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: Xu Dong Zhang

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The manuscript entitled “Simultaneous modulation of the intrinsic and extrinsic pathways by simvastatin in mediating prostate cancer cell apoptosis” described simvastatin-induced apoptosis through the intrinsic and extrinsic pathways in cultured human prostate cancer cells and tumor xenografts. The authors demonstrated that simvastatin induced intrinsic apoptosis by dephosphorylation of Bad, reducing the expression of Bcl-2, Bcl-xL and enhancing cleaved caspases 9/3, and extrinsic apoptosis by increasing the expression of Fas-L, Traf1 and cleaved caspases 8. These findings are of interest but lack of mechanism insights. Furthermore, this manuscript does not appear to be proofread properly.

Concerns

1. In Figure 1, there are only 3 figures whereas 4 figure legends. Simvastatin-induced apoptosis should be verified using more than one method, such as Annexin V/PI staining or blotting of caspases and substrates. In addition, additional prostate cancer cell lines should be tested.

2. In Figure 2A, which band is Bim? Although Bim has 3 isoforms, there are 2 bands that are not clearly labeled. Moreover, the figure for Bad blotting should be shown. Simvastatin-induced intrinsic apoptotic signaling needs to be better addressed, e.g. testing changes in mitochondrial outer membrane permeability. More cell lines should be tested.

3. In Figure 3, it would be better to show results from PC3 cell tumor xenografts.

4. In Figure 4A, the blots for Bad and PARP should be shown. In addition, the Caspase3 blot was over exposed.

5. In Figure 5, the blot for DN-caspase 9 is not in publishable quality.

6. In Figure 7, the blot for caspase 8 should be shown.

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.