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Molecular Differences May Be Used to Predict Early vs. Late Hormone Receptor-Positive Breast Cancer Recurrence

- Molecular differences exist at diagnosis of hormone receptor-positive breast cancer.
- Understanding tumor biology will help tailor treatment.

SAN ANTONIO — Researchers may have discovered a series of genes that will help predict whether or not a woman with hormone receptor-positive invasive breast cancer will experience early, late or no recurrence of her disease.

Minetta C. Liu, M.D., associate professor of medicine and oncology and director of translational breast cancer research at Georgetown Lombardi Comprehensive Cancer Center, presented the findings at the 2011 CTRC-AACR San Antonio Breast Cancer Symposium, held Dec. 6-10, 2011.

“There are clear biological differences within the supposedly unified group of hormone receptor (HR)-positive breast cancers, and these differences distinguish subtypes relative to the time at which they recur,” Liu said. “Understanding what drives these distinctions will allow us to tailor treatment and improve patient outcomes.”

Women with HR-positive breast cancer are frequently treated with tamoxifen, which is credited with saving the lives of hundreds of thousands of women. Although tamoxifen prevents or delays cancer recurrence in many women, some will recur 10 years or more from their original diagnosis. Until now, the molecular basis for this recurrence pattern was unknown.

Liu and colleagues, in collaboration with investigators from the University of Edinburgh, evaluated high-quality frozen tumor samples obtained at the time of breast cancer diagnosis. These tissue samples were linked to data on treatment and clinical outcomes,

allowing researchers to analyze gene expression patterns present before the initiation of any systemic therapy.

Together with engineers at Virginia Polytechnic Institute, Liu and colleagues identified significant gene expression patterns among the tumor samples. These patterns correlated strongly with the development of distant metastatic disease.

“We confirmed what many have already suspected,” said Liu. “There are biological drivers that define — at the time of tumor development — whether or not breast cancer will recur early, late or not at all. Now we need to validate these findings and take our knowledge to the next step.”

Liu hopes that this research can be used to help personalize treatment in day-to-day clinical practice. “Endocrine therapy and chemotherapy are not without toxicity,” she said. “The ability to predict which patients will recur early in their treatment course can lead to more appropriate recommendations for adjuvant chemotherapy. It might also identify those women who would benefit most from studies using investigational agents to enhance the effects of tamoxifen or aromatase inhibitors.”

She added: “At the other extreme are those patients with HR-positive tumors who recur long after completing five years of endocrine therapy. These are the patients for whom extended endocrine therapy and its related side effects are really worth it.”

The team’s next step is to validate their predictive model for the timing of recurrences on tamoxifen so that physicians and patients can make more informed decisions about the potential added benefits of adjuvant chemotherapy, extended endocrine therapy and involvement in clinical trials. They will also investigate combinations of molecular targets with the ultimate goal of delaying or preventing the development of metastatic breast cancer, Liu said.

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The mission of the CTRC-AACR San Antonio Breast Cancer Symposium is to produce a unique and comprehensive scientific meeting that encompasses the full spectrum of breast cancer research, facilitating the rapid translation of new knowledge into better care for patients with breast cancer. The Cancer Therapy & Research Center (CTRC) at The University of Texas Health Science Center at San Antonio, the American Association for Cancer Research (AACR) and Baylor College of Medicine are joint sponsors of the San Antonio Breast Cancer Symposium. This collaboration utilizes the clinical strengths of the CTRC and Baylor and the AACR’s scientific prestige in basic, translational and clinical cancer research to expedite the delivery of the latest scientific advances to the clinic. The 34th annual symposium is expected to draw nearly 8,000 participants from more than 90 countries.

Presenter: Minetta C. Liu, M.D.

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Title: Molecular Signaling Distinguishes Early ER Positive Breast Cancer Recurrences Despite Adjuvant Tamoxifen.

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Background: Unlike recurrences with other therapies, ER+ breast cancers (BC) can recur >10 yrs after an apparent successful period of adjuvant endocrine therapy. The molecular basis for this pattern of resistance is unresolved. We addressed the hypothesis that early recurrences during tamoxifen (TAM) treatment exhibit different biological characteristics than those that recur years later by assessing for variation in their respective transcriptomes.

Methods: Appropriate tumors were identified from a set (BC030280) of snap-frozen tumor biopsies collected in Edinburgh from subjects with stage I-III BC before starting TAM (no chemotherapy); all had >10 yrs follow-up. Using rigorous standard operating procedures, high quality total RNA was extracted from samples with >50% malignant epithelium and arrayed on Affymetrix U133 Plus 2.0 GeneChips. Raw data were normalized using PLIER and analyzed with an adapted validated training and internal cross-validation workflow to avoid gene selection bias. A published dataset (Loi) was used for independent classifier validation that best fit our criteria for sample size, treatment (TAM only), data quality, and recurrence distribution. Early (E) vs late (L) recurrences were defined as distant relapse <3 vs >10 yrs from diagnosis. To explore putative mechanistic associations driving the transcriptome differences, a novel computational procedure was developed to integrate gene expression data with protein-protein interaction (PPI) data and create a statistical network model of the signaling. Metropolis sampling, a Markov Chain Monte Carlo method that can be implemented as a modified random walk procedure, identified ER network topology represented by the genes (nodes) and their predicted interconnections (edges).

Results: A support vector machine with recursive feature elimination was used for the binary classification tasks on the BC030280 dataset. The optimized classifier for E vs L recurrence was independently tested on the Loi dataset with high levels of accuracy, specificity, and sensitivity.

	E vs L (n)	accuracy	accuracy	sensitivity	AUC	PPV; NPV	HR; <i>p</i>
BC030280	24 vs 15	0.90	0.95	0.81	0.87	0.91; 0.81	3.45; <0.0001
Loi	12 vs 19	0.77	0.83	0.74	0.81	0.88; 0.67	3.11; 0.0004

Classifier validation is supported by the respective survival curves (not shown). Gene set enrichment analysis reveals the top PPIs are primarily related to apoptosis (23/50; $p=2.9e-13$) and proliferation (14/50; $p=6.8e-5$). Substantial overlap of the network features and topology was seen between datasets. Specifically, increased relative expression of ESR1, ESR2, EGFR, BCL2, and AR was seen in L vs E recurrent tumors, and increased expression of CALM1, CALM2, CALM3, SRC, CDK1, and MAPK1 was seen in E vs L recurrent tumors. Several hubs (nodes with >5 edges) independently predicted for recurrence in additional public datasets of ER+ BC.

Discussion: Our work provides clear evidence that robust molecular differences exist between ER+ BC that recur early vs. much later despite adjuvant TAM. Exploiting these differences will improve our understanding of involved signaling pathways, allow for the reliable prediction of early treatment failure, and guide use of novel therapeutics specifically directed at preventing E vs L recurrences on endocrine therapy.