Reviewer's report

Title: Histone deacetylase inhibitors strongly sensitise neuroblastoma cells to TRAIL-induced apoptosis by a caspases-dependent increase of the pro- to anti-apoptotic proteins ratio.

Version: 1 Date: 5 July 2006
Reviewer: Roberto R. Rosato

Reviewer's report:

General
The present manuscript à€œHistone deacetylase inhibitors strongly sensitise neuroblastoma cellsà€¦à€ by Mühlethaler-Mottet et al. describes the interactions in terms of induction of cell death in neuroblastoma cell lines, between receptor-mediated apoptosis inducing agent TRAIL and HDAC inhibitors belonging to two different structural types, i.e., the short-chain fatty acid Na Butyrate and the hydroxamic acid derivatives TSA and SAHA. The authors show that synergism in terms of cell killing is mediated by HDACIs activation of the mitochondrial apoptotic pathway which sensitises NB cells to TRAIL-induced apoptosis enhancing the amplitude of the caspases cascades. In addition, they demonstrate that these interactions are further increased by caspases-dependent activation of pro-apoptotic proteins (Bid, BimEL) and inactivation of anti-apoptotic proteins (XIAP, Bcl-XL, RIP and surviving).

This is an interesting article that extends previous observations using HDACIs in combination with TRAIL described in a variety of cell models to neuroblastoma cells. The results are conclusive and although not completely novel, provide strong evidence of the mechanisms involved in the pro-apoptotic response to TRAIL/HDACIs.

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)
NONE

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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)

Some suggestions that need to be considered and that may improve this article are related mostly to the presentation of some figures:

- it would be very helpful for the reader to have available in the same graph the corresponding legends, especially when several different bars are included in the same graph. These legends could be added to most of the Figures where more than one type of bar is used.
- Manuscript, section Legends to Figures: Figure 3a, what does M2 (125ng/ml) refer to?
- Fig. 5c: says Bcl-x ; please complete
- Fig. 6: since surviving 100 and 25 in the siRNA experiments give similar results, in order to simply the figure, I would recommend to use only one concentration in the graph and eventually the authors could mention the other one in the text as data not shown.
- Western blots of XIAP in Fig. 5b and 5c: although the images reflect what is happening under the different treatments, they are not very neat and can certainly be improved; this also may help to a better understanding and presentation.

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Discretionary Revisions (which the author can choose to ignore)
NONE

What next?: Accept after minor essential revisions

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No
Declaration of competing interests:
'I declare that I have no competing interests'