Reviewer's report

Title: Tissue Factor/FVIIa Activates Bcl-2 and Prevents Doxorubicin-Induced Apoptosis in Neuroblastoma Cells

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Reviewer: Arnold Spek

Reviewer's report:

General

The authors study the role of tissue factor in chemotherapy-induced apoptosis of neuroblastoma cells. It is suggested that tissue factor dependent activation of Bcl-2 might be responsible for the observed chemotherapy resistance. Although the paper is certainly interesting, the data are not all that convincing and several (experimental) issues should be addressed.

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

The data in figure 1 suggest that tissue factor by itself (without FVIIa) is of major importance in the observed chemotherapy resistance. Therefore all cell lines (with different amount of tissue factor) should be analysed with respect to chemoresponse.

To confirm the involvement of tissue factor in chemotherapy resistance, its important to check the effect of TF siRNA in this setting (thus the effect of tissue factor silencing on chemotherapy induced cell death should be studied.

A majority of the experiments aiming at the signal transduction cascades are performed with SK-N-SH cells (tissue factor negative) transfected with tissue factor. It would be more straightforward to have used the naturally expressing tissue factor cells (these data have to be added).

The paper needs proof of principal experiments. The authors show that tissue factor induces 1) chemotherapy resistance; 2) Jak/Stat and bcl-2 activation; 3) Akt phosphorylation and 4) tissue factor mutants are as effective as wildtype in Jak/Stat activation. However, there are no experiments that connect these data. For instance, bcl-2 or Akt inhibition should block tissue factor induced chemotherapy resistance. Furthermore, the effect of tissue factor mutants should be tested in the cell survival experiments.

Figure 5: pStat5 is increased by FVIIa in cells that do not express tissue factor. This should be explained.

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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)

Discretionary Revisions (which the author can choose to ignore)

Experimental details are lacking. It should be indicated which primary antibodies are used, or the interval between siRNA treatment and the experiments, etc

It is unclear why the authors use different assays for cell survival experiments depicted in figure 1 and figure 2.

Figure 4: the 5 minute time point discussed in the text is not indicated.

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, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests