Validation of biomarkers associated with 5-fluorouracil and thymidylate synthase in colorectal cancer.

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Previous studies from our laboratory have identified a number of genes associated with chemosensitivity to 5-fluorouracil (5-FU) using an in vitro colon cancer cell line model. In this study, the in vivo significance of several marker genes in terms of prognostic potential was evaluated using colorectal cancer patient samples. Eight marker genes were selected based on their functional roles and significant fold changes in expression. They are SERTA domain containing 1 (SEI1), ribonucleotide reductase M2 polypeptide (RRM2), origin recognition complex, subunit 6 homolog-like (ORC6L), eukaryotic translation initiation factor 4E (EIF4E), thymidylate synthase (TS), SET and MYND domain containing 3 (SMYD3), Dickkopf homolog 4, and methyl-CpG binding domain protein 4 (MBD4). Forty-eight snap frozen clinical colorectal samples (24 normal and 24 paired colorectal cancer patient samples) were selected with detailed clinical follow-up information. cDNAs were synthesized and the expression levels of marker genes were quantified via qRT-PCR analysis. The statistical significance of these markers for disease prognosis was evaluated using the two-tailed paired Wilcoxon test. Survival curves were plotted according to the method of Kaplan-Meier and compared using the log-rank test. Based on the quantitative expression analysis, RRM2 (p=0.0001; 95% CI, 2.0-4.5), ORC6L (p=0.0001; 95% CI, 1.8-4.6), EIF4E (p=0.0002; 95% CI, 0.3-0.9), TS (p=0.0005; 95% CI, 0.7-2.2) and SMYD3 (p=0.0001; 95% CI, 0.8-1.5) were overexpressed in tumor tissues. However, the expression of SEI1 was decreased in tumors (p=0.02; 95% CI, 0.1-1.3), consistent with the function of SEI1 as a potential tumor suppressor. Kaplan-Meier survival analysis indicated that MBD4 is a significant prognostic factor for patient survival (p=0.03). MBD4 was a key protein involved in DNA methylation. The expression of TS was associated with tumor stage as it had a significantly higher expression level in UICC stage I and II compared to stage IV patients (p=0.03). MBD4 may be a potential novel prognostic marker for predicting patient survival for colorectal cancer.

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