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

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\textbf{Running Title:} Translating Triple-Negative Breast Cancer

\textbf{Disclosure of Potential Conflicts of Interest}

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Summary

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.

Main Text

In this issue of Clinical Cancer Research, Burstein and colleagues describe the findings of a genomic analysis of triple-negative breast cancers (TNBCs) (1). 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 2 (HER2), although recent studies suggest that TNBC is actually quite heterogeneous (2). Using DNA and RNA profiling of 198 TNBC tumors, Burstein and colleagues describe 4 subtypes of TNBC 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) (1). LAR tumors express the androgen receptor (AR), ER (although ER negative by immunohistochemistry), prolactin, and cell surface mucin (MUC-1) whereas the MES subtype is characterized by insulin-like growth factor 1 (IGF-1), 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), while 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 4 subtypes based on discrete molecular markers, which then can be used to identify potentially effective targeted agents.
How do we apply this 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 et al previously described 6 subtypes of TNBC, and identified an indolent, androgen receptor expressing subset (2). Burstein and colleagues describe 4 subtypes, with some overlap, and were unable to reproduce Lehmann’s subtype definitions. Burstein’s classification also differs from Perou’s categorization defining claudin low, luminal A, luminal B, HER2 positive, and basal like subtypes (3), and from Curtis’ grouping using copy number aberrations (4). 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 has already been tested in laboratory models and clinical trials, with intriguing results. Lehmann’s group noted a high frequency of phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha mutations in AR differentiated TNBC, 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 TNBC patients and found that 12% expressed AR (6). Treatment with the
AR antagonist bicalutamide resulted in a 19% 6 month clinical benefit rate – impressive for a TNBC subtype. Ongoing studies are testing alternate AR inhibitors in AR positive TNBC. Therapies already exist that target additional gene products identified in Burstein’s study including IGF-1 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 (1) 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 the 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 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 Burstein’s study were from primary tumors, hence it is possible that the molecular targets described may vary or have additional complexity in the metastatic setting. Armadas and colleagues 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 (8). Evaluation of matched primary and metastatic tumor biopsies may help to understand these potential confounding factors and further define targets within TNBC. Blackwell et al 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 (9). This data, and that of others, suggests that genetic composition evolves over time and with exposure to treatment. Clearly, further research is needed to define targets for both primary and metastatic TNBC.

Several ongoing trials may further elucidate the activity of targeted therapies chosen based on specific tumor mutations in a variety of malignancies. The National Cancer Institute’s Molecular Analysis for Therapy Choice Program (MATCH) is a multi-arm phase II trial for advanced cancer patients (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 1300 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 towards 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 US 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.

The current study together with previous work, illustrate 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.

References


**Figure 1.** The genomic landscape of TNBC as defined by Burstein’s study. Genomic profiling of TNBC tumor tissue identifies distinct subtypes of TNBC (LAR, MES, BLIS, or BLIA), with specific molecular targets.

LAR: Luminal Androgen-Receptor, MUC-1: cell surface mucin, AR: androgen receptor, ER: estrogen receptor, MES: mesenchymal, IGF-1: insulin-like growth factor 1, BLIS: Basal-Like Immune-Suppressed, SOX: Sry-related HMG box, VTCN1: V-set domain containing T cell activation inhibitor 1, BLIA: Basal-Like Immune-Activated, STAT: Signal Transducer and Activators of Transcription
Figure 1:
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