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Integrated breast cancer genomics

Predicting survival and therapy responses of breast cancer patients is a significant challenge. Two studies in this issue of *Cancer Cell* present a novel integrated analysis of genomic and transcriptomic profiles of 145 primary breast cancers and 51 established cell lines. Data from clinical tumors highlighted mechanisms of disease and facilitated identification of potential therapeutic targets and prognostic biomarkers. An extensive well-characterized cancer cell line resource opens up opportunities to explore the determinants of cellular responses to existing and emerging therapies. Taken together, these studies illustrate how integrated molecular profiling may one day significantly impact diagnosis and therapeutic choice in human breast cancer.

Since the early days of microarray technology, numerous investigators have analyzed clinical cohorts of human breast cancers in order to better understand disease pathogenesis, and to provide a molecular explanation for the heterogeneity in the outcome and therapeutic response of breast cancer patients. A PubMed search identifies 827 publications with the keywords "microarray" and "breast cancer." Most of the research has focused on the characterization of transcriptional profiles of breast cancer (Table 1). For example, Perou et al. (2000) and Sørlie et al. (2001) established the classification of breast tumors into five different phenotypic subtypes. van 't Veer et al. (2002) and van de Vijver et al. (2002) divided breast cancer patients into those with favorable and unfavorable outcome with high accuracy, suggesting the potential of microarrays as a diagnostic test to select patients who would need adjuvant therapies. Many other studies have also identified gene signatures predictive of distant metastasis or survival (Wang et al., 2005; Naderi et al., 2006). Several authors have also studied profiles of genomic DNA copy numbers (Hicks et al., 2005; Bergamaschi et al., 2006; Fridlyand et al., 2006) using array-based comparative genomic hybridization (CGH). These studies have identified numerous specific genetic alterations and have also defined subtypes of breast cancers at the genomic level.

Few of the previous studies have integrated genomic and transcriptomics profiles from the same patient cohorts (Bergamaschi et al., 2006). This is a key contribution of the Chin et al. (2006) paper appearing in this issue of *Cancer Cell*. With 101 tumors comprehensively profiled at the DNA and RNA levels, the authors were able to better define the impact of specific genetic events on breast cancer phenotypes and clinical outcome. They indicate that genomic profiles provide additional prognostic information as compared to what is available from transcriptomics profiling alone. For example, patients whose tumors had one or more DNA amplifications had a poor prognosis independently of the previously defined five major gene expression classes (Sørlie et al., 2001). Interestingly, copy number imbalance (i.e., any deviation from diploidy) may be prognostically important for a specific region at 8p11-p12. Integrative DNA/RNA microarray profiling may also suggest novel therapeutic opportunities. Chin et al. list nine potential therapeutic targets, which, like the prototype HER2 oncogene, are activated by recurrent gene amplifications in breast cancer and may show an association with aggressive tumor types. Many of these are potentially druggable by small-molecule inhibitors. For example, two potential amplification targets, the GRB7 and PNMT genes, reside in the HER2 amplicon at 17q12 and are coactivated in breast cancer with HER2. Their targeting could provide synergistic therapeutic responses with Her2 inhibition or contribute to poor responses against Herceptin (Kao and Pollack, 2006).

Clinical tumor profiling is informative but at best associative in nature. In order to identify causative links between genes and tumor phenotypes, it is necessary to use cell lines. The Neve et al. (2006) paper describes the DNA and RNA microarray profiling data for a comprehensive resource of 51 different breast cancer cell lines,

Table 1. Selected previous microarray profiling studies of human breast cancer

Publication	No. of samples (gene expression)	No. of samples (array-CGH)
Chin et al., 2006	130	145
Neve et al., 2006	51	51
Bergamaschi et al., 2006	89	89
Fridlyand et al., 2006		67
Hicks et al., 2005		101
Naderi et al., 2006	135	
Perou et al., 2000	65	
Sørlie et al., 2001	78	
van 't Veer et al., 2002	98	
van de Vijver et al., 2002	295	
Wang et al., 2005	286	

including most of those available today in the public domain. In contrast to the commonly expressed reservations among cancer researchers, as a group the breast cancer cell lines were found to be surprisingly representative of the primary tumors. Although cell lines had a much higher number of genetic changes per sample than primary tumors, genetic events that were exclusively seen in the breast cancer cell lines were rare. As has been demonstrated with the extensively studied NCI-60 cancer cell line set (http://dtp.nci.nih.gov/index.html), molecular profiles of cancer cell lines could help to identify pharmacogenomic predictors of response to therapeutic compounds. For example, Neve et al. (2006) treated cell lines with Herceptin and identified protein levels and genomic aberrations that were correlated with response and resistance. Indeed, if more cancer drug response data became available, this "UCB-51" set could be much more representative and informative than the NCI-60 data series for targeted exploration of therapeutic hypotheses in breast cancer.

As much as these two studies advance the field, there are also many important aspects that remain to be explored in the future. First of all, every clinical study is dependent on the patient selection and therapies administered. These effects cannot be fully evaluated in retrospective studies. The present studies focused on amplifications, yet deletions and unbalanced translocations inactivating or activating cancer genes may also be important. As compared to the ~1 Mb resolution of the BAC arrays used in these studies, the latest generation oligo-array-based CGH can approach theoretical limits of about 10 kb across the nonrepetitive genomic DNA. Transcriptional profiling technologies also continue to advance. For example, alternatively spliced versions of genes are detectable with exon-level analysis, and detection of noncoding RNAs may pinpoint new information. The present studies focused on genetic profiles, but epigenetic profiling has also been shown to be of significant importance. Metabolic and proteomic fingerprints as well as the mathematical analysis and modeling of all the "omics" data are needed to complete a comprehensive understanding of the molecular deregulation of the breast cancer cells in vitro and in vivo. Finally, taking molecular profiles toward the clinical diagnostic setting is the "final frontier" and will require standardized technologies, quality control, and prospective testing in large series of patient cohorts. This is a major effort for any single molecular profiling platform, and an enormous challenge for the clinical application of integrated multiplatform profiling.

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Radiation resistance and stem-like cells in brain tumors

The concepts of stem cells being resistant to therapy, stem-like cells existing in brain tumors, and these tumors initially responding to therapy followed by recurrence are well documented. On this foundation, a recent paper in *Nature* has demonstrated that CD133-expressing glioma cells in vivo and in culture are relatively resistant to radiation. The mechanism of resistance involves the cell-cycle-regulating proteins CHK1/CHK2. The data raise many questions about the details of radiobiology of stem-like cells in their native environment within tumors in vivo. These answers may lead to better optimization of radiation treatments and schedules for these patients.

Radiation biologists were the first to formulate the concept of stem cells. The term "stem cell" was coined in the context of clonogenic cells surviving radiation that were able to repopulate the spleen (McCulloch and Till, 1960, 2005). In the gut, cells with a relatively low baseline proliferation rate were found to be relatively resistant to radiation and respond