Use of gene expression signature to predict response to combination chemotherapy in breast cancer clinical subgroups.

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Abstract:

Background: Accurate stratification of patients prior to treatment with combination chemotherapy would allow non-responders to receive an alternative treatment in a timely manner and potentially improve clinical outcomes. We describe a 22-gene signature that accurately predicts response to antimitotic combination chemotherapy for breast cancer. This signature was selected in a well characterized system that models a key step disrupted in tumorigenesis: the formation of spatially accurate mammary ductal units by breast epithelial cells. Hence the 22 genes represent a biological process that is independent of any specific patient set or predefined clinical classification. **Methods:** To determine whether genes with differential expression during human mammary acinar morphogenesis predict response to combination chemotherapy in breast cancer, we have analyzed results from two published microarray datasets (Fournier, et al., 2006; Popovici et al., 2010). Expression levels of the majority of genes that were coordinately down regulated during acini formation were significantly associated with response to combination chemotherapy treatment. A 22-gene signature representing the down regulated genes was evaluated independently in each of three breast cancer clinical subgroups, ER-positive (n=146), HER2-positive (n=41), and triple negative (n=90) using two methods of analysis, hierarchical clustering and logistic regression. **Results:** Hierarchical cluster analysis results showed that the 22 genes accurately stratified patients in each of the three subgroups by response (Fisher's Exact $p<0.05$). Logistic regression with 3-fold cross validation demonstrated that different models accurately predicted response in these subgroups (AUC ≥ 0.7). We have observed that the 22-gene signature is broadly effective across independent patient clinical subgroups in its ability to stratify patients according to chemotherapy response in breast cancer. **Conclusions:** The 22-gene signature has the potential to provide patients, early in the care process, with accurate and personalized information to predict response to combination chemotherapy.