Reviewer's report

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

Version: 1 Date: 19 November 2007

Reviewer: Lars C Petersen

Reviewer's report:

General
Coagulation factor VIIa (VIIa) induces intracellular signalling in certain cells transfected with its receptor, tissue factor (TF), and this response has been shown in previous reports to prevent apoptosis of these cells e.g. when serum starved. The present work takes this observation into a physiologically very relevant setting by a thorough characterization of the relation between cell survival and the TF-expression on neuroblastoma cells; and also by demonstrating a possible link to chemotherapy resistance. The relevance of the TF expression level is demonstrated by silencing of TF with siRNA and by TF overexpression. The signalling pathway in neuroblastoma cells is mapped with relevant techniques; and the resistance to doxorubicin is measured to illustrate chemotherapy resistance.

The study underscores the possible importance of neuroblastoma classification with respect to TF expression, and the putative use of TF-blocking agents in combination with chemotherapy to obtain optimal sensitivity to drug-induced apoptosis.

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

None

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

Apoptosis assay: How are cells detached and kept undamaged before FACS analysis?

Page 9: rationale for FVIIa and doxorubicin concentrations applied is missing. A relevant control would be to prevent FVIIa-mediated cell survival by a TF blocking antibody which might also be relevant in a clinical perspective.

Page 12: Fig 4C do not show dose-dependency as claimed in the text. The sentence in the Discussion (P 15, line 12) suggestng that the TF-mediated response to chemotherapy is dependent on ligation by FVIIa would be more
relevant if this had been tested with a TF blocking antibody.
All figures need a closer inspection / revision with respect to a clearer indication of whether or not the data in curves and bars shown are Means +/- S.D. (n=?).

Discretionary Revisions (which the author can choose to ignore)
Functional analysis of TF expression by measuring FVIIa-mediated FX activation on the cell surface.
MAPK phosphorylation was an important parameter in earlier TF-related apoptosis studies. Has this been tested? In any case it might be relevant to discuss.

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

Declaration of competing interests:
I declare that I have no competing interests.