TFAP2E-DKK4 and chemoresistance in colorectal cancer.

Abstract:
Chemotherapy for advanced colorectal cancer leads to improved survival; however, predictors of response to systemic treatment are not available. Genomic and epigenetic alterations of the gene encoding transcription factor AP-2 epsilon (TFAP2E) are common in human cancers. The gene encoding dickkopf homolog 4 protein (DKK4) is a potential downstream target of TFAP2E and has been implicated in chemotherapy resistance. We aimed to further evaluate the role of TFAP2E and DKK4 as predictors of the response of colorectal cancer to chemotherapy. We analyzed the expression, methylation, and function of TFAP2E in colorectal-cancer cell lines in vitro and in patients with colorectal cancer. We examined an initial cohort of 74 patients, followed by four cohorts of patients (total, 220) undergoing chemotherapy or chemoradiation. TFAP2E was hypermethylated in 38 of 74 patients (51%) in the initial cohort. Hypermethylation was associated with decreased expression of TFAP2E in primary and metastatic colorectal-cancer specimens and cell lines. Colorectal-cancer cell lines overexpressing DKK4 showed increased chemoresistance to fluorouracil but not irinotecan or
oxaliplatin. In the four other patient cohorts, TFAP2E hypermethylation was significantly associated with nonresponse to chemotherapy (P<0.001). Conversely, the probability of response among patients with hypomethylation was approximately six times that in the entire population (overall estimated risk ratio, 5.74; 95% confidence interval, 3.36 to 9.79). Epigenetic alterations of TFAP2E were independent of mutations in key regulatory cancer genes, microsatellite instability, and other genes that affect fluorouracil metabolism. TFAP2E hypermethylation is associated with clinical nonresponsiveness to chemotherapy in colorectal cancer. Functional assays confirm that TFAP2E-dependent resistance is mediated through DKK4. In patients who have colorectal cancer with TFAP2E hypermethylation, targeting of DKK4 may be an option to overcome TFAP2E-mediated drug resistance. (Funded by Deutsche Forschungsgemeinschaft and others.).