FOXK2: A novel oncogene that is amplified and over-expressed in breast cancer

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Background: Activation of oncogenes through DNA amplification/overexpression plays important roles in cancer initiation and progression. The chromosome 17 is a frequent site of cancer-associated genetic anomalies. This cytogenetic anomaly is strongly associated with poor prognosis and is a significant predictor of relapse in breast cancer. Previous studies of breast cancer have revealed the amplification of several genomic regions on 17q. These amplifications are typically discontinuous and complex in structure, suggesting that multiple oncogenes in this chromosomal segment may be co-selected during breast carcinogenesis. By integrative analysis of public genomic datasets of breast cancers from The Cancer Genome Atlas (TCGA), we have found that FOXK2 displayed frequent genomic amplifications and correlated gene expression changes in breast cancer. FOXK2 gene is located in 17q25 and encodes a transcriptional factor with a fork head DNA binding domain, but has not yet been reported to be associated with cancer-causal genetic aberrations. Gene amplification in the 17q chromosomal region is observed frequently in breast cancers.
Hypothesis: We hypothesize that FOXK2 is an important oncogene in breast cancer and it might be a novel therapeutic target and biomarker for breast cancer.
Methods: The status of FOXK2 located at the Chromosome 17q25 was explored by mining the breast cancer TCGA datasets including 910 tumor cases and 981 normal controls. To determine whether *FOXK2* amplification/overexpression is required for breast cancer cell proliferation, we assessed the effect of FOXK2 stable knockdown on proliferation and anchorage-independent growth in four cell lines with high FOXK2 expression status (MDA-MB-231, MCF-7, HCC1954 and MDA-MB-361) using lentivirus mediated shRNAs. The oncogenic activity of FOXK2 was assessed by colony formation assay.The potential interacting molecules/pathways were explored using RNASeq technique on the FOXK2 knockdown breast cancer cells.
Results: Frequent genomic amplifications of *FOXK2* were detected in breast cancers compared to normal controls in all subtypes of breast cancers classified by PAM50 by integrative analysis of public genomic datasets and its overexpression was associated with poor overall survival of breast cancer patients. FOXK2 knockdown in several breast cancer cell lines inhibited breast cancer cell proliferation and anchorage-independent growth. More importantly, overexpression of FOXK2 and oncogene RAS induced MCF10A cell colony formation, indicating that FOXK2 is an oncogene in breast cancer. Several pathways, including regulation of cell proliferation, regulation of cell division, cell adhesion and regulation of cell metabolism, were regulated by FOXK2 in breast cancer cells. Our data provide compelling evidence that FOXK2 is an oncogene in breast tumorigenesis, and it might be a novel therapeutic target and a biomarker predicting poor outcome.
Future plan: We will assess the incidence and significance of FOXK2 amplification in human breast cancer specimens using immunohistochemistry and FISH modality on TMA tissue blocks to determine the prognostic value of FOXK2 amplification for overall prognosis and treatment resistance. We will also validate the molecular mechanism of FOXK2 in breast cancer malignancy according to the identified potential interacting molecules/pathways through RNASeq analysis. The long-term goal of this proposal is to improve the outcome of breast cancer patients by identifying and validating potential novel diagnostic/prognostic marker and molecular target for therapeutic intervention of this devastating disease in women