Discussion, page 10, lines 7-10.

Minor comments. Typing and grammatical errors have been fixed. The term ‘consecutive’ has been deleted.