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TFAP2E-DKK4 and Chemoresistance in Colorectal Cancer

TO THE EDITOR: Ebert et al. (Jan. 5 issue)[1] report that hypermethylation of the gene encoding transcription factor AP-2 epsilon (TFAP2E) reduces its expression and is associated with chemoresistance in patients with colorectal cancer and in colorectal-cancer cell lines in vitro.

The test has dramatic clinical value: the response rate increased from less than 15% among hypomethylated tumors to more than 80% among hypermethylated tumors. Methylation of this gene had a huge biologic and clinical effect.

However, we have several questions. First, the methylation status differs between primary tumors and metastases in approximately 30% of tumors: were these tumors considered to be hypermethylated or not?

Second, the design of in vitro tests is not consistent with clinical data: patients were treated with drug combinations or chemoradiation, and cells were exposed to single drugs.

The antiproliferative activity reported was limited, even if drug concentrations for irinotecan (20 μM), oxaliplatin (60 μM), and fluorouracil (382 μM) were very high and not comparable to clinical data.[2,3] Concerning the evaluation of methylation in vitro, drug combinations might confound the effects,[4] and it is unclear whether azacytidine or aza-2-deoxycytidine was used.

Finally, in vitro data show increased resistance only to fluorouracil, whereas clinical data suggest that alterations of *TFAP2E–DKK4* could represent a more global chemotherapy-resistance marker.

Elisa Giovannetti, M.D., Ph.D.
VU University Medical Center
Amsterdam, the Netherlands

Giovanni Codacci-Pisanelli, M.D.
University La Sapienza
Rome, Italy
giovanni.codacci-pisanelli@uniroma1.it

Godefridus J. Peters, Ph.D.
VU University Medical Center
Amsterdam, the Netherlands

No potential conflict of interest relevant to this letter was reported.

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THE AUTHORS REPLY: We are fully aware of the shortcomings and limitations of our study. Since most patients with colorectal cancer underwent combination therapy, we were not able to address the role of *TFAP2E* in fluorouracil monotherapy. Thus, based on our findings, we concluded that *TFAP2E* may present a more global resistance marker. For the in vitro studies, different agents, including azacytidine, were used; the role of drug combinations in the predictive value of *TFAP2E* was not addressed in our study. We agree that the methylation status differs in a subgroup of primary and metastatic lesions; however, no response data on the patient cohorts that were used to assess methylation in primary and metastatic lesions were available. We believe that our observations need to be prospectively evaluated in a clinical trial. So far, our study is a retrospective analysis with evidence from in vitro experiments that may indicate a role of *TFAP2E* in predicting treatment response.

Matthias P.A. Ebert, M.D.
Ruprecht-Karls-Universität Heidelberg
Mannheim, Germany
matthias.ebert@umm.de

Marc Tänzer, M.A.
Technische Universität München
Munich, Germany

Since publication of their article, the authors report no further potential conflict of interest.