Commentary

Molecular Cancer Therapeutics

Countering Breast Cancer's Counterpunch

Brion W. Murray

In recognition of breast cancer awareness, we highlight advances in breast cancer therapies that build on a long history of discovery yet demonstrate an accelerating pace of development. Breast cancer has challenged physicians and researchers for over 5,000 years (1). The ancient Egyptians reported lumps in breasts that had no cure (Edwin Smith Papyrus). Hippocrates ("the father of medicine") proposed that biological imbalances rather than supernatural forces cause cancer; however, he argued that the disease should not be treated. The Roman physician Aulus Cornelius Celsus defined four stages of breast cancer (i.e., cacoethes, carcinoma without skin ulceration, carcinoma with ulceration, and exophytic lesions) and favored surgical intervention for the earliest stage of disease because "the excised carcinomas have returned and caused death." From the first century AD through the 1700s, surgical resection of tumors in the breast became more refined (2). Treating breast cancer as a disseminated disease traces back to the mid-18th century when the French surgeons Henri Le Dran and Louis Petit postulated that cancer develops locally, spreads through lymphatics, and requires removal of axial lymph nodes "to preclude recurrences." Preventing disease relapse improved with the advent of adjuvant therapies that minimize disseminated tumor cells (radiotherapy, 1930s–1940s; cytotoxic chemotherapy combinations, 1970s). Targeting the molecular underpinnings of breast cancer, not just eliminating tumor cells, traces back to George Beatson's observations in 1896 that removing the ovaries from a patient shrank her breast tumor–a crude antihormonal treatment. This discovery set off research that ultimately led to the development of antihormonal drugs such as tamoxifen (FDA approval 1977) and research into the molecular segmentation of breast cancer for the selection drugs that target a patient's specific tumor cell biology. Breast cancer biology is now characterized by three markers (ER/PR/HER2), gene expression, and patient-specific genomic analysis to facilitate selection of appropriate therapies. These innovations and many others have improved patient outcomes for patients with breast cancer. In 2019, 30% of cancer diagnoses for U.S. women are estimated to be breast cancer but it will account for only 15% of female cancer-related deaths. Despite the progress, disease recurrence through drug resistance remains a major issue to address.

Breast cancer is not a static disease but a moving target, as Celsus described over 2,000 years ago. Defining disease dynamics at the molecular level is enabling the design and deployment of more effective therapies. In this issue of *Molecular Cancer Therapeutics*, seven articles highlight a range of approaches that seek to remedy different aspects of disease recurrence. These articles cover many segments of breast cancer biology and a range of drug resistance mechanisms.

Phenotype switching, such as epithelial-to-mesenchymal transition (EMT), is implicated in breast cancer disease progression and drug resistance (3). Epithelial carcinoma cells within a primary tumor acquire mesenchymal features to disseminate and then revert to epithelial phenotype to form a secondary mass at a metastatic site. This phenotypic change is driven by a wide range of transcriptional and epigenetic changes that alters many molecular and cellular processes to affect drug response. Kufe and colleagues define roles of two oncogenic proteins upregulated in triple-negative breast cancer (TNBC): TWIST1 and MUC1-C. TWIST1 is a transcription factor that regulates EMT and MUC1-C is known to facilitate oncogenic reprogramming via an epigenetic regulation. Furthermore, the authors demonstrate that MUC1-C has an indirect autocrine function to induce TWIST1 expression as well as direct interactions with TWIST1 to affect EMT, stemness, and drug resistance. Understanding the molecular mechanism of phenotype switching for TNBC creates therapeutic opportunities for intervention.

There are approved drugs that would synergize with current therapies if the proper tumor biology was defined. For example, cyclin D_1 and CDK4 regulate the G_1–S cell-cycle transition and are known to be dysregulated in breast cancer. However, selective CDK4/6 drugs were found to be ineffective as single agents in the clinic. Subsequent preclinical studies revealed that estrogen receptor–positive breast cancer cell lines respond to CDK4/6 drugs and synergize with approved estrogen antagonists, leading to drug combinations that deliver profound clinical benefit to patients with ER^+ breast cancer (4). In addition to the G_1–S cell-cycle transition, other aspects of the cell cycle could be targeted for breast cancer therapies that may synergize in combination with current therapies. The spindle assembly checkpoint (SAC) of mitosis is regulated, in part, by the protein kinase MPS1. Unfortunately, inhibitors of this kinase have not yet found clinical utility. Linardopoulos and colleagues show that the MPS1 inhibitor BOS172722 preferentially inhibits cancer cells with abbreviated spindle SAC activity–TNBC characteristics. Many current therapeutic regimens for breast cancer contain a taxane that induces the SAC. The authors show a synergy of MPS1 inhibition with taxane therapy through intervening in complementary aspects of mitosis that are preferentially dysregulated in the TNBC subset of breast cancer.

Turning Point Therapeutics, San Diego, California

Corresponding Author: Brion W. Murray, Turning Point Therapeutics, 10628 Science Center Drive, Suite 100, San Diego, CA 92121. Phone: 858-356-5480; Fax: 858-356-5368; E-mail: brion.murray@tptherapeutics.com

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Since George Beatson's crude antihormonal treatment, therapeutic intervention in estrogen-dependent breast cancer has become quite sophisticated with direct mechanisms (e.g., estrogen antagonists) and indirect mechanisms (e.g., aromatase inhibitors). However, ER^+ breast cancer treatment is imperfect, necessitating additional advancement and discovery. Countering aromatase drug resistance requires the precise selection of when to use a drug versus when the use of a drug would not be appropriate. For example, Creevey and colleagues built a case that tumor cells that develop a resistance to aromatase inhibitors have enhanced sensitivity to PI3K-targeted therapies. Furthermore, they identify biomarkers (SGK3, PKIB) associated with poor response to endocrine therapy. On the other hand, some drugs should be excluded from therapeutic regimens. For example, steroids have been routinely used to counter the pain of cancer or the side effects of chemotherapy. In this issue, Jordan and colleagues explore the context where glucocorticoid drugs should not be used. Mechanistically, glucocorticoids are shown to block estrogen-induced apoptosis in breast cancer cells deprived of estrogen through inhibition of estrogen-dependent activation of adipose inflammatory factors. As such, glucocorticoids interfere with cancer therapies in patients that have aromatase drug–resistant ER^+ breast cancer. This refined understanding of biological consequences of drug treatment can enable more effective use of therapies currently available.

For HER^+ breast cancer, there are a range of therapeutic modalities with antibody–drug conjugates (ADC) of HER2-targeting antibodies emerging more recently. Despite the revolutionary impact that HER2-targeted drugs have had on overall survival of patients with breast cancer, a subset of patients develop mechanisms to evade these therapies. Although ADC as a drug modality seems to be the simple combination of a targeting antibody with a cytotoxic drug, the mechanism is more complex because of differential cell targeting, epitope regulation, drug selection, drug load, ADC internalization, and mechanisms of drug release. Joncour and colleagues introduce a new ADC drug (XMT-1522) that is effective in killing tumor cells that evade other HER2-targeted therapies, even the ADC trastuzumab-emtansine (T-DM1). T-DM1 resistance can be rooted in a range of expected mechanisms (e.g., increased drug efflux and HER2 expression) but the authors propose a new mechanism: increased HER2 expression on secreted extracellular vesicles. XMT-1522 binds to a domain distinct from trastuzumab, has a high drug load of tubulin inhibitor (12 drug moieties per antibody), and has the drug load tethered with a biodegradable linker–all properties designed to overcome limitations of T-DM1.

Drug resistance occurs when the range of tumor cell heterogeneity is not sufficiently treated. Eliminating the tumor bulk mass but not niche populations such as cancer stem cells (CSC) leads to disease recurrence. Sulaiman and colleagues show how drug combinations delivered with nanoparticles (nanotherapy) can be used to eliminate a wider swath of tumor heterogeneity in patients with TNBC. In TNBC, CSC encompass distinct subpopulations: $ALDH^+$ epithelial cells enriched in WNT signaling and $CD44^+/CD24^-$ mesenchymal cells enriched in YAP signaling. Nanoparticles that target TNBC cells deliver two drugs (paclitaxel and verteporfin) that inhibit signaling processes (NFκB, YAP, Wnt) critical to bulk tumor cells and both CSC populations.

Repurposing drugs designed for different diseases is a swift way to create new therapies. For example, a drug designed to inhibit the receptor tyrosine kinase c-MET (crizotinib) was known to have an off-target activity toward the ALK tyrosine kinase. Upon the discovery of the fusion gene *EML4-ALK* (5), crizotinib swiftly became the standard of care for patients with $EML4\text{-}ALK^+$ lung cancer (6). For patients with breast cancer, taxane-based therapies provide substantial improvements in survival. Sadly, drug resistance frequently occurs. Gupta and Srivastava explore the utility of the antiprotozoal drug atovaquone to treat paclitaxel-resistant disease by attenuating β-catenin/HER2 signaling. Studies like these show that although chemotherapy has been in use for over 40 years, its performance has room to improve.

The articles highlighted in this issue show progress in understanding fundamental aspects of disease biology, define when and when not to use targeted therapies, reveal new drugs or drug combinations, ways to deliver drug combinations, and provides a rationale to use an approved drug for new indications. Taken together, these articles demonstrate a range of ways that researchers are "counter-punching" breast cancer to minimize disease recurrence.

Read the editorial and research articles of the Patient-Focused Therapies in Breast Cancer Collection online at mct.aacrjournals.org/brca

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