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Understanding the heterogeneity of breast cancer: Referencing the normal breast luminal epithelium

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Although molecular sub classification has impacted on breast cancer treatments and outcomes, patient response to targeted therapy or chemotherapy remains highly unpredictable. Dissection of the normal epithelium is fundamental to understanding breast cancer heterogeneity. Terminal ductal lobular unit (TDLU) is the primary site, where the breast carcinogenesis initiates. It consists of two types of cells: Luminal epithelium and myoepithelium. Even inside the luminal epithelium, different cell types are present. For instance, only approximately 10-20% of luminal cells express ER, while the majority of the luminal cells are ER negative. We studied the co-expression of AR and ER in normal breast luminal cells and found that their distribution pattern is the same as what was revealed in invasive breast carcinomas, indicating that ER/AR positive luminal cells may serve as the "cell of origin" of ER/AR positive tumors. These different types of luminal cells could be subjected to different genetic mutations, which could further confound the inter-tumor heterogeneity. We found that Tocopherol-Associated Protein (TAP), a vitamin E binding protein, was co-expressed with ER in normal/benign breast luminal cells, but was down regulated in 46% of ER positive breast carcinomas. This down regulation of TAP was associated with poorer clinical outcome in ER positive breast cancer patients. Further, our study on p53 alteration in breasts of BRCA carriers and non-carriers revealed that p53 positive normal/benign luminal cells were ER negative, indicating that they are the "cell of origin" of p53+/ER tumors. We hypothesize that these cells could serve as the "p53 signature" to predict future risk of a high grade breast carcinoma.

Biography

Xi Wang has completed her Medical education in the Sun Yet-Sen University Medical School in China. She then went to Harvard School of Public Health to be the Research Fellow and later became Research Associate. She has also completed her Residency training in Pathology in West Virginia University and Fellowship training in Sloan-Kettering Cancer Center. She is currently the Associate Professor in Department of Pathology in University of Rochester Medical Center, with the major interests in breast and GYN pathology.

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