Editorial Commentary

High-mobility group A1 proteins may be involved in estrogen receptor status of breast cancer

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The three types of breast cancer

Breast cancer is one of the most common of cancers in woman. About 316,700 new cases were diagnosed as breast cancer in US woman in 2019 and 41,760 were predicted to die from it (1). Breast cancer has a characteristic of therapy-targeting receptors: hormone receptors (HR) that are estrogen receptor [ER: human ERα protein (NCBI protein accession NP_000116.2) encoding the *ESR1* gene (RefSeq NM_000125.4)], and progesterone receptor (PR). In addition to ER and PR is the tyrosine kinase-type receptor, erythroblastic oncogene B2 (ERBB2), also called HER2. These receptors are important for managing breast cancer in advanced stages as well as early stages. Accordingly, breast cancer is categorized into three subtypes: HR+/ERBB2–; ERBB2+ (HR+ or HR–); and triple-negative (ER–, PR–, ERBB2–). Seventy percent of breast cancer cases respond to anti-estrogen therapy through ER positivity, but one-third develop resistance within 15 years. Mutations of the *ESR1* gene have been frequently found in these cases. ERBB2+ (also called HER2+) is found in 20–25% of breast cancers and a humanized monoclonal antibody raised against ERBB2 called trastuzumab was developed. Estimated overall survival rate was 92% for trastuzumab plus doxorubicin and cyclophosphamide followed by docetaxel treatment. Triple negative (ER–, PR–, ERBB2–) accounts for 10–20% of breast cancers with the worst prognosis of the three types (2).

HMGA1 proteins: old and new proteins in breast cancer

HMGA1 (previously called HMGI/Y) is a member of the high-mobility group (HMG) proteins that were found from their high mobility characteristics during polyacrylamide electrophoresis of non-histone chromatin-associated proteins (3). The oncogenic property for these proteins was reported 35 years ago (4). Since then, proteins related to the HMG box (5), the DNA-binding motif of this protein family, have been found mostly related to cancer (6). HMGI/Y was first implicated as an oncogenic product from studies showing it expressed in a highly malignant phenotype in a ras oncogene transformed rat thyroid epithelial cell line (7) and transformed human breast epithelial cell (8). It was detected in fast proliferating, undifferentiated cells, and also in an aggressive derivative of a relatively benign prostate cell line (9). The growing number HMG proteins led to the novel nomenclature of each member (10). HMGI/Y was renamed as HMGA proteins.

The involvement of HMGA proteins in breast cancer was first documented as growth factor-induced overexpression in a highly metastatic breast cancer cell line compared to a nonmetastatic one (11). HMGA1 was shown to be related to its DNA unwinding properties as an architectural transcription factor (12), in matrix attachment of breast cancer cells (13). HMGA1 proteins have been detected as

a stem cell signature in triple negative breast cancer (14). Silencing of HMGA1 in this type of breast cancer transformed the cells from a mesenchymal-like, spindle-shape to a cuboidal, epithelial-like morphology (15).

The function of HMGA1 proteins in metastasis and stem cell signature have been studied and documented in many previous studies in many cancer types as well as breast cancer shown above. However, its contribution to estrogen-independence, tumorigenesis, and prognosis in breast cancer need to be further evaluated. Gorbounov *et al.* (16) have checked HMGA1 immunoreactivity in primary breast cancer in a large cohort of Asian women and compared it with two Western cohorts. Their staining followed current guidelines using an ER antibody raised against the C terminus (550 aa~) of human ERα protein. Immunoreactivity of HMGA1 was detected in ER-negative primary breast cancer tumors in their Korean cohort. Intriguingly, the overall survival was predicted to decrease in the high *ESR1* gene expression group by the Molecular Taxonomy of Breast Cancer International Consortium (METABRIC) cohort. It was predicted that HMGA1 proteins repress *ESR1* gene expression where HMGA1 itself is induced by estrogen (11). Thus, continuous exposure of breast cancer cells to estrogen may induce HMGA1 proteins that in turn represses its receptor. This implicates an additional role of HMGA1 proteins in ER-positive breast cancer and needs further investigation at the molecular level.

Perspectives

One clue may come from the emerging findings of HMGA1 proteins as sequence-specific RNA-binding proteins. The DNA-binding AT-hooks found in the HMG-box of HMGA1 proteins make it unique among the HMG proteins. The first evidence of its sequence-specific RNA-binding function came from its involvement in sporadic Alzheimer's disease, where it induces aberrant exon 5 skipping by preventing the release of U1 snRNP from the 5' splice site adjacent the HMGA1a RNA-binding site (17). These AT-hooks contain glycine-arginine-proline (G-R-P) tripeptide cores flanked by basic amino acids making its RNA-binding a magnitude higher than its original DNA-binding feature (18). It would be interesting if there is a specific protein modification of the AT-hook of HMGA1 proteins that differentiates their RNA- and DNA-binding, as well as the specific signal that induces each modification, since HMGA1 proteins are one of the most highly modified protein in the human cell (19). Other examples of sequence-specific RNA-binding for HMGA1 proteins have been reported for 7SK small nuclear RNA (20), for alternative splicing of the HIV RNA genome (21), and recent reports for regulating alternative splicing of the *ESR1* gene (22,23) in ER-positive breast cancer cell lines. The protein resulting from HMGA1a-induces alternative splicing of the *ESR1* gene is an exon-skipped form of exon 1 between non-coding exon E/F and exon 2 that lacks the N terminal domain, designated as ERα46. ERα46 suppresses the estrogen-independent activation function 1 (AF1) activity of the full length ERα (24). ERα46 has an intact C terminal domain that is recognized by the ER antibody that is used to detect ER positivity. Further studies similar to Gorbounov *et al.* (16) that analyze the correlation of HMGA1 proteins and ERα46 in hormone-resistant ER-positive breast cancer may help us find the mechanism of resistance not based on ESR1 mutations.

Taken together, the report of Gorbounov *et al.* (16) re-opens a field of research to decipher the role and therapeutic target related to ERα regulation by HMGA1 proteins in breast cancer.

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Footnote

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