Comparative microRNA profiling of sporadic and BRCA1 associated basal-like breast cancers

Yan et al, BMC Cancer

This is a very interesting manuscript which characterizes the molecular differences between BRCA1 mutant and non-BRCA1 breast tumors of the basal phenotype. The authors begin by carefully assessing the distinctions in miRNA profiles between the different subtypes of breast malignancies, and use this information to project differences which might exist in miRNA target genes. They then proceed to use a data mining strategy to collect evidence for alterations in the respective mRNA levels. However, realizing that the majority of miRNA targets are translationally repressed without a decrease in mRNA level, the authors proceed to assess which target genes might be impacted specifically at the protein level. The end result is a panel of three proteins of particular interest for which collective immunohistochemical analyses reveal a strikingly high level of sensitivity (inverse correlation) for BRCA1 mutant status. The most immediate practical application of these results relates to the use of this three protein IHC signature as a diagnostic biomarker, however, the data may also provide new insight into the biology of basal breast cancer and the relationship of BRCA1 mutant status to disease phenotype and clinical outcome.

These studies address important issues pertaining to triple negative breast cancer, a disease for which no specific targeted therapeutic approach has yet been identified or successfully implemented. The analyses have been carefully executed, utilizing a rather large collection of primary breast tumor specimens, producing valuable data which complement, validate, and extend the work of several other groups pursuing similar questions. The methods have been described in great detail and the experimental outcomes explicitly documented and made available for further analysis by other investigators.

Major Compulsory Revisions: None

Discretionary Revisions:

1. The authors have identified three proteins for which a specific negative correlation with BRCA1 mutation status has been established, which collectively might be useful as a diagnostic biomarker for this special category of breast
cancer. However, specific biological implications have not been discussed. The authors might want to take this opportunity to expound on possible connections between these three proteins and BRCA1 itself, the phenotype associated with BRCA1 mutation, and/or the clinical behavior of these tumors. For instance, cyclin D1 has been found to serve as a direct target of Notch1 in triple negative breast cancer, an antibody targeting neuropilin-1 has entered clinical trial, and the authors’ own previous publication describes an association between FOXP1 and familial breast cancer.

2. The use of the scoring system (0 – 7) adds considerably to the depth of information gained from the immunohistochemical analyses of the three proteins of interest, beyond categorical positivity or negativity. Although the degree of statistical significance of the IHC score is given (Table 3), it might be of considerable additional benefit if the distribution of scores was provided, either in graphical form or described in the text. For instance, are the scores bimodal? (suggesting more than one distinct population), or does a closer examination reveal that either one of the contributing parameters (% of cells positive or intensity of immunoreactivity) correlates particularly well with BRCA1 status?

3. The authors might consider mentioning the degree of overlap between the gene lists included in Supplemental tables 4 and 5 (or perhaps highlighting those genes in common, e.g. C9orf86 and XIAP which are included in both).

4. The principle component analysis graph (Supplemental figure 4) provides a valuable visual representation of the authors’ findings regarding the relationship between BRCA1 mutant status and the basal breast cancer phenotype overall. The authors might consider including this graph within the main manuscript.

Minor Essential Revisions:

1. Please clarify the status of CD99 expression in the BRCA1 versus other basal breast tumors. In the Results section, the text states that CD99 is “predicted to be upregulated” in BRCA1 vs. sporadic basal cancers. Yet the next sentence includes CD99 in the list of proteins which exhibit reduced positivity in BRCA1 mutant cancers, although the statistic provided (85% vs. 37%) and the table itself (Table 3) agree with the first sentence that CD99 is actually increased in BRCA1 mutant tumors. The next paragraph describing the data obtained with the second validation cohort states “an opposite association for CD99 … with sporadic basal cancers showing increased expression compared to BRCA1 cancers”, though the data for CD99 is not included in Table 4. The Discussion states that CD99 was reduced in BRCA1 mutant tumors in the initial cohort. -- It is clear that the results obtained for CD99 differed between the two experimental groups examined, however the text is not absolutely clear and it seems at least one of the statements may be incorrect.

Minor issues – not for publication:

1. Conclusion section: “… highly relevant to clinical trials investigated …” should probably be “investigating…”
**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.