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Editorial

The Elevated Expression of UNC-45A and its Relationship to Breast Cancer

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Editorial

The UNC-45 family serve as molecular myosin chaperones that have found to be essential for cell division. My colleague, friend, and mentor, the late Henry F. Epstein, MD, PhD, dedicated his career to the scientific investigation of its role in molecular chaperone regulation. Dr. Epstein's team of investigators demonstrated that UNC-45A mRNA and protein expression were elevated in human breast carcinomas and in cell lines that were derived from breast carcinoma metastases.

Previously, Guo and Epstein examined the expression of UNC-45A in 54 human tissue arrays (BR1005) of ductal breast carcinomas of different grades obtained from US Biomax Inc. Immunohistochemistry (IHC) studies were performed using monoclonal anti-UNC-45A antibody (Ab) as primary Ab followed by BioModule IHC Staining for Tissues (Invitrogen Corp.) Enhanced IHC reactions of monoclonal anti-UNC-45A Ab were found to increase with increasing grades in these specific human tissue arrays of primary breast tumor samples. UNC-45-A in mRNA and protein accumulation were evaluated in a battery of human cell lines using HMEC (Human Mammary Epithelial Cells) as control derived from immortalized breast epithelial cells. T47D, MCF7, and MDA-MB-231 were isolated from pleural effusions in patients with breast ductal carcinoma. The MDA-MB-231 cell line is experimentally metastatic and is negative for estrogen and progesterone receptors, whereas T47D and MCF-7 are positive for both receptors and require estrogen supplementation to show metastatic activity. Knockdown of UNC-45A by shRNA resulted in decreased proliferation and invasion rates of breast carcinoma cells. All three breast carcinoma cell lines had significantly elevated UNC-45A mRNAs by quantitative real-time PCR measurements when compared to the control HMEC cell line. Moreover, the most invasive cell line, MDA-MB-231 (ER-/PR-), showed significant elevation of the specific mRNA compared to the other breast carcinoma cell lines. All three carcinoma cell lines were significantly elevated over the HMEC control cells. The authors concluded that expression of the UNC-45A chaperone correlated with the severity of breast carcinoma progression in human breast tumor samples and cell lines derived from human breast carcinomas [1].

I had the opportunity to present our follow up study entitled "UNC 45-A expression correlates with progesterone receptor status in invasive ductal breast cancer" at the 14th St. Gallen International Breast Cancer Conference in Vienna, Austria on March 19, 2015. UNC45-A appears necessary for motor function of non-muscle myosin IIA, a protein essential to cell proliferation and invasion, and for transcriptional activity of the PR, a biomarker and therapeutic target in breast cancers. This study was performed using human breast cancer biopsies to establish if the levels of UNC-45A expression correlated with respect to steroid receptors, histological grade, proliferative rate, Her 2 neu status and patient age. IHC studies were performed on 33 paraffin sections of invasive ductal carcinomas using mouse monoclonal UNC-45-A Ab (Purified from Hybridoma cells –gift from Dr. David O. Toft). After deparaffinization/rehydration, Ag retrieval was performed by Vector kit H-3300. The slides were then treated with 3% H_2O_2 and washed. The non-specific streptavidin and biotin activities were blocked with Vector kit SP-2001. UNC-45-A primary Ab was dissolved in PBS containing 5% horse serum (10 µg/ml) and incubated at room temperature. The 2nd Ab (BA-2000 Vector) was prepared 1:250 in PBS containing 5% horse Serum. Peroxidase reaction performed using Vector VECTASTAIN ABC kit PK-6100 and Substrate kit SK-4105. Slides were counterstained with hematoxylin QS H-3404 (Vector), dehydrated/mounted with H-5000 (Vector). The expression of UNC-45-A was scored by a single breast pathologist as background compared to 1+ to 3+. The results were statistically evaluated using a Pearson Correlation coefficient matrix. We found that UNC-45-A protein expression was elevated in human breast carcinoma samples with measurable PR and negatively correlated with Her 2 neu at a significance of 0.05. No significance was demonstrated with correlation of UNC-45A expression with ER,

Ki 67, grade of tumor or age of patient.

In general steroid hormone receptors travel intracellular undergoing nuclear import and export. The progesterone receptor, liganded and unliganded, is predominantly nuclear [2]. After ligand binding the PR travels into the nucleus and functions as a transcription factor. The progesterone receptors are escorted by molecular chaperones which regulate their function. The HSP90 complex binding with the chaperone maintains the receptor in a folded and hormone responsive state which thereby regulates their function [3,4].

Other investigators have reported on the relationship of GCUNC-45 as a regulator for the progesterone receptor/HSP90 chaperoning pathway. GCUNC-45 has been demonstrated to bind to HSP90 through its TPR domain. Their results showed GCUNC-45 to be a biologically significant positive cofactor for modulating the activity of the progesterone receptor, to regulate the ATPase activity of HSP90 and to block the progression of HSP90 chaperoning. They established that GCUNC-45 is a positive cofactor for the cellular transcriptional activity of PR but its primary localization in the cytoplasm and its association with HSP90 implies its role as a chaperone [4-7].

Based on our findings the measure of UNC-45-A may be a surrogate for HSP90. This implies that if the PR is measurable and the UNC-45-A is overexpressed then HSP90 may be a potential therapeutic target for breast cancer treatment. When using cell lines with ER-PR- cells, the higher expression of the UNC-45A chaperone correlated with the severity of breast carcinoma progression in human breast tumor samples and cell lines derived from human breast carcinomas, specifically triple negative disease. However this also underscores that the tumor microenvironment and/or tumor heterogeneity may produce confounding results when compared to homogeneous in- perpetuity cell lines. This certainly adds a layer of complexity as UNC-45A moves into translational investigation.

References

1. Guo, W., Chen, D., Fan, Z., et al. Differential turnover of myosin chaperone UNC-45A isoforms increases in metastatic human breast cancer. (2011) J Mol Biol 412(3): 365-378.
2. Hatch, S. S., Eltorky, M. A., Li, S., et al. UNC 45-A expression correlates with progesterone receptor status in invasive ductal breast cancer" at the 14th St. Gallen International Breast Cancer Conference. (2015)
3. Lim, C. S., Baumann, C.T., Htun, H., et al. Differential localization and activity of A- and B-forms of the human progesterone receptor using green fluorescent protein chimeras. (1999) Mol Endocrinology 13(3): 366-375.
4. Chadli, A., Graham, D., Abel, M. G., et al. GCUNC-45 is a Novel Regulator for the Progesterone Receptor/hsp90 Chaperoning Pathway. (2006) Mol Cell Biol 26(5): 1722-1730.
5. Pratt, W. B., Toft, D. O. Regulation of signaling protein function and trafficking by the hsp90/hsp70-based chaperone machinery. (2003) Exp Biol Med (Maywood) 228(2): 111-133.
6. Haverinen, M., Passinen, S., Syvala, H., et al. Heat shock protein 90 and the nuclear transport of progesterone receptor. (2001) Cell Stress & Chaperones 6(3): 256-262.
7. Echeverria, P. C., Picard, D. Molecular chaperones, essential partners of steroid hormone receptors for activity and mobility. (2010) Biochim Biophys Acta 1803(6): 641-649.