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...
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, while the total number does not allow statistical comparison. Bieche et al. [8] found that their previous gene lists were able to predict the tumour class 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. 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 show 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.

References


