Reviewer’s report

Title:Fas Activated Serine-Threonine Kinase Domains 2 (FASTKD2) mediates apoptosis of breast and prostate cancer cells through its novel FAST2 domain

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Reviewer: Alexander Tinnikov

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The paper is further development of investigation of a novel apoptotic pathway reported by the team earlier. They found previously that expression of a nuclear protein NRIF3 caused apoptosis in different breast cancer cells and identified a novel 30 amino acid domain in NRIF3 (“death domain” – DD1) responsible for the effect. The effect was specific for breast cancer. Later they found that NRIF3/DD1 strongly interacts with DIF-1, a transcriptional repressor, and showed that the effects of NRIF3/DD1 were mediated by blocking the repressing activity of DIF-1. They further identified a pro-apoptotic FASTKD2 gene as a target of DIF-1 repression in breast cancer cells.

Thus, NRIF3/DD1-DIF1-FASTKD2 pathway resulted in apoptosis only in breast cancer cells (prostate cancer cell were not tested in the earlier studies). Expression of pro-apoptotic FASTKD2 gene was shown to cause apoptosis in all tested cells.

The aim of the present study was to investigate the NRIF3/DD1-DIF1-FASTKD2 pathway in prostate cancer cells, because there are certain similarities between breast and prostate cancer. The authors showed that all prostate cancer cell lines tested, both androgen dependent and independent, rapidly undergo apoptosis in response to NRIF3/DD1 through the rapid expression of the FASTKD2 gene. FASTKD2 is related to 4 other proteins encoded in the human genome (FASTKD1, 3, 4, 5), and the authors demonstrated that only expression of FASTKD2 gene leads to apoptosis. The authors also studied which domain of FASTKD2 is critical for apoptosis and finally successfully identified a novel 81 amino acid FAST2 domain responsible for the initiation of apoptosis. This represents an important achievement meeting high standards of current studies of molecular mechanisms in cell biology.

This is a meticulously planned study essentially detailing the mechanisms of NRIF3/DD1 induced apoptosis the team discovered several years ago. The team is using up-to-date methods relevant to the tasks and the methods are adequately described. The authors present high quality convincing data and the title, abstract, discussion and conclusions are relevant to the aims and results. The data are presented in 6 figures with concise figure legends briefly describing the experiments and methods. The paper cites 22 references and acknowledges the funding agency and researchers who provided some DNA constructs used in the study.
The study is an important contribution to our understanding of the biology of breast and prostate cancers, especially in combination with the previous team's publications on NRIF3/DD1, DIF1 and FASTKD2. Breast and prostate cancer are a major cause of morbidity and mortality among women and men respectively in the United States and the world, and the data obtained is of potential translational significance.

This is a high quality original research paper and I recommend it for publishing in BMC Cancer.

Minor Essential Revisions (Errata):

INTRODUCTION (Page 3): We refer to this region as Death Domain-1 (DD1) since it is necessary and sufficient to mediate apoptosis of breast cancer cells. We refer to this region as Death Domain-1 (DD1) since it is necessary and sufficient to mediate apoptosis of breast cancer cells. DOUBLE SENTENCE

RESULTS (Page 5): In addition, evidence that NRIF3/DD1-mediated apoptosis in breast cancer cells involves caspase-2 comes from studies indicating that knockdown of caspase-2

This is consistent with a role for caspase-2 in

Legend for figure 2 (Page 19): GAL4 fusion proteins to ensure nuclear localization

Level of interest: An article of outstanding merit and interest 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