In the current issue of Clinical Cancer Research, Andre et al. apply high-resolution arrays to elucidate copy number anomalies in breast cancer. They identify distinct copy number anomaly patterns in different breast cancer subtypes that implicate a number of genes as potential therapeutic targets and as potential markers of therapy responsiveness.

In this issue of Clinical Cancer Research, Andre et al. (1) integrated high-resolution analysis of copy number anomalies (CNAs), in 106 breast tumors with transcriptional profiling data in an attempt to map regions and identify drivers of CNAs. The purpose of this study was to determine if this integrated high-resolution approach could advance breast cancer classification and identify new targets for the development of novel therapies.

Multiple studies have sought to map patterns of CNAs in breast cancer to identify potential predictive markers and targets for therapy (2–9). Although much progress has been made, the identification of driver genes whose aberrant function plays a role in selection of the shape and location of CNAs remains problematic. It is likely that multiple drivers exist for most CNAs in breast cancer and that these drivers function in concert with other abnormalities during the development and selection of CNA structure. Validation of driver genes can be facilitated by the demonstration of alterations at the DNA, RNA, and protein levels; functional effects on the phenotypic behavior of breast epithelial cells; and an effect on tumor initiation, progression, or therapy responsiveness, all observations that support a critical role for these genes in breast carcinogenesis and as potential targets for novel therapies.

Using a nonnegative matrix factorization method, three comparative genomic hybridization–based breast tumor clusters were identified. The class I, II, and III clusters possessed, on average, 81, 95, and 48 CNAs, respectively. The class I cluster contained significantly more triple-negative/basal breast tumors, class II included most (9 of 11) HER2-overexpressing and (9 of 13) luminal B tumors, whereas class III was characterized by the highest frequency (17 of 32) of luminal A tumors. Chromosomal aberrations that were relatively characteristic of these classes included gains at 6p21 and 6p23 and loss between 15q14 and 15q22 (class I), gain at 17q11 and 17q24 (class II), and gains at 1q22-31 with frequent losses in 16q (class III). This suggests that the underlying mechanisms and selection of CNAs are likely to be different between these classes and the triple-negative/basal, HER2-overexpressing, and luminal tumors that are enriched in the classes, supporting the contention that these tumors have different etiologies and will respond optimally to different therapeutic approaches. Furthermore, the integration of genomic, transcriptional, and likely functional proteomic data should facilitate identification of more homogeneous subgroups within the established breast cancer subtypes that possess shared exploitable molecular targets.

To identify potential driver genes, minimum common regions were identified as the maximal overlapping zones across samples within each abnormal chromosomal region. Although most of the CNAs had been identified previously, the current analysis increases the resolution as well as the number of patient samples analyzed. Eleven minimum common regions were gained in >20% of cases. Several genes residing within the minimum common regions identified have previously been linked to breast cancer biology (e.g., MYC, ERBB2). Two transmembrane tyrosine kinases (ERBB2 and FGFR1) showed amplification in three or more consecutive probe sets in at least 10 of 106 samples. Thirty-seven minimum common regions were lost in >20% of samples. The frequently lost genes include BRCA1, signal transducer and activator of transcription (STAT) 3, STAT5A, STAT5B, and MAPT. Intriguingly, a minimum common region on 17q12 that was lost in 17% of cases included genes encoding 8 chemokines that potentially alter immune or inflammatory tumor responses. Specifically, triple-negative breast cancers were characterized by more frequent gains of genes at 6p21-25 including VEGFA, E2F3, and NOTCH 4 as well as by more frequent epidermal growth factor receptor (EGFR) gain and PTEN loss.

The comprehensive approach used by Andre et al. (1) increases the likelihood that novel targets and markers will be identified. However, it is important that the lists of potential driver genes within CNAs identified by the approaches used in this study be treated with caution. Even after high-resolution analysis, most CNAs contain multiple genes that could act as...
drivers. Furthermore, CNAs may be selected by mechanisms other than a drive to increase the RNA and protein levels of potential targets. Other possible mechanisms of CNA selection include genomic rearrangements, promoter and enhancer element alterations, aberrant splicing, and changes in non-coding RNA. Clearly, further mechanistic studies are required to validate aberrant genes identified in the current study as novel therapy targets and/or markers. With these caveats, FGFR1, RAB11FIP, BRF2, ASH2L, ERLIN2, WHSC1L1, EIF4EBP1, BAG4, LSM1, DDHD2, ERBB2, PNMT, PERLD1, GRB7, and STARD3 are both located within amplicons and increased at the RNA level in breast cancer and thus could represent useful therapeutic targets or markers warranting further evaluation. Using a similar approach, Chin et al. (3) previously showed that recurrent CNAs differ between breast tumor subtypes defined by gene expression profiling and that coordinate assessment of RNA levels and CNAs can classify patients according to outcomes. Sixty-six potential target genes were deregulated by high-level amplification in breast cancer in this study, with nine of the genes proposed to be “druggable” (FGFR1, IKKβ, ERBB2, PROCC, ADAM9, FNTA, ACACA, PNMT, and NR1D1). We and others have used multiple
approaches to validate Rab25 (1q22), PIK3CA (3q26.3), FGFR1 (8p11), PVT1, MYC (8q24.2), CCND1, FGF3/4, PAK1 and EMSY (11q13), HER2 (17q12), AKT2 (19q13.2), and AIB1 (20q13.2) as potential driver genes in breast cancer (1, 3–8). The study by Andre et al. (1) extends the repertoire of potential markers and targets for future investigation.

The integration of comprehensive data characterizing CNAs and sequence alterations along with the transcriptional and functional proteomic effects of these aberrations unearths the possibility of applying a systems approach to understanding the complex molecular interactions that contribute to breast carcinogenesis (Fig. 1). Indeed, recent studies have begun to show that an integrated view of complex CNAs and sequence alterations in cancer can identify a limited number of pathways that could prove useful for cancer diagnosis and therapy (10). A recent study of glioblastoma has proposed coordinate high-resolution analysis of CNAs, mutations, methylation, and transcriptional profiles with integration of these data into functional networks as a more efficient approach to identify drivers (11). Such advances will allow the development of novel therapy strategies in cancer that exploit global pathway activation patterns rather than the function of individual targets. Because the development of resistance to novel treatments frequently involves reactivation of the pathway that mediated the oncogenic effects of the inhibited target (12), this approach may be less susceptible to the development of resistance than current targeted therapy approaches.

Further advances in comparative genomic hybridization technologies as well as in the comprehensive assessment of large numbers of tumors have the potential to provide higher resolution of CNAs. Technological advances such as molecular inversion probe (MIP) profiling are also beginning to allow comprehensive study of the genome in formaldehyde-fixed paraffin-embedded samples because this will facilitate the interrogation of large numbers of stored cancer samples with long term follow-up data. Ultimately, an improved ability to combine information from global genomic, transcriptional, proteomic, and functional technologies (Fig. 1) to identify and characterize cooperating events between multiple genes and genomic aberrations will be necessary to address the complexity of breast tumorigenesis and fully exploit these aberrations for patient management.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

References
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