Translating the Molecular Message of Triple-Negative Breast Cancer into Targeted Therapy

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Triple-negative breast cancer (TNBC) has a poor prognosis with limited treatment options. Genomic analysis of TNBCs offers the opportunity to decode TNBC into biologically relevant subtypes with unique molecular targets. With further research, these findings may be translated into effective targeted therapeutic options. Clin Cancer Res; 21(7); 1511–3. ©2014 AACR.

In this issue of Clinical Cancer Research, Burstein and colleagues describe the findings of a genomic analysis of triple-negative breast cancer (TNBC). TNBC has been conventionally described as breast cancer that does not express the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor (HER2), although recent studies suggest that TNBC is actually quite heterogeneous. Using DNA and RNA profiling of 198 TNBC tumors, Burstein and colleagues describe four subtypes of TNBCs with prognostic significance, identified by specific gene amplifications, termed luminal-androgen receptor (LAR), mesenchymal (MES), basal-like immune-suppressed (BLIS), and basal-like immune-activated (BLIA; ref. 1). LAR tumors express the androgen receptor (AR), ER (although ER negative by immunohistochemistry), prolactin, and cell-surface mucin (MUC1-1), whereas the MES subtype is characterized by insulin-like growth factor 1 (IGFI), prostaglandin F receptor, and c-Kit. The BLIS subgroup showed Sry-related HMG box (SOX) transcription factors as well as V-set domain-containing T-cell activation inhibitor 1 (VTCN1), whereas signal transducer and activators of transcription (STAT), cytotoxic T-lymphocyte–associated protein 4 (CTLA-4), and cytokines were noted in the BLIA group. The authors conclude that TNBC can be categorized as four subtypes based on discrete molecular markers, which then can be used to identify potentially effective targeted agents.

How do we apply these data to the clinic? TNBC is a difficult to treat subtype of breast cancer, with a high propensity for systemic metastases and poor survival. Chemotherapy resistance is common, and, to date, there are no effective alternative treatments. In the clinic, it is clear that TNBC represents a heterogeneous subset of cancers, with markedly different natural histories and response to therapy, and that additional tumor specific information is critical to finding effective therapies. Lehmann and colleagues previously described six subtypes of TNBC and identified an indolent, AR-expressing subset. Burstein and colleagues describe four subtypes, with some overlap, and were unable to reproduce Lehmann and colleagues’ subtype definitions. The classification by Burstein and colleagues also differs from Prat and Perou’s (3) categorization defining claudin low, luminal A, luminal B, HER2-positive, and basal-like subtypes, and from the grouping of Curtis and colleagues (4) using copy-number aberrations. These differences, which may be due in part to methodology and datasets, complicate ultimate definitions but may not be clinically relevant, as the identification of actionable targets is most important to the clinic, providing a path for directed clinical research. Indeed, these studies expand the paradigm of TNBC from a disease that has been defined by the absence of hormone or HER2 receptor expression into a heterogeneous cancer defined by the presence of specific gene products (Fig. 1).

Data from these efforts have already been tested in laboratory models and clinical trials, with intriguing results. Lehmann and colleagues noted a high frequency of phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha mutations in AR-differentiated TNBCs, and found that combining phosphoinositide 3-kinase inhibitors and AR antagonists in this subtype had an additive inhibitory effect, suggesting a role for combined therapy with further differentiation of AR-positive TNBC (5). A study from the translational Breast Cancer Research Consortium tested tumor samples from patients with TNBC and found that 12% expressed AR (6). Treatment with the AR antagonist bicalutamide resulted in a 19% 6-month clinical benefit rate, which is impressive for a 1TNBC subtype. Ongoing studies are testing alternative AR inhibitors in AR-positive TNBC. Therapies already exist that target additional gene products identified by Burstein and colleagues, including IGFI and prostaglandin inhibitors for MES tumors, pembrolizumab (anti-programmed cell death 1 antibody) and VTCN1 antibodies for BLIS tumors, and STAT inhibitors and ipilimumab (anti–CTLA-4 antibody) for BLIA tumors. Clinical trials focusing on these targets are the next step.

This work adds to efforts translating molecular markers into precise cancer therapies. While Burstein and colleagues have identified several gene products for different TNBC subtypes, there is significant genetic diversity within these subtypes. A prior study showed that TNBC has a high mutation rate, leading to
acquisition of various point mutations with resulting clonal diversity (7). Therefore, several genomic alterations may be responsible for a tumor’s growth, increasing the difficulty of transforming a molecular marker into an effective therapy. A single mutation may exist in only a portion of the tumor, and this may change under the pressure of treatment. This heterogeneity within a tumor makes combination therapy not only appealing but also highly challenging.

Molecular evolution occurs as cancer progresses, so resistance may develop to targets identified on a primary tumor, or new mutations may appear in a metastatic lesion. Essentially, all of the biopsy specimens in the study by Burstein and colleagues were from primary tumors; hence, it is possible that the molecular targets described may vary or have additional complexity in the metastatic setting. Arnedos and colleagues (8) performed whole exome sequencing of 93 pairs of metastatic breast cancer biopsy and blood samples and noted that mutations in estrogen receptor 1 (ESR1), tuberous sclerosis 1/2 (TSC1/2), and DOT1-like histone H3K79 methyltransferase (DOT1L) occurred in 5% of metastatic specimens, but were seen in less than 1% of early tumors. The evaluation of matched primary and metastatic tumor biopsies may help us to understand these potential confounding factors and further define targets within TNBC. Blackwell and colleagues (9) performed exome sequencing of metastatic and primary tumor samples from 38 patients with metastatic TNBC and found marked genetic heterogeneity, with increased mutations in metastatic tumors. These data, and those from other researchers, suggest that genetic composition evolves over time and with exposure to treatment. Clearly, further research is needed to define targets for both primary and metastatic TNBCs.

Several ongoing trials may further elucidate the activity of targeted therapies chosen based on specific tumor mutations in a variety of malignancies. The NCI’s Molecular Analysis for Therapy Choice Program (MATCH) is a multiarm phase II trial for patients with advanced cancer (10). Patients will undergo tumor biopsies with DNA sequencing. Those whose tumors have targetable mutations will be assigned to treatment with the appropriate targeted agent; the primary endpoint is tumor response across tumor types. The ongoing French SAFIR02 trial has a similar design, including both lung and breast cancers.

Aiming to Understand the Molecular Aberrations in Metastatic Breast Cancer (AURORA) is a program enrolling 1,300 patients with metastatic breast cancer in Europe (11). Patients’ primary tumors, metastatic lesions, and peripheral blood undergo DNA sequencing to determine individual cancer genomic profiles. Patients are then directed toward clinical trials investigating targeted agents. The peripheral blood analysis will establish whether this can be used as an alternative source of tumor DNA to track genomic changes with disease progression. The U.S. Founder’s Fund project will have similar objectives, but will also construct a laboratory model of metastatic breast cancer using patient-derived tumor cells to test targeted drug efficacy in vitro (12). These large collaborations are essential given the focus on smaller subsets of disease and will enable a new approach to the treatment of both early- and late-stage disease.

This study, together with previous work, illustrates that TNBC is more complex than a subset of breast cancer not expressing ER, PR, and HER2. However, this study also highlights the extent of entropy in the genomic landscape of breast cancer. With ongoing research efforts, we will one day be able to translate these molecular targets into effective personalized therapies for TNBC.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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Conception and design: N. Vidula, H.S. Rugo
Development of methodology: N. Vidula

Figure 1.
The genomic landscape of TNBC as defined by Burstein and colleagues (7). Genomic profiling of TNBC tumor tissue identifies distinct subtypes of TNBC (LAR, MES, BLIS, or BLIA), with specific molecular targets.
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): N. Vidula
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): N. Vidula, H.S. Rugo
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References
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