Reviewer's report

Title: Gene expression meta-analysis identifies metastatic pathways and transcription factors in breast cancer

Version: 1 Date: 23 June 2008

Reviewer: Martin Abba

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Manuscript: “Gene expression meta-analysis identifies metastatic pathways and transcription factors in breast cancer” by Thomassen et al.

General:

In this manuscript, the authors identified several pathways that are differentially modulated in metastasizing human breast carcinomas compared to non-metastasizing counterparts. These findings are based on in silico meta-analysis of eight publicly available DNA microarray gene expression profiling studies. The authors employed the GSEA (Gene Set Enrichment Analysis) resource to compare the independently derived gene expression data set as was previously described by Subramanian et al., (2005). The bioinformatics design was mostly straightforward and in general the paper is well written. Finally, they described the roles of these gene sets in affecting the metastatic potential of breast cancer cells.

Major Compulsory Revisions

1) My major criticism towards this study relates to the biological relevance of the data presented. The authors identified 10 common biological mechanism involved in metastasis of breast cancer cells: (1) Cell cycle and proliferation related genes, (2) growth factors related genes, (3) metabolism, (4) angiogenesis pathway, (5) Gleevec pathway, (6) migration, (7) signal transduction related genes, (8) proteasome pathway, (9) immune system, and (10) DNA damage sensing and repair.

The conclusions that can be drawn from such enrichment analysis are limited due the global aspect of the information. Furthermore, what is truly novel about these findings, particularly given the authors’ findings that most of these pathways can be found to be differentially expressed in various other studies?

2) Breast cancer is not a single disease due to the characteristic cellular and molecular heterogeneity of breast tumors. Gene expression profiling of breast carcinomas identifies five molecular intrinsic subtypes of breast cancer associated with different clinical outcomes. In addition, development of metastases requires that a cancer cell must complete a series of steps involving complex interactions with the host microenvironment. This process involves the dysregulation of multiple
genes and transcriptional programs. In this sense, a specific molecular intrinsic subtype could differ from each other in the invasive capability, metastatization route, proliferation pathway etc. However, the authors suggest that all metastatic breast carcinomas behave similarly. Why the authors suppose it?

3) While the approach is reasonable, this work is essentially descriptive. There is not mechanistic, functional or gene expression validation of any of the differentially expressed gene sets/ pathways discovered in this study. This work would be much stronger if the authors had verified key gene changes by alternative techniques such as western or quantitative RT-PCR. Without such data, it is not possible to interpret the significance of these findings.

Minor Essential Revisions
None

Discretionary Revisions
None

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

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