Reviewer's report

Title: Simultaneous modulation of the intrinsic and extrinsic pathways by simvastatin in mediating prostate cancer cell apoptosis

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Reviewer: Vladimir Ivanov

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The study of Anna Goc et al. describes a role of regulation of the intrinsic and extrinsic apoptotic pathways by simvastation in prostate cancer cells. This is interesting and potentially important study, which, however, should be improved both technically and ideologically before publication in BMC Cancer.

So, despite the already high number of experiments, I would like to suggest some extras which would be able to underline the impact of the study.

Major Compulsory Revisions

1) One of the problems of this study is the performance of all experiments using only PC3 prostate cancer cells without “normal” control or a contrast prostate cancer line, such as LnCAP. All data regarding levels of apoptosis and total death are presented as changes in “fold of increase”. It would be very useful to demonstrate, at least on Fig. 1, these data as % of cells. Otherwise, I am quite confused on real effects of simvastatin and docetaxel in induction of apoptosis in prostate cancer cells.

2) The second problem is connected with Western data on Fig. 2, 4 and 5. The authors interpreted the data as effect of simvastatin on “expression of Bcl-2, Bcl-xL…” It is necessary to use more precise terminology as “protein expression or protein levels of Bcl-2…” for Western data and provide a reference for Table 1 that demonstrates gene expression data.

Furthermore, it would be very useful to indicate a real activity of Caspase-9 and caspase-3 based on spectrophotometric detection, because Protein:Actin ratio for these enzymatic proteins on Fig.2 and 4 does not look very convincing. I am also quite confused by extremely high levels of cleaved caspase-3 in Western analysis of control cells, see Figure 4.

3) A real disaster occurred with the presentation data on Fig.5. It is critically important to have enzymatic activity of Caspase-9 in control and transfected cells! There is an error in labeling vertical arm: Apoptosis(% of control) on Fig. 5, panel B.

4) Data of Table 1 and the corresponding protein analysis on Fig. 7 and 8 are very interesting and important. It would be very useful to present additionally surface expression levels of Fas Receptor in PC3 cells (based on immunostaining and FACS analysis) before and after simvastatin and Docetaxel
treatment.

Furthermore, an introduction of anti-FasL inhibitory antibody will allows the authors to receive a final proof on Fas-L/Fas-mediated apoptosis induced by simvastatin treatment.

5) Figure 9 needs in quite dramatic improvement, especially for the extrinsic pathway.

My general impression is that this study is still premature for publication in BMC Cancer and needs quite substantial revision with new experiments. However, I am quite enthusiastic on this study after a proper revision.

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.