Breast Cancer RESEARCH

VIEWPOINT

Tracking the genomic evolution of breast cancer metastasis

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Abstract

Therapeutic choices for metastatic tumors are, in most cases, based upon the histological and molecular analysis of the corresponding primary tumor. Understanding whether and to what extent the genomic landscape of metastasis differs from the tumors from which they originated is critical yet largely unknown. A recent report tackled this key issue by comparing the genomic and transcriptional profile of a metastatic lobular breast tumor with that of the primary tumor surgically removed 9 years earlier. The extent of the differences suggests a high degree of mutational heterogeneity between primary and metastatic lesions and indicates that significant evolution occurs during breast cancer progression.

During the metastatic process, breast cancer cells leave the original (primary) tumor site and migrate to other parts of the body, often bones or lungs, via the bloodstream or the lymphatic system. Breast cancer metastases are primarily responsible for morbidity associated with this tumor type [1]. The biological events involved in invasion and metastasis of breast cancer cells are fairly well understood, but very little is known about the genomic changes that occur during this process. Assessing whether the primary tumor and its corresponding metastasis share the same genetic alterations would be of utmost relevance to predict whether therapeutic strategies targeting oncogenic events found in primary lesions can also be effective on metastatic sites.

In a recent paper, Shah and colleagues [2] used whole-genome high-throughput sequencing to compare the genetic drift of an estrogen receptor-α-positive metastatic lobular breast tumor with that of the corresponding primary tumor from which it originated and that was surgically removed 9 years earlier.

Massive parallel paired-end sequencing of the genome and transcriptome of the metastatic lesion led to the identification of multiple genetic aberrations, including single-nucleotide variants (SNVs), insertions/deletions, gene fusions, translocations, inversions, and copy number alterations. Alternative splicing, biased biallelic expression, and RNA editing changes were also assessed. Comparison of the sequence of tumor and normal DNA samples led to the identification of somatic changes. The prevalent genetic alterations were SNVs (32 non-synonymous coding point mutations), whereas a handful were gene copy number gains. Interestingly, somatic genomic rearrangements, such as translocations, inversions, or fusions, were not identified. This is somewhat surprising if we consider that in other cancer types, such as prostate cancer [3] and lung cancer [4], gene fusions have been detected by the use of the same technology, and these genetic rearrangements are currently considered among the prevalent genetic events in prostate tumors. As the analysis was performed on a single specimen, additional breast tumor samples would be required to verify whether this is a tissue-specific or a patient-specific pattern. Moreover, none of the 32 mutated genes was listed as a CAN breast gene in a previous analysis performed on estrogen receptor-positive breast tumors [5]. Eleven mutated genes were also present in the current release of the Catalogue of Somatic Mutations in Cancer (COSMIC) [6]. However, the changes occur at positions different from those previously identified.

The most relevant aspect of the analysis is the comparison of the somatic changes found in the metastasis with those present in the primary tumor. Only 11 of the 30 evaluated mutations were detected in the DNA of the primary tumor. These results suggest that, at least in this patient, considerable genetic evolution occurred in the metastatic process. It is tempting to speculate that some of the metastasis-specific mutations could be associated with the acquisition of invasive properties of breast cancer cells. However, this

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conclusion cannot be definitively drawn as the patient received both radiotherapy and chemotherapy, which are known to affect the genetic milieu of cancer cells [7].

The authors also exploited deviation from the theoretical ratio of 0.5 for a heterozygous allele to assess the frequencies of the somatic changes between the primary and metastatic lesions. The somatic mutations identified in the primary tumor showed three patterns of abundance: prevalent, rare, and undetectable. Notably, of the 11 shared somatic mutations, only 5 were prevalent in the primary tumor (frequency of more than 20% for heterozygous variants), whereas 6 were present at lower frequencies (1% to 13%). On the other hand, all of them were found at prevalent frequencies in the metastatic site. These data are consistent with the expansion of a single clone that left the heterogeneous primary site and homed to generate the distant metastasis. Interestingly, the metastatic tumor looks genetically less heterogeneous compared with the primary tumor, suggesting that a strong selective pressure at the ectopic site likely prevented further genetic heterogeneity from developing during the metastatic growth.

This work raises a few key questions: to what extent does the genetic profile of the primary tumor (often the only one available) reflect that of the corresponding metastases? Second, would therapies designed to target the genetic lesions found in the primary tumor be effective on the metastasis? And would molecular analysis of the metastatic site be useful to guide therapeutic choices? For example, in this particular patient, the molecular analysis of the primary lesion would have missed the metastasis-specific ERBB2 mutation. Assuming that this mutation acts as a driver, would an ERBB2 inhibitor have been clinically effective in this patient?

Abbreviation

SNV = single-nucleotide variant.

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Competing interests

The authors declare that they have no competing interests.

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