Reviewer's report

Title: An association of a simultaneous nuclear and cytoplasmic localization of Fra-1 with breast malignancy

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Reviewer: Karin Milde-Langosch

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General
The AP-1 transcription factor Fra-1 has obtained increasing interest in the last years, since its overexpression in tumor cells is often associated with increased motility, invasiveness and possibly metastasis of several tumor cell types. Song et al. analyze the expression of Fra-1 in benign and malignant breast neoplasias by immunohistochemistry. The authors found nuclear Fra-1 immunoreactivity in all cases, whereas cytoplasmic staining was found in only 15% of the benign lesions, but in 90% of the carcinomas.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)
1. These results are in contrast to those published earlier for breast cancer cell lines and tumors, where high Fra-1 expression was undetectable in receptor-positive, highly differentiated cells, but strong in poorly differentiated tumor cells (Philipps et al., 1998; Bamberger et al., 1999; Zajchowski et al., 2001; Belguise et al., 2005). The reasons for these differences are not discussed.
2. In the light of these differences, more data regarding the specificity of the antibodies used in their study are needed. The application of another method, at least for some samples would be useful.
3. The assessment of Fra-1, ER, PR and ErbB2 expression is not convincing. Why did the authors chose to count only the percentage of positive tumor cells? (was the staining intensity always the same in all samples?) Was the evaluation of the staining results done independently by two persons?
4. ErbB2 staining should not be classified as positive/negative since only strong staining (generally found in about 25% of the cases) reflects gene amplification.
5. The authors discriminate between weak or strong cytoplasmic Fra-1 staining in carcinomas. Yet, the differences in cytoplasmic staining intensity in Fig. 2B and 2C are not convincing, if only malignant cells are regarded. In addition, Fig. 2D suggests that staining intensity might be heterogeneous.
6. There are discrepancies in the numbers of tumors with cytoplasmic Fra-1 staining between Table 2 and Tables 3/4 (37 vs. 32 positive cases).
7. The positive nuclear immunoreactivity for Fra-1 in all tumors is unexpected. Was there a correlation of nuclear staining intensity with histological markers or ER, PR, or ErbB2 results?
8. In the discussion, the authors state that Fra-1 staining tended to be correlated with differentiation. These data are not given in the results.

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 Fig. 1-3, the magnification should be given.
2. Page 9, top: The p-value should be more precise; probably it is not zero (0.00).

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: Needs some language corrections before being published

Statistical review: No

Declaration of competing interests:

I declare that I have no competing interests.