

News

Novel Biomarker for Prediction of Survival in Colorectal Carcinomas Revealed

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CHICAGO -- Levels of a protein called thymidylate synthase (TS) within two separate compartments of a tumor cell—the nucleus and the cytoplasm—may be critical markers predicting survival in colorectal cancer, according to a study at Yale University School of Medicine.

The study revealed two different and independent predictors of survival in colorectal cancer. One was TS levels in the nucleus—the higher the levels, the lower the survival time; and one was the ratio of TS levels in the nucleus to levels in the cytoplasm—the higher the ratio, the lower the survival time.

“TS levels have been known as a marker for decreased survival and response to therapy, but this is the first study to show that the relationship between nuclear and cytoplasmic levels of TS can predict survival,” said first author Mark D. Gustavson, Ph.D., a postdoctoral fellow in Yale’s Department of Pathology.

Results were presented at the first meeting on Molecular Diagnostics in Cancer Therapeutic Development, organized by the American Association for Cancer Research.

To determine subcellular TS levels, Gustavson and his colleagues used AQUA™, a system that combines fluorescence-based imaging with automated microscopy and high-throughput tissue microarray technologies. Developed at Yale and licensed to HistoRx, AQUA can measure protein concentrations within specific cells and cellular compartments in a highly reproducible and unbiased manner, Gustavson said.

Working with tissue samples from 518 colorectal cancer patients diagnosed between 1970 and 1981, the researchers found that just 51 percent of patients with high TS levels in the nucleus survived for five years compared to 71 percent of those with lower levels. The difference was highly statistically significant. TS levels in the cytoplasm were also higher in patients with lower survival times, though they were not as strong a predictor of survival as TS levels in the nucleus.

The researchers next looked at the ratio between TS levels in the nucleus and in the cytoplasm and discovered that a high ratio predicted decreased survival. Moreover, the cytoplasmic-to-nuclear ratio appeared to be an independent marker, not correlated with high nuclear levels. Among patients with a high ratio, more than half (55 percent) did not have high nuclear levels.

“The ratio identifies a group of patients with worse prognosis that would otherwise be missed,” Gustavson said.

After taking into account other predictors of survival, including stage, age at diagnosis, gender, and race, both nuclear TS levels and the cytoplasm-to-nucleus ratio emerged as independent predictors of survival.

“This is a new potential biomarker for predicting survival in patients with colorectal cancer,” said Gustavson. Up to now, standard immunohistochemistry has been used to measure only absolute levels of TS. However, this study shows that TS expression levels within different subcellular compartments and their relationships should also be considered, he said.

The researchers also note that the markers may help in predicting response to therapy with 5-FU, one of the standard chemotherapy drugs used in colorectal cancer, since TS levels have been shown to be critical in modulating response to the drug. Currently a retrospective study is examining whether these two biomarkers can predict response to 5-FU.

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The mission of the American Association for Cancer Research is to prevent and cure cancer. Founded in 1907, AACR is the world’s oldest and largest professional organization dedicated to advancing cancer research. The membership includes more than 24,000 basic, translational, and clinical researchers; health care professionals; and cancer survivors and advocates in the United States and more than 60 other countries. AACR marshals the full spectrum of expertise from the cancer community to accelerate progress in the prevention, diagnosis and treatment of cancer through high-quality scientific and educational programs. It funds innovative, meritorious research grants. The AACR Annual Meeting attracts more than 17,000 participants who share the latest discoveries and developments in the field. Special Conferences throughout the year present novel data across a wide variety of topics in cancer research, treatment, and patient care. AACR publishes five major peer-reviewed journals: Cancer Research; Clinical Cancer Research; Molecular Cancer Therapeutics; Molecular Cancer Research; and Cancer Epidemiology, Biomarkers & Prevention. Its most recent publication, CR, is a magazine for cancer survivors, patient advocates, their families, physicians, and scientists. It provides a forum for sharing essential, evidence-based information and perspectives on progress in cancer research, survivorship, and advocacy.

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