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Breast Cancer RESEARCH

VIEWPOINT

Who's driving anyway? Herculean efforts to identify the drivers of breast cancer

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Abstract

The continuing advancement of sequencing technologies has made the systematic identification of all driving somatic events in cancer a possibility. In the June 2012 issue of *Nature*, five papers show some significant headway in this endeavor, each a herculean effort of genome sequencing, and transcriptome and copy number analysis resulting in data on thousands of breast cancers. Integrating these massive datasets, the authors were able to further subdivide breast cancer and identify a number of novel driver genes. While the studies represent a leap forward in describing the genomics of breast cancer, and clearly highlight the tremendous diversity between tumors, the studies only scrape the surface of molecular changes in breast tumors, with more granularity to come from the study of epigenomics, single cell sequencing, and so on. The immediate importance of the data to clinical care is currently unknown, and will depend upon detailed identification and functional analysis of driver mutations.

Background

It is now accepted that breast cancer can be divided into at least five subtypes based solely on transcription profiling. Although this profiling has been an extremely useful tool for identifying biological differences and similarities between breast cancers, it speaks little to the driver events that lead to each of the subtypes. Identification of these driver events has been the focus of many large-scale projects, including The Cancer Genome Atlas.

Defining the genomic landscape of cancers has accelerated dramatically with advances in sequencing technologies. However, a single snapshot of acquired genomic changes is inherently limited in defining processes important to the initiation, development, and progression of a particular tumor. No genome is static, especially a cancer genome with compromised DNA repair capabilities. Point mutations, copy number changes, and structural changes can all be critical events driving tumor evolution or can be bystander passenger events not contributing to the disease. Further complicating the picture, the vast genetic heterogeneity between tumors within a given subtype is made worse by the extensive heterogeneity within each tumor. Understanding the somatic events driving the evolution of breast cancers will undoubtedly lead to novel therapeutic targets. However, as the five articles in the June release of *Nature* show [1-5], novel driver events are present in increasingly rare groups of individuals, making their identification extremely difficult and raising serious challenges to drug development and clinical trials design.

Articles

The authors profiled either unselected [3-5], triple-negative [1], or estrogen-receptor positive breast cancer [2] utilizing various technical approaches, including whole-genome sequencing, whole-exome sequencing, copy number profiling, and transcriptome analysis. Curtis and colleagues [5] integrate expression and copy number to identify ten subtypes of breast cancers and reveal aberration hotspots responsible for these groups. These hotspots contain known (*ERBB2*, *MYC*) and candidate driver loci that can impact patient prognosis. Stephens and colleagues [4] combined copy-number and sequencing to identify a number of novel driver genes (*MAP3K1*, *MAP2K4*, *MAP3K13*, and *AKT2*), albeit each at relatively low frequency. Together, however, these mutations all impact JUN signaling activation and encompass approximately 50% of all breast tumors, thus identifying a major recurrent pathway alteration in breast cancer. Banerji and colleagues [3] similarly utilize sequencing to identify driver mutations and copy number events, including collaborating events in *CBFB* and *RUNX1*. In triple-negative breast cancers (TNBCs) a recurrent *MAGI3-AKT3* fusion was identified leading to

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constitutive activation of AKT signaling. Interestingly, somatic activating mutations in *ERBB2* without amplification were observed. Shah and colleagues [1] also report somatic mutation of *ERBB2* in TNBC, revealing that this pathway may be critical in the absence of amplification. Following their genome/exome-wide sequencing efforts, somatic mutations were re-sequenced at 20,000× to determine clonal frequencies and distributions of these mutations. This revealed a wide spectrum of clonal frequencies and total number of clonal populations. Within TNBCs, basal cancers tended to have more clonal frequency groups compared to non-basal cancers. Further, this reveals that extensive clonal evolution has already occurred in treatment-naïve tumors. Finally, Ellis and colleagues [2] focus on estrogen receptor-positive breast tumors to identify mutations that result in resistance to neoadjuvant aromatase inhibitor therapy. Resistant tumors tended to have increased mutation rates, indicating that genetic heterogeneity may negatively impact treatment response. *TP53* mutations were also found at a higher rate in the poorer prognosis luminal B subtype while *MAP3K1* mutations were found more in luminal A tumors. Further, *GATA3* mutations tended to correlate with strong response to aromatase inhibitors.

Viewpoint

Together these studies effectively integrate orthogonal datasets to understand breast cancer drivers. One of the major themes throughout the studies is the negative impact of genetic heterogeneity on the tumor prognosis and/or response to therapy. Intuitively this makes sense; a genetically diverse tumor is evolutionarily strong and can quickly adapt to changing physiological conditions and/or targeted therapies. Unfortunately, this makes application of these findings to the clinic extremely difficult. However, it is encouraging that rare mutations were reproduced in independent studies, including *GATA3* mutations in estrogen receptor-positive disease [2-4], *ERBB2* mutations in TNBC [1,3], and *TBX3* [2,4], *CBFB*, and/or *RUNX1* mutations [2,3]. The combination of rare or unique somatic events into pathways has identified, and will likely continue to identify, drivers of breast cancer. It is important to note that the analyses undertaken on these multiple and massive datasets are only the tip of the iceberg, but serve as an excellent resource for many additional scientific questions. These include, but are not limited to: 1) what is the level of mutational heterogeneity within primary and metastatic tumors and is this heterogeneity critical to patient prognosis and response to therapy; 2) how do genetic aberrations alter and/or co-operate with epigenomic and proteomic changes to drive tumor progression; and 3) what are the minimal number of events needed to reliably identify major prognostic subtypes in breast cancer. Future studies examining how somatic events evolve during therapy and progression will likely identify more clinically actionable drivers.

Abbreviations

TNBC, triple-negative breast cancer.

Competing interests

The authors declare that they have no competing interests.

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