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Editorial

EDITORIAL

TP53 Status and Estrogen Receptor-Beta in Triple-Negative Breast Cancer: Company Matters

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Estrogen receptor β (ESR2) shares a structural homology at the DNA and ligand binding domains (96% and 58%, respectively) with estrogen receptor α (ESR1), the major type of estrogen receptor in breast cancer (1,2). Similarities notwithstanding, ESR2 has functions and expression patterns distinct from ESR1 and is widely expressed in both basal and luminal epithelial cells (3–6). The exact role of ESR2 in breast cancer is not clear, with both antiproliferative and proliferative roles being described (7, 8). The mechanisms for these opposing actions of ESR2 in breast tumorigenesis have not been fully elucidated; this, in part, is due to different isoforms and binding partners.

In this issue of the Journal, Mukhopadhyay et al. (9) provide a mechanistic explanation for the plastic nature of ESR2 function in triple-negative breast cancer (TNBC) related to its interactions with TP53 status (wildtype or mutant). In wild-type TP53-expressing cells, silencing of *ESR2* augmented apoptosis, whereas its over expression resulted in increased proliferation. Opposite effects were observed following silencing or overexpression of ESR2 in mutant TP53 cells, suggesting the important role of TP53 status in determining ESR2's function. Mechanistically, ESR2-mutant TP53 interaction mediates sequestration of mutant TP53, leading to the TP73 activation and antiproliferative effects. Treatment with tamoxifen (4-hydroxy tamoxifen) also increases *ESR2* expression and reactivates TP73 in mutant TP53 cells, providing an explanation for its beneficiary effects. Analysis of the Molecular Taxonomy of Breast Cancer International Consortium TNBC subgroup of basal-like tumors (n = 259), based on ESR2 levels and TP53 mutation status, confirmed the impact of these interactions on survival, that is, mutant TP53-expressing tumors with high ESR2 levels have better survival.

The strengths of this study include provision of a mechanistic understanding for the dual role of ESR2 in breast cancer based on *TP53* mutational status with further validation of the hypothesis in clinical cohorts. Considering that basal-like TNBC cases are enriched in TP53 mutations (10), Mukhopadhyay et al. (9) suggest that the company of ESR2 with mutant TP53 can prognosticate TNBC patients and more importantly help select a population for tamoxifen therapy. The beneficial effects of endocrine therapy in unselected ESR1-negative breast cancer and TNBC cohorts have been previously described (11–14). The ability to selectively administer endocrine therapy should, in principle, lead to greater response rates. It is unclear what the impact of ESR2-TP53 interactions have in ER-positive breast cancer, particularly because all patients are offered endocrine therapy.

Many tumor-related genes have been documented to have a dualistic nature being associated with progression in some, but not all, cancers. The opposing effects exist for many biomarkers even within the same cancer as in the case of ESR2 in breast cancer. Understanding the molecular basis of this phenomenon, although not always possible, is a laudable goal. A number of different mechanisms have been described to explain the duality of protein function. The first and foremost is the tissue type. The cellular milieu of different organs is distinct, and the role that individual pathways play in maintaining cellular phenotype can be dramatically different. This is, at least in part, the explanation offered for the tissue-specific impact of mutations in BRCA1, a gene involved in DNA repair. Mutations can also lead to altered splicing pattern or posttranslational modifications resulting in mislocalization of proteins and acquisition of novel functionality. Abnormal nuclear localization of EGFR, and MUC1 and cytoplasmic localization of BRCA1, and TP53 have been described in breast cancer and represent good examples for this concept (15); these may be because of mutations in the gene itself or its binding partners. Duality of function can also be induced by splicing factors inducing alternative transcripts of the gene as illustrated by progesterone A and B isoforms in breast cancer. Mutations can lead to constitutive activation or suppression of function. Mutations leading to stabilized mutant TP53 proteins may simultaneously gain novel functions,

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primarily through protein–protein interactions with other transcription factors within the cellular neighborhood (16). Proteins that partner with mutant TP53 may transactivate or disrupt target gene activation with consequent changes in cellular function, suggesting the importance of the neighborhood actors. Epithelial splicing regulatory protein (ESRP1), a splicing factor, exhibits a dual role based on the tissue and cancer type (17). Low ESRP1 expression has been associated with the development of epithelial to mesenchymal transformation (EMT) by alternative splicing in ER-negative breast cancer models (MDA-MB-231 cells) (18, 19). In contrast, knockdown of ESRP1 in ER-positive models did not result in development of mesenchymal phenotype (16). This may be because of the lack of key EMT transcription factors in ER-positive breast cancer, suggesting that "company matters."

Beyond the obvious, the current study has broader implications. It documents the important principle of company matters in understanding the impact of markers and mutations in cancers, including breast cancer. The intracellular environment is a complex milieu wherein changes in one player can have a dramatic impact on DNA, RNA, and protein interactions. The players in the neighborhood could further affect cellular phenotype. Acknowledging these processes also provides a reality check for those of us involved in precision medicine, wherein treatments are being prescribed based on the presence of single gene mutations (20). The cooperativity and interactions of cellular networks may, to a large extent, determine the prognostic and predictive utility of mutations in patients. The study by Mukhopadhyay et al. (9) is a good step in this direction and provides compelling reasons to understand the combinatorial impact to determine clinically actionable strategies and solutions.

Notes

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