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Editorial

EDITORIAL

Microenvironmental Heterogeneity Among Triple-Negative Breast Cancer Subtypes and the Promise of Precision Medicine

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The advent of molecular tumor characterization has clearly identified that breast cancer is not a single disease entity but rather a class of several distinct subtypes, each with its own natural history and therapeutic susceptibilities. The field initially focused on characterizing tumors by using gene expression profiling to identify those that were estrogen receptor positive (ER+) or negative (1), with subsequent microarray analyses revealing four or five major subtypes that are now viewed as canonical determinants of prognosis, treatment selection, and risk stratification (2–4). In this framework, triple-negative breast cancers (TNBCs) became the most therapeutically challenging and prognostically adverse group because they did not have a clear oncogenic target: neither ER and progesterone receptor for endocrine modulation nor HER2/neu amplification for HER2-directed therapy.

The development of immune checkpoint blockade (ICB) has led to a renaissance in immune-oncologic (IO) approaches in the treatment of cancer. ICB has demonstrated marked activity in melanoma, non-small cell lung cancer, bladder cancer, head and neck cancer, gastric cancer, and microsatellite unstable cancers, among many other tumor types (5). Interestingly, the primary markers of response to ICB and other IO agents appear not to involve canonical oncogenic taxonomy of cancers but rather an antigen presentation–focused lens on the genome and the contents of their immune microenvironment (6). In ER+ breast cancers, responses to ICB have been modest to date (7); however, comprehensive examinations of the microenvironment using single-cell approaches have identified that high-grade ER+ tumors have high levels of immunosuppressive tumor-associated macrophages (PD-L1+) that may require alternative therapies (8). Unfortunately, these studies included only a few TNBCs, leaving a gap in our understanding of those tumors (8).

TNBC does, however, have promising clinical data suggesting activity of anti–PD-L1 agents in the first-line metastatic setting, although which subsets of TNBC benefit from these agents or are susceptible to other immunologic interventions may require additional prospective study (9). Interestingly, among all breast cancers, TNBCs exhibit the highest quantity of tumor-infiltrating lymphocytes in addition to the highest tumor mutation burden, both surrogates for response to ICB in other cancers. In this issue of the Journal, Bareche and colleagues (10) sought to better understand the immune microenvironment in different subsets of TNBC and to develop a framework to think about combination immuno-oncologic strategies. They aggregated greater than 1500 cases and subdivided them into previously established subtypes, including basal-like (BL), immunomodulatory (IM), luminal-androgen receptor, mesenchymal, and mesenchymal stem-like. Among the many interesting findings that appear to distinguish the microenvironments of the various TNBC tumors, the differential distribution of key immune targets is of particular interest for therapeutic selection. Notably, the IM subtype exhibited the highest expression of canonical immune targets, whereas BL tumors suffered an immunosuppressed microenvironment characterized by activation of an immuno-modulatory machinery not seen among other subtypes. An alternative classification using the tumor immune microenvironment schema of $CD8^+$ tumor-infiltrating lymphocyte spatial distribution was largely consistent, showing that fully inflamed lesions were most likely to be of the IM subtype, highly expressing well-studied immune targets. Most directly, these distinctions suggest a rational approach to breast cancer trial design whereby IO is preferentially evaluated in "hot" IM tumors rather than their "cold" BL counterparts. The non-IM lesions may otherwise benefit from ancillary approaches to make them more susceptible to immune recognition or to entirely different treatment strategies.

Indeed, this work may be more generally applicable in that it defines not only immunologic differences between TNBC subtype microenvironments, but it reveals higher-level domains that can serve as discrete classifiers by which one can begin to study therapeutic strategies, namely immune

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response, vascularization, stromal involvement, and metabolic processes, along with the presence of specific immune components and their localization (via the tumor immune microenvironment). These features all link directly to the defining hallmarks of cancer (11) and may further be modulated using combination approaches with agents that are readily available or in development. Moreover, variations along these axes may explain differential responses to therapies that have already been studied and can yet serve to stratify trial candidates for various future investigational approaches. For example, the authors note that mesenchymal stem-like tumors were mainly associated with high levels of lymphangiogenesis. Although vascular endothelial growth factor inhibition has not become a mainstay of breast cancer therapy, every trial cohort has comprised at least some number of extraordinary responders who derive clinically significant benefit (12–16). Might these have been the most "angiogenically dependent" tumors with the greatest susceptibility to vascular endothelial growth factor inhibition? It stands to reason that future rationally designed studies might take this "precision medicine" approach, preferentially employing a given agent among those tumors with the most probable susceptibility. Indeed, other malignancies appear to benefit from combinations of antiangiogenic and immunotherapies (17); perhaps this breast cancer subgroup is ripe for similar study.

The issue raised by Bareche et al. (10) is of urgent clinical relevance as the panoply of targeted breast therapies grows, but their appropriate target population remains somewhat obscure. The advent of CDK4/6 inhibitors, poly-ADP ribose polymerase inhibitors, novel HER2-targeted therapies, and antiangiogenic agents, among others, has heralded an era in which predictive biomarkers are of the utmost importance. Indeed, early results raise the notion that novel combinations of these agents may synergize in previously unanticipated ways, particularly with regard to potentiation of the immune response (18). The work presented herein, which looks at variations in the tumor microenvironment of TNBCs, is but one necessary foray toward identifying predictive classifiers for a growing armamentarium of precision agents.

Notes

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