Reviewer's report

Title: Dermcidin exerts its oncogenic effects in breast cancer via modulating ERBB signaling

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Reviewer: Samaya Krishnan

Reviewer's report:

The authors of the paper “DERMCIDIN EXERTS ITS ONCOGENIC EFFECTS IN BREAST CANCER VIA MODULATING ERBB SIGNALING” aim to understand the mechanism by which dermcidin elicits its oncogenic, prosurvival effects. The study reports that DCD expression correlates with HER2 in breast cancer. Knockdown of DCD reduces ERBB signaling, decreases resistance to oxidative stress, and a reduction in tumor volume in xenograft assays was also observed. The authors conclude that DCD mediates its oncogenic activities through the ERBB receptor signaling.

Major compulsory revisions

Previously, the authors have published a gene expression profiling study upon DCD knockdown in HER2+ (MM361) breast cancer cell line (Genes up- and down-regulated by dermcidin in breast cancer: a microarray analysis. Genet Mol Res. 2008 Sep 30; 7(3):925-32). One of the major conclusions drawn from this research article was that the expression of EGFR and its ligands were downregulated upon DCD knockdown. Fig4 from the present manuscript also draws similar conclusion. However, the Genet Mol Res. publication was not cited anywhere in the present manuscript. Details about the differences in the experimental methodology or method of data analysis, if any in comparison with the previous work, need to be explained in the present study.

The overexpression of the DCD-splice variant in breast cancer cells is an interesting observation; however, no further studies were pursued to understand the biological function of the variant. It is also unclear whether the knockdown of DCD also results in the reduction of the DCD-SV, and how these different isoforms integrate to regulate the ERBB signaling pathway.

The major conclusion of the paper that the pro-survival effects of DCD are due to the regulation of the ERBB signaling pathway is unsupported. It is also possible that the downstream signaling molecules analyzed such as AKT and p38 could also be phosphorylated by other signaling pathways. Specific inhibitors need to be used to confirm that DCD regulates PI3K/AKT and MAPK pathway through ERBB. Through RT-PCR, the authors found that DCD induces the expression of EGFR and other ERBB receptors, however, the protein levels of total EGFR (Fig6G) does not seem to be altered upon DCD expression. The author's comment on the biological significance of the upregulation of the transcript, but
not of the protein is needed in the discussion section. The strength of the data could be greatly increased if the author’s could validate the expression of the other ERBB receptors and their ligands at the protein level. Also, the author’s insight on how DCD could regulate the expression of these important receptors and their ligands need to be included in the discussion section.

Minor essential revisions

In addition, the manuscript needs to be edited to incorporate the correct figure numbers, for instance, Fig3E has not been labeled in the figures section, Fig2B and 2C are inter-changed in the text, no x-axis label in Fig5B and many more. Some of the conclusions drawn from the data are incorrect, such as, in Fig 5A, no difference in EGF, NRG1 is observed from the graph. However, the text claims that there is a decrease. Statistical analysis is missing in many graphs, and total protein for AKT, MAPK, and the input protein for pEGFR needs to be included. Methods explained is insufficient, need to be thorough.

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