MAP3K3/MEKK3 Is an amplified and overexpressed novel oncogene in breast cancer

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Background: Gene amplification in the 17q chromosomal region is observed frequently in breast cancers. An integrative bioinformatics analysis nominated MAP3K3 gene, located in 17q23, as a potential therapeutic target in breast cancer. This gene encodes the mitogen-activated protein kinase kinase kinase 3 (MEKK3), but has not yet been associated with cancer-causal genetic aberrations.

Methods and Experiments: An integrative method of bioinformatics was deployed to identify MAP3K3/MEKK3 as a candidate oncogene that might be amplified in breast cancer through mining the public cancer genomic databases. Genomic quantitative PCR and FISH analysis was performed to confirmed that MAP3K3/MEKK3 amplification and overexpression in multiple breast cancer cell lines and in primary breast cancer specimens. The effect of MAP3K3 knock-down by shRNA on the malignant transformation and tumour cell proliferation in human breast cancer cell lines was also evaluated.

Results: We found that MAP3K3 was amplified in approximately 8-20% of breast carcinomas, and that its over-expression was an independent prognostic marker for poor outcome with respect to relapse-free and overall survival, especially among the estrogen receptor-positive breast cancer patients. shRNA-mediated knockdown of MAP3K3 expression significantly inhibited cell proliferation and colony formation of MAP3K3-amplified breast cancer cell lines MCF7 and MDA-MB361, and promoted breast cancer cell apoptosis induced by TNFα, TRAIL, or a doxorubicin. In addition, ectopic expression of MAP3K3, in collaboration with Ras, induced colony formation in both primary mouse embryonic fibroblasts and immortalized mammary epithelial cells (MCF-10A).

Conclusions: Together, these results suggest that MAP3K3 is a potential biomarker indicating poor prognosis, contributes to resistance to therapy, and is an oncogene in breast carcinogenesis. Therefore, therapeutic targeting of MAP3K3 may be attractive in breast cancer patients with MAP3K3-amplified breast cancer.

Biography

Dr. Amy Hong Zhang, M.D., Ph. D., is currently an Assistant Professor in the Department of Pathology in University of Texas-M.D. Anderson Cancer Center in Houston, TX, specializing on breast cancer pathology. Prior to joining UT-MDACC, Dr. Zhang was an Assistant Professor in the Department of Pathology in the Baylor College of Medicine from 2006 to 2009. Dr. Zhang is an American Board certified practicing pathologist since 2003. Dr. Zhang has expertise in diagnosing breast cancer and the interpretation of the biomarkers relevant to breast cancer for patient care. Dr. Zhang is also actively participating in clinical teaching for the residents/fellows on surgical pathology. As an independent laboratory researcher, Dr. Zhang supervises research scientists and trainees on translational and laboratory research working on the characterization and development of new molecules significant for breast tumorigenesis. Her academic activities in recent years have led to a series of first author, co-author and senior author publications in recognized peer-reviewed journals.

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