The American Journal of Pathology, Vol. ■, No. ■, ■ 2017

The American Journal of PATHOLOGY
ajp.amjpathol.org

Breast Cancer Theme Issue

REVIEW

Discerning Clinical Responses in Breast Cancer Based On Molecular Signatures

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Accepted for publication August 3, 2017.

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Breast cancer represents a heterogeneous collection of diseases with disparate clinical behaviors, responses to treatment, and patient outcomes, despite common histopathological features at diagnosis. Examination of molecular signatures of breast cancer (based on complex gene expression patterns) enabled identification of several intrinsic molecular subtypes: luminal A, luminal B, human epidermal growth factor receptor 2 enriched, and basal like. The intrinsic subtypes are associated with measures of clinical aggressiveness, but do not perfectly predict patient outcomes. Several molecular signatures have been developed for prediction and prognostication of breast cancer outcomes. This review describes the molecular classification of breast cancer and the use of predictive/prognostic molecular signatures for guiding treatment decisions in breast cancer patients. *(Am J Pathol 2017, ■: 1–9; http://dx.doi.org/10.1016/j.ajpath.2017.08.002)*

Q5 Breast cancer is well recognized as a heterogeneous collection of neoplastic disorders affecting the breast tissue, with various morphologic presentations and disparate clinical behaviors and outcomes. The challenge for clinicians who treat breast cancer is prediction of which patients will benefit from specific interventions, minimizing overtreatment of patients with indolent disease and providing appropriate treatment for patients with aggressive disease.

Traditional histopathological classification of breast cancers provides a crude guide for therapeutic strategies applied to individual patients. This classification scheme is based on various features of the primary neoplasm, including morphologic appearance and associated pathological features. The most common histological breast cancer subtype is invasive ductal carcinoma (representing 80% of invasive breast cancers), followed by invasive lobular carcinoma (representing approximately 10% of invasive breast cancers), with the balance composed of less common histological subtypes, including mucinous, cribriform, micropapillary, papillary, tubular, medullary, metaplastic, and inflammatory carcinomas.[1,2] Although these histological subtypes are used in the clinical classification of breast cancer in individual patients, it is known that histological appearance alone does not reliably predict clinical behavior of the disease in individual patients. Other pathologic features of breast cancer provide additional insights into probable clinical behavior, including tumor size, cellular features (nuclear grade and proliferation index), nodal status, and invasion of the lymphatics or vasculature. In addition, the expression (or lack of expression) of specific protein markers is associated with aggressiveness of disease, in particular hormone receptor status [expression of estrogen receptor (ER) and progesterone receptor] and human epidermal growth factor receptor 2 (HER2).[3] On the basis of

Supported by the UNC Lineberger Comprehensive Cancer Center Q2 (W.B.C.), the UNC Center for Nanotechology Excellence (W.B.C.), the UNC Department of Pathology and Laboratory Medicine (W.B.C.), Novartis (C.K.A.), Sanofi (C.K.A.), toBBB (C.K.A.), GERON (C.K.A.), Angiochem (C.K.A.), Merrimack (C.K.A.), PUMA (C.K.A.), Lily (C.K.A.), Merck (C.K.A.), Oncothyreon (C.K.A.), Cascadian (C.K.A.), Nektar (C.K.A.), and Tesaro (C.K.A.).

Q3 Disclosures: C.K.A. serves in an uncompensated advisory role to Novartis, Sanofi, toBBB, GERON, Angiochem, Merrimack, Lily, Genentech, Nektar, and Kadmon, related to various breast cancer clinical trials.

This article is part of a review series on next-generation breast cancer omics.

http://dx.doi.org/10.1016/j.ajpath.2017.08.002

these clinical characteristics, breast cancer presents as several distinct entities, but none of these accurately predicts disease aggressiveness, responses to treatment, likelihood of recurrence or metastasis, or long-term patient outcomes.

The extent of heterogeneity among breast cancers was not fully realized until transcriptomic approaches began to characterize molecular signatures based on gene expression patterns.[4–6] Early molecular classification of breast cancer was achieved using microarrays to interrogate concurrent gene expression patterns across a large number of transcripts.[4–6] Subsequently, breast cancer molecular subtypes were shown to be associated with distinct clinical outcomes,[7] to be useful in patient prognositication,[8] and to predict responses to neoadjuvant chemotherapy.[9] These studies (and more recent investigations) have improved our understanding of the biology of breast cancer subtypes, the extent and nature of breast cancer heterogeneity and diversity, and how molecular classification of breast cancer in individual patients might be used in the clinic.

Since the first recognition of intrinsic subtypes among breast cancers,[10] several methods and approaches have been used to subclassify breast cancers and/or to prognosticate/predict clinical behaviors based on complex gene expression patterns. This review highlights some of these gene expression signatures and their potential for clinical application in personalized breast cancer medicine. A comprehensive review of gene expression signatures identified in breast cancer is beyond the scope of this review. Rather, the molecular signatures discussed herein reflect those that have scientific importance for our understanding of diversity among breast cancers and molecular signatures that have found clinical utility as Federal Drug Adminstration (FDA)–approved tests or that have great potential for clinical impact based on research studies.

Molecular Classification of Breast Cancer

The Intrinsic Molecular Subtypes

Early microarray-based transcriptomic studies used hierarchical clustering to identify subsets of breast cancer using genes whose expression varied across individual cancers, but not between repeated analysis of the same cancer.[5,7,10] Hierarchical clustering analysis is a method for identification of similarity and dissimilarity among individuals (or breast cancers in this case) based on complex patterns that emerge from large data sets of quantitative traits (such as gene expression patterns). Four major molecular subtypes emerged from these early transcriptomic studies: i) luminal, ii) HER2 enriched, iii) basal like, and iv) normal like. The gene expression patterns that appear to drive these classifications are associated with the expression (or lack of expression) of several major gene families, including ER, ER-related genes, genes associated with cell proliferation, HER2, and genes proximal to HER2 in the amplified region of chromosome 17q12.[5,7,10–12]

The normal-like subtype presents a conundrum as these cancers tend to be associated with poor prognosis and can be either ER positive or ER negative. It has been suggested that the normal-like breast cancers may fail to be appropriately classified into one of the other subtypes because of the presence of excess contaminating normal breast epithelium.[12] This molecular subtype is frequently reported in gene expression studies, but rarely discussed as a biological entity.

Among the remaining major molecular classifications of breast cancer, the luminal cancers are ER positive, whereas the HER2-enriched and basal-like cancers are ER negative. The luminal breast cancers are routinely subdivided into two (luminal A and luminal B) or three (luminal A, luminal B, and luminal C) groups.[10] However, subdivision of the luminal breast cancers into luminal A and luminal B appears to be the most robust and reproducible. The distinction between luminal A and luminal B breast cancers is linked to the overexpression of HER2 and proliferation markers, with luminal A breast cancers expressing low levels of proliferation-associated genes and luminal B breast cancers expressing high levels of proliferation-related genes. Emerging from the basal-like breast cancers are two subtypes: basal-like breast cancers and claudin-low breast cancers.[13] The claudin-low breast cancers are enriched for markers of epithelial-to-mesenchymal transition and stem cell–like and/or tumor-initiating features.[13]

The Cancer Genome Atlas Network published results on comprehensive analyses of gene expression patterns, gene mutations, DNA copy number, DNA methylation, and miRNA expression patterns across a large cohort of approximately 800 breast cancers.[14] Using multiple platforms for gene expression analysis (including microarrays and next-generation sequencing), The Cancer Genome Atlas Network study reproduced the well-recognized ER-positive and ER-negative molecular subtypes of breast cancer.[14] Of significance, The Cancer Genome Atlas Network study was able to link other genetic and epigenetic lesions with the molecular subtypes identified through gene expression analyses. For instance, HER2-enriched and basal-like breast cancers display a high rate of somatic mutation in the *TP53* tumor suppressor gene (72% to 80%), whereas the other breast cancer subtypes exhibit *TP53* gene mutations much less frequently (12% to 29%).[14] Luminal A, luminal B, and HER2-enriched subtypes displayed significant rates of mutation in the *PIK3CA* gene (45%, 29%, and 39%, respectively), whereas basal-like breast cancers were rarely associated with mutation of this gene (9%).[14] It is notable that numerous genes (involving at least 177 cancer-associated genes) were mutated in small percentages of cancer (>20,000 nonsilent somatic mutations among 510 breast cancers), but few genes were found to be mutated in >10% of breast cancers within or across the molecular subtypes.[14]

Copy number variations (reflecting gene deletions and amplifications) were found to affect numerous genes and gene regions, including amplifications affecting chromosomal regions that harbor *PIK3CA* and *ERBB2* and deletions

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