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Reciprocal regulation of Her-2 and annexin A2 in Her-2 negative breast cancer

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Abstract

Annexin A2 (AnxA2) a known calcium dependent phospholipid binding protein is highly expressed in various invasive phenotypes of cancers. Although a correlation between AnxA2 expression level, angiogenesis and invasiveness has been demonstrated in breast cancer, little is known about the cell signaling events mediated by AnxA2 and the significance of AnxA2 expression in Her-2 negative breast cancer.

The aim of this study is to analyze the expression pattern of AnxA2 and to delineate its signaling role in Her-2 negative breast cancer. AnxA2 and Her-2 expression in various breast cancer cell lines were analyzed by Western, qPCR and Immunohistochemistry. siRNA was used to knockdown Anx A2 and Her-2 in different cell lines and the expression of respective proteins and downstream signaling molecules was studied. Tissue micro-array was used to study the expression of these proteins in different breast cancer cases.

Immunohistochemical analysis demonstrated that AnxA2 expression is inversely correlated with Her-2 staining pattern ($p<0.008$) in breast cancer. AnxA2 staining is a good indicator of cancer progression in Her-2 negative breast cancer ($p<0.002$). Cell line analysis revealed that TNBC cells with basal or nil Her-2 levels express high levels of AnxA2 and cell lines with Her-2 amplification demonstrate a very low level of AnxA2. Increased membrane localization and secretion of AnxA2 was observed in TNBC cells. Her-2 downregulation through siRNA or anti-Her-2 antibody treatment resulted in concomitant induction of AnxA2 and EGFR. We validated the role of AnxA2 in the downstream arm of the EGFR pathway in TNBC cells. AnxA2 has an active role in the constitutive activation of the EGFR downstream signaling molecules and in further regulation of cancer cell metastasis, survival and apoptosis. This observation supports the role of AnxA2 as a potential tissue and serum biomarker and a therapeutic target in TNBC.

Biography

Vishwanatha is the Dean of the Graduate School of Biomedical Sciences, Professor of Molecular Biology and Immunology, and Director of the Texas Center for Health Disparities at the University of North Texas Health Science Center at Fort Worth. Dr. Vishwanatha received his Ph.D. in biological sciences from the University of South Carolina in 1983. He has published over 100 papers in peer-reviewed journals. Dr. Vishwanatha's research is in cancer molecular biology and experimental therapeutics.