Published OnlineFirst December 1, 2011; DOI: 10.1158/2159-8290.CD-RW120111OL-25

Breast Cancer

Major finding: MAST kinase and Notch gene rearrangements are present in 5%–7% of breast cancers.

Approach: Breast cancer cell lines and tumors were analyzed by paired-end transcriptome sequencing.

Impact: Identification of targetable gene fusions could benefit a subset of breast cancer patients.

MAST AND NOTCH FUSIONS DRIVE A SUBSET OF BREAST CANCERS

Recurrent gene fusions and translocations are increasingly being identified as driving genetic lesions in solid tumors. To identify tumorigenic gene rearrangements in breast cancer, Robinson and colleagues performed paired-end transcriptome sequencing on a panel of 89 breast cancer cell lines and tumors. Among the chimeric transcripts that encoded open reading frames and were validated by fusion-specific quantitative PCR, 2 classes of recurring fusions were identified involving either microtubule-associated serine–threonine (MAST) kinases or Notch family genes. Ectopic expression of each MAST fusion increased proliferation of benign breast cells, suggesting that these are functional gene products that confer a proliferative advantage and drive tumorigenesis. Indeed, knockdown of MAST2 in breast cancer cells harboring an *ARID1A-MAST 2* fusion completely abrogated tumor formation in a mouse xenograft model. The Notch fusion genes also encoded functional protein products, as Notch-responsive transcriptional activity was increased in cell lines with these fusions and introduction of *NOTCH1* and *NOTCH2* fusion alleles into benign breast cells induced Notch target gene expression and morphologic alterations. Moreover, treatment of breast cancer cell lines with a γ-secretase inhibitor that blocks Notch processing specifically impaired the proliferation and tumorigenicity of cells harboring a Notch fusion gene. Based on the mutual exclusivity of MAST and Notch gene fusions in breast cancers and the identification of additional gene fusions in a larger cohort of breast cancer samples by targeted sequencing of MAST and Notch family genes, the authors estimate that these alterations may be found in up to 5% to 7% of breast cancers. The characterization of these rare, but functional and potentially targetable gene fusions has therapeutic implications for a subset of breast cancer patients and demonstrates the utility of sequencing-based approaches in personalized medicine.

Robinson DR, Kalyana-Sundaram S, Wu YM, Shankar S, Cao X, Ateeq B, et al. Functionally recurrent rearrangements of the MAST kinase and Notch gene families in breast cancer. Nat Med 2011 Nov 20. [Epub ahead of print].

Cancer Discovery; Published OnlineFirst December 1, 2011; doi:10.1158/2159-8290.CD-RW120111OL-25

Published OnlineFirst December 1, 2011; DOI: 10.1158/2159-8290.CD-RW120111OL-25

AACR American Association for Cancer Research

CANCER DISCOVERY

Mast and Notch Fusions Drive a Subset of Breast Cancers

Cancer Discov 2012;2:OF6. Published OnlineFirst December 1, 2011.