Reviewer's report

Title: The type II transmembrane serine proteases hepsin and TMPRSS3 are associated with breast cancer survival

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Reviewer: Brian F Clem

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The article by Pelkonen et.al. presents interesting data regarding the association and prognostic value of transcript and protein expression of both Hepsin and TMPRSS3 alone or in combination with respect to clinicopathological parameters and survival in a cohort of breast cancer patients. The authors demonstrate that, while Hepsin and TMPRSS3 are elevated in malignant breast tumors, low expression of both transcript and protein associate with poorer cancer specific survival and serve as independent prognostic biomarkers for breast cancer. This is intriguing in light that these proteins are members of type II serine transmembrane serine protease family (TTSPs), which have been proposed to be involved in extracellular matrix remodeling and promotion of tumor progression and invasion. However, there does seem to be considerable variation among the published literature on the role of these TTSPs in cancer progression among various tumor types, including prostate, renal cell carcinoma, and now breast. Even though, prior studies have examined Hepsin expression in breast cancer patients, this is the first report on the relationship of TMPRSS3. While the substantial amount of data supports the authors' conclusions, there are some issues/concerns that need to be addressed.

Major Compulsory Revisions

1. In paragraph 1, line 5, within the results section, the authors state that both TMPRSS1 and TMPRSS3 mRNA expression is higher in malignant breast tumors compared to the benign tumors. However, while the data for TMPRSS1 is confirmed within the statistical analysis in supplementary table S1, TMPRSS3 levels show no statistical difference and even a lower median expression within malignant tumors compared to benign. Within paragraph 1 of the discussion section, the authors narrow this description to well-differentiated tumors. In order to make this conclusion for TMPRSS3, statistical analysis should be performed between benign and the samples that the authors are describing as “well-differentiated” malignant tumors.

2. From the published literature, there appears to be a discrepancy between levels of these TTSPs and their association with cancer risk among various tumor types with some reports associating high expression with advanced disease while others demonstrate lower expression correlating with lower survival. The authors cite a published report by Xing et.al. (2011) as a reference for increased expression of Hepsin in breast cancer. However, they did not
discuss the clinical portion of that study, which demonstrated a significant association between high Hepsin expression and higher tumor stage as well as lymph node metastasis. This is in direct contrast with the data presented within this manuscript. At the least, the authors need to acknowledge this difference and discuss them in light of the present findings.

3. Notwithstanding their data demonstrating the association of low expression with decreased survival, the authors introduce TTSPs and their activity as a cellular mechanism to promote tumor progression and invasion and then conclude their findings by suggesting that Hepsin and TMPRSS3 have potential as therapeutic targets in breast cancer. In light of the observed alterations of these proteins during breast cancer progression, the authors should more adequately address the potential mechanism for therapeutic intervention. There are new reports (Han, ACS Med. Chem. Lett. 2014, 5, 1219) characterizing inhibitors of TTSPs, including Hepsin activity, and their potential as anti-cancer agents. Would these data suggest that these may be detrimental to breast cancer patients, especially in terms of treatment as it relates to disease stage of the patient? In addition, previous reports have demonstrated that endogenous inhibitors of TTSPs, HAI-1 and HAI-2, are down-regulated in advanced breast cancer specimens (Clin. Cancer Res., 10:202). It is not intuitive, why both target and endogenous inhibitor would be decreased during breast cancer progression.

Minor Essential Revisions

1. The axis for Supplementary Figure S2D needs to be changed in order to be consistent with the other figures within the manuscript.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:

I declare that I have no competing interests