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Signature molecular biomarkers of prognosis of gastric adenocarcinoma: A study of 114 cases using genome-wide technique and FISH

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Background: Accumulated evidence suggests that multiple genetic alterations are involved in the complex carcinogenetic process of gastric adenocarcinoma (GAC). Although a number of genetic changes have been reported in GAC, including amplification of *CMET and FGFR2*, mutation of *E-cadherin and KRAS*, and loss of heterozygosity on 5q and 18q, the molecular events leading to GAC and its progression remain largely unknown. To assess global molecular changes in GAC, we use whole genomic assay to evaluate human GAC samples.

Methods: Oligonucleotide array comparative genomic hybridization (aCGH) was performed on 46 GAC samples using a high-density (244K) aCGH system (Agilent Technologies). For each aCGH probe, each sample was classified as having normal, gained, or lost DNA copy number based on log 2 ratio thresholds of 0.15. An independent set of tissue arrayed samples (n=68) was further validated by fluorescent in-situ hybridization (FISH) by using probes visualizing 19q13.3 (red signal) and the centromere (green signal). Amplification of 19q13.3 was defined if the ratio of 19q13.3 to centromere is greater than 2.2. The mean patient's survival follow-up time was 58 months.

Results: aCGH identified 1271 genes with DNA copy loss and 1449 genes with DNA copy gain in gastric cancer. Among these identified genes, 11 deleted and 198 amplified genes were observed to have significant association with patient's survival. Forty-eight of amplified genes were specifically located on chromosome 19q13.3, including *CRX, DACT3, DKKL1, EHD2, EMP3, HIF3A, HRC, IGFL2, IGFL3, KPTN, LIG1, PNKP,* and *PTOV1*. Compared with all other patients, those (n=14) with gene amplification on 19q13.3 had a significantly poorer prognosis ($p<0.01$), independent of other conventional prognosis factors including TNM stage. These results were further confirmed by FISH method and amplification of 19q13.3 was identified in 18 cases with unfavorable clinical outcome.

Conclusions: This genome-wide study identified a panel of critical genes associated with progression of GAC. Amplification of the genes on chromosome 19q13.3, a possible signature event in gastric carcinogenesis, represents a potentially useful prognostic biomarker for this aggressive malignancy. Further functional studies are needed to confirm the potential value of these genes in the management of gastric cancer.

Biography

Dr. Dongfeng (Dan) Tan is a professor at MD Anderson Cancer Center. After medical education and graduate study (1978-1987) in Tongji Medical College, Wuhan, Dr. Tan did postgraduate training in pathology and genetics at Essen University in Germany (1987-90) and Columbia University (1991-94) in New York. After pathology residency at Yale University Medical Center, Connecticut, from 1994 to 1998, he completed an oncologic surgical pathology fellowship at Memorial Sloan-Kettering Cancer Center in New York. Certified by American Board of Pathology in 1998, Dr. joined Roswell Park Cancer Institute as an assistant professor of pathology in 1999. In 2004, he became an associate professor at The University of Texas (UT) Health Science Center at Houston. In 2006, he joined the faculty of UT M. D. Anderson Cancer Center. Currently, Dr. Tan focuses on oncological pathology and molecular diagnostics. Dr. Tan has published more than 120 peer-reviewed articles, one textbook, and a number of book chapters. In recognition of his contributions to the field, Dr. Tan has been invited to present at a number of national and international meetings as well as grand rounds at varied institutions. He has also served on grant review committees for private and government agencies, and has been invited to serve on the editorial boards of ten peer-reviewed journals.