

VIEWPOINT

Needles in a haystack: finding recurrent genomic changes in breast cancer

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Abstract

Significant advances over the past decade have enabled scientists to obtain increasingly detailed molecular profiles of breast cancer. The recent analysis by The Cancer Genome Atlas published in the September 2012 issue of *Nature* is the most comprehensive description of breast cancer 'omics' to date. This study is impressive in its scope and scale, with the findings reconfirming the heterogeneity of breast cancer and highlighting the future challenges in translating these findings for clinical benefit.

Background

Breast cancers are a heterogeneous group of tumors that were originally classified by their clinicopathological features. Improvements in molecular techniques, specifically in gene expression analysis, allowed for the grouping of breast cancers into five subtypes (luminal A, luminal B, basal-like, HER2-enriched (HER2E), and normal-like) over a decade ago [1,2]. Typically, luminal subtypes are associated with the expression of estrogen receptor (ER) and progesterone receptor, while HER2E subtypes usually lack hormone receptor expression but have amplification and/or over-expression of HER2. Basal-like tumors are commonly described as triple-negative breast cancers (TNBCs) lacking in expression of hormone receptors and HER2.

While receptor subtypes are associated with different prognostic and therapeutic implications, the full clinical consequences of these molecular subtypes have not been established. In 2006 and 2007, two studies published in *Science* detailed the complexity of the breast cancer mutation spectrum and highlighted the major difficulties this diversity raises in designing therapies [3,4]. In June 2012, five studies were published in *Nature* examining

hundreds of primary breast tumors by integrating various profiling techniques [5-9]. These recent papers demonstrated a vast array of clonal frequencies and genetic diversity among breast cancers, highlighting that breast cancer is truly many different diseases.

A comprehensive look at a complex molecular landscape

The Cancer Genome Atlas (TCGA) is a collective effort tasked with providing a comprehensive genomic analysis for 20 cancers, including breast cancer. In this latest study, TCGA analyzed 825 primary breast tumors with matched germline samples using six different platforms (whole exome sequencing, messenger RNA array, genomic DNA copy number array, DNA methylation array, microRNA sequencing and reverse-phase protein array) [10]. The sequencing and array data corroborated the mutation and gene expression patterns documented in previous studies. For instance, compared to the noted low frequency of mutation for numerous genes across all breast cancers, *TP53* (37%), *PIK3CA* (36%), and *GATA3* (11%) were the only genes found to be mutated at a level greater than 10% overall. In addition, when grouped according to gene expression subtype, the mutations not only tracked well with expected frequency but also with the type of mutation. Notably, basal-like tumors harbored nonsense *TP53* mutations while luminal tumors harbored mostly missense mutations. In addition to identifying nearly all genes previously implicated in breast cancer, the authors also discovered a handful of novel mutated genes.

TCGA also parsed out individual, overarching features associated with each of the four subtypes: luminal A, luminal B, HER2E, and basal-like. Despite having a relatively low mutation rate, luminal/ER+ tumors were found to have the most diverse mutation spectrum and heterogeneity. Conversely, basal-like and HER2E tumors had a very high rate of mutation in only a few select genes, such as *TP53*. The data also showed that clinically defined TNBCs and HER2+ cancers did not fall exclusively within their classically associated subtypes, basal-like and HER2E, respectively. In fact, only 50% of clinically defined HER2+ cancers were classified as

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HER2E while the other half tracked well with ER+ status and other luminal subtype features. As for TNBCs, 25% of tumors comprised the three other mRNA subtypes besides the basal-like group. Interestingly, through further analysis of the basal-like subset of tumors, TCGA noticed strikingly similar characteristics and mutations as in their previous studies with serous ovarian cancers. Both tumor types featured widespread genomic instability, MYC amplification, and loss of BRCA1, TP53, and RB1, leading to the authors' conclusion that patients with basal-like tumors may benefit from poly ADP-ribose polymerase (PARP) inhibitors or platinum-based therapies.

Viewpoint

While multiple groups have attempted to create consensus mutation spectrums and molecular landscapes for primary breast cancers, TCGA was able to draw from a large database across multiple platforms and provide the most comprehensive portrait of human breast tumors thus far. All six recent profiling analyses detailed the same intricate and heterogeneous nature of breast cancers and emphasized the difficulties this causes with respect to the development of effective therapies. However, the sobering truth is that common targets are the exception in breast cancer, and if there were any remaining doubts, TCGA has put them to rest. How to move this information forward for clinical benefit becomes the challenge for the next decade. Although the technical merits and scale of this study cannot be discredited, in reality no new clinical benefit can yet be derived, as even the idea to use PARP inhibitors or platinum agents to treat TNBC has already been an intense area of clinical research. In addition, future studies will need to address issues with intratumor heterogeneity and clonal evolution. It is hoped that the classification of breast cancers along with further technologic advances can lead to the development of more rational therapeutics, so that ultimately the vision of individualized therapy for breast cancer becomes a reality.

Abbreviations

ER, estrogen receptor; HER2E, HER2-enriched; PARP, poly ADP-ribose polymerase; TCGA, The Cancer Genome Atlas; TNBC, triple-negative breast cancer.

Competing interests

BHP is a consultant for GlaxoSmithKline and serves on the Scientific Advisory Board of Horizon Discovery, Ltd.

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