Reviewer's report

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

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Reviewer: M Mitzi Brentani

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General
The authors measured expression of fra-1 by immunohistochemistry in breast tumors. They reported that alterations in Fra-1 distribution correlated with breast malignancy. The addressed question is interesting as it deals with the role of the transcription factor Fra-1 in breast cancer and will be important to begin to understand the functional mechanism of the presence of Fra-1 in the cytoplasm, already reported in other tumors.

Western blot experiments and CDNA array expression have shown that Fra-1 over expression is predictive of aggressive behavior in breast tumor cells and it is associated with the expression of proteins implicated in tumor progression. As an additional level of complexity, the present work shows that Fra-1 cellular localization is altered in invasive breast cancer, implying that cytoplasmic Fra-1 expression may allow discrimination between benign and malignant states. However, presence of cytoplasmic Fra-1 was not associated to loss of nuclear Fra-1 and the authors suggested that cytoplasmic staining is a consequence of an excess of nuclear accumulation expressed by 73% of carcinomas. However 55% of benign tumors also expressed a high staining score although positivity was restricted to the nucleus. Fra-1 was weakly detectable in the nucleus of normal epithelial cells. Fra-1 expression in the nucleus seems to be an early event in the process of breast epithelial cell transformation.

The dissociate expression of cytoplasmic and nuclear Fra-1 suggests different biological roles for Fra-1 depending on its subcellular localization. Is the presence of nuclear FR-ra-1 a marker of breast epithelial cell proliferation and the presence in the cytoplasmic indicates an induction of epithelial mesenchymal transition? It is possible that cytoplasmic Fra-1 by a non transcriptional mechanism may interfere with cellular adhesion, favoring transformation (Vial et al, 2003).

The present communication is merely descriptive and lacks meaningful information of biological consequences of Fra-1 appearance in the cytoplasm. Much of the present data are preliminary and the conclusions concerning cytoplasmic presence of Fra-1 are speculative. Furthermore no strongly correlations of cytoplasmic Fra-1 expression were found for any biochemical pathological parameters of the investigated carcinoma samples. Its is important to know the potential significance of this mislocalization of Fra-1 as a marker of carcinoma progression in a higher number of samples or together with the analysis of other markers otherwise it may have limited applicability. It is recommended to add some new relevant information relative to this kind or shorten the manuscript.

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

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Discretionary Revisions (which the author can choose to ignore)