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Review of: Gene expression profiling identifies molecular subtypes of inflammatory breast cancer

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F. Bertucci, P. Finetti, J. Rougemont, E. Charafe-Jauffret, N. Cervera, C. Tarpin, *et al*. Gene expression profiling identifies molecular subtypes of inflammatory breast cancer. ***Cancer Research*** 2005; **65**(6): 2170–8.

Abstract of the original article
Breast cancer is a heterogeneous disease. Comprehensive gene expression profiles obtained using DNA microarrays have revealed previously indistinguishable subtypes of non-inflammatory breast cancer (NIBC) related to different features of mammary epithelial biology and significantly associated with survival. Inflammatory breast cancer (IBC) is a rare, particular, and aggressive form of disease. Here we have investigated whether the five molecular subtypes described for NIBC (luminal A and B, basal, ERBB2 overexpressing, and normal breast-like) were also present in IBC. We monitored the RNA expression of approximately 8,000 genes in 83 breast tissue samples including 37 IBC, 44 NIBC, and 2 normal breast samples. Hierarchical clustering identified the five subtypes of breast cancer in both NIBC and IBC samples. These subtypes were highly similar to those defined in previous studies and associated with similar histoclinical features. The robustness of this classification was confirmed by the use of both alternative gene set and analysis method, and the results were corroborated at the protein level. Furthermore, we show that the differences in gene expression between NIBC and IBC and between IBC with and without pathologic complete response that we have recently reported persist in each subtype. Our results show that the expression signatures defining molecular subtypes of NIBC are also present in IBC. Obtained using different patient series and different microarray platforms, they reinforce confidence in the expression-based molecular taxonomy but also give evidence for its universality in breast cancer, independently of a specific clinical form.

Review

Inflammatory breast cancer (IBC) is the most aggressive variant of the disease with a distinct clinical presentation, microscopically characterized by tumour emboli in lymphatic vessels, and a poor prognosis [1,2]. Similar to the group of Bieche *et al*. [3], Bertucci *et al*. last year published an interesting paper [4] revealing differences in gene expression profile between IBC and non-inflammatory breast cancer (NIBC) based on a list of 109 genes. They also provided a second list of 85 genes associated with pathological complete response in IBC. Here, in the same cohort of patients, they explored the subtype classification previously reported by Perou *et al*. and

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Sørlie *et al*. [5,6] for (NIBC) in inflammatory cancer. While this classification has been confirmed by others in NIBC [7], so far it has not been evaluated in IBC.

First, using the 500 gene list of Sørlie *et al*., they extracted 120 genes common to their gene list and the one used by Sørlie *et al*. They validated this list on the Sørlie dataset [6], predicting correct classification of 89% of the samples before analysing their own set of tumours (37 IBC and 44 NIBC). Analysing their 44 NIBC tumours, 32 of these samples could be classified into one of the five subclasses defined according to Sørlie *et al*. [6], while 12 tumours could not be classified. Surprisingly, among their 37 IBC, 36 could be classified according to this system. Most interestingly, while the total number does not allow statistical comparison, their finding of 14 and 3 tumours, respectively, in the luminal A and B class was unexpected, suggesting the incidence of tumours belonging to each of these classes is not much different in IBC compared with what has been recorded previously for NIBC. The surprise rest primarily on the knowledge that luminal A tumours in particular are associated with high expression of ER alpha, while IBC in general is known to express little responsiveness to hormonal manipulation.

Finally, Bertucci *et al*. compared the tumour classification according to Sørlie *et al*. to their own previously identified 109 gene list discriminating between IBC and NIBC as well as their 85 gene list, predicting responsiveness to chemotherapy in IBC. Importantly, they found that their previous gene lists were able to discriminate between IBC vs. NIBC as well as responsiveness to therapy across all tumour classes.

The findings by Bertucci *et al*. suggest some interesting biological interpretations. The 'molecular portraits' discriminating the different classes identified by Perou *et al*. and Sørlie *et al*. are likely due to early events in tumour development; the finding of a particular cytokeratin profile associated with the 'basal' subgroup may indicate a different cell of origin compared to the luminal tumours. Interestingly, in a recent paper Zhao *et al*. [8] were able to shown that among lobular carcinomas, about 50% of the tumours harboured a distinct gene profile different from all the subgroups identified by Perou *et al*. and Sørlie *et al*. for ductal carcinomas, while the other 50% could be separated into the subclasses identified for ductal cancers. Bieche *et al*. [3] found the major discriminators between IBC and NIBC to be genes associated with transcription, growth factors and growth factor receptors; the discriminators were uniformly up-regulated in IBC. Whether this could mean that achievement of an IBC profile could be a late event, related to mutations in genes critical to growth arrest that may occur, to some degree, independent of earlier events, is too early to say, but is definitely a possibility.

Similar to Sørlie *et al*. and Bertucci *et al*. found the tumour subclasses to be associated with prognosis, although the difference between the luminal A class and the other classes were not as distinct as in our material [6]. What needs to be emphasized however is that the tumours analysed in this study were all from patients treated in prospective protocols, incorporating administration of tamoxifen for 5 years to all patients harbouring a receptor positive tumour [9,10]. This may likely have improved outcome among patients with luminal A tumours but not those with tumours belonging to the receptor negative classes, substantiated by the finding that the prognostic impact of the luminal A class was of a smaller magnitude among the node negative patients reported by the Amsterdam group that were not exposed to adjuvant therapy [11,12]. Use of adjuvant endocrine therapy was not accounted for in detail in the papers by Bertucci *et al*. [4,13], and we lack information on whether the 'luminal A' gene profile is associated with hormone sensitivity in IBC.

The achievements through microarrays and gene profiling have up to now been encouraging but also disappointing. The list of conventional prognostic factors in breast cancer is long; what we currently are observing is an increasing list of molecular signatures identified by supervised clustering with limited overlap of genes [14,15], the finding that multiple signatures may be derived from a single dataset [16] and the challenging question whether use of conventional factors in a combined index may provide prognostic information of similar value [17]. Although statistical associations between gene expression profiles and treatment outcome have been reported [4,18–21], they lack the sensitivity to be of clinical use selecting patients for therapy. To improve therapy, we need to explore not only statistical associations but to identify the biological mechanisms behind phenomenon as the metastatic process and drug resistance [22,23]. As such, this paper by Bertucci *et al*., together with the papers by Perou *et al*. and Sørlie *et al*., defining breast cancer subclasses, and the recent study by Glinsky *et al*. [24] reporting a stem-cell signature across tumour forms, may add information to our understanding of the biological mechanisms controlling vital processes in cancer development and behaviour.

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