Reviewer's report

Title: CD40L induces multidrug resistance to apoptosis in breast carcinoma and lymphoma cells through caspase independent and dependent pathways.

Version: 1 Date: 30 November 2005

Reviewer: Angeles Garcia-Pardo

Reviewer's report:

General

This manuscript describes that CD40L has an anti-apoptotic effect in several tumor cell lines, inducing multidrug resistance. While the protective effect is well documented in both lymphoma and breast cancer cells, no conclusive mechanism for this effect is provided in this study. This is probably due to the differential behaviour observed among different cell types and even cell lines within the same lineage, as even acknowledged by the authors (pg. 2, line 5 of Results: “inconsistent increase of caspase-3 activity”; also in other parts of the text). While it might be difficult to identify the molecular mechanism, downstream of caspase-3 activation, for the anti-apoptotic effect of CD40L in carcinoma cells, further characterization of the effect of CD40L on lymphoma cells should be carried out before acceptance of the manuscript.

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

1. Fig. 4 shows a differential effect of caspase inhibitors on apoptosis of lymphoma versus breast cancer cell lines. The role of caspase-8 but not caspase-9 is indirectly implied from these experiments. However this needs to be further supported by western blots showing that caspase-8 (and no caspase-9) is activated under these conditions, and that some of the caspase-8 substrates, such as Bid, are cleaved.

2. The use of numbers to identify the different histograms in Figs. 1, 2 and 4 is highly confusing and difficult to follow. These Figures should be re-done and appropriate labels included in the figure (i.e., white, dark, dashed squares with the corresponding names, etc). Alternatively, labels could be added at the bottom of each condition. Figures need to be presented in a more comprehensible format.

3. Statistical analyses of the data should be performed and included in Figs 1 and 4.

4. While Table 3 certainly shows a protective effect of CD40L L cells, in some cells this is very partial, particularly with respect to C6. There seems to be large variations between cell lines and also between the ceramides used and this should be at least reflected in the text (pg. 13).

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

5. The Abstract should not contain abbreviations
6. Abbreviations should be define in the text the first time used, for example, on pg. 3, line 16, the authors refer to DHFR or MTX without previous definition
7. Some sentences could be improved so that they read better in English. For example, the last line
on pg. 4: “no mechanism studies has however been reported”, should be changed to: “no mechanistic studies have been reported”. And other sentences throughout the manuscript need to be corrected also.

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: Needs some language corrections before being published

Statistical review: No