Loss of SMAD4 gene in certain colorectal cancers is associated with poor prognosis

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Among colorectal cancers, loss of the gene SMAD4 was significantly more common in cancers arising in the hindgut (the left side of the colon to the rectum) than in cancers arising in the midgut (the right side of the colon) and patients with hindgut-derived tumors with SMAD4 loss had worse recurrence-free survival compared with those with hindgut-derived tumors that retained SMAD4, according to data presented at the AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics, held Nov. 5–9.

"A focused review of the literature led us to hypothesize that loss of the gene SMAD4 might be more common in colorectal cancers originating in the hindgut, which includes the splenic flexure, descending colon, sigmoid colon, and rectum, than in cancers originating in the midgut, which includes most of the small intestine, the ascending colon, and the majority of the transverse colon," said J. Joshua Smith, MD, PhD, assistant member of the Colorectal Service in the Department of Surgery at Memorial Sloan Kettering Cancer Center in New York. "To investigate this we used data from The Cancer Genome Atlas [TCGA] and analyzed surgically resected tumor tissue from 388 patients with colorectal cancer treated at Memorial Sloan Kettering Cancer Center.

"The data provide evidence to support our hypothesis and suggest that cancers arising in the hindgut that have loss of SMAD4 are a distinct subset of colorectal cancers with poor prognosis," continued Smith. "We are now investigating whether these colorectal cancers have unique biological features because this has the potential to provide clues that could lead to new treatments."

Smith and colleagues used TCGA data on 595 patients with colorectal cancer to investigate whether SMAD4 loss was associated with tumor origin and other genetic alterations linked to colorectal cancer, including mutations in genes involved in DNA mismatch repair. They also analyzed surgically resected tumor tissue from 388 patients with colorectal cancer using immunohistochemistry to establish levels of SMAD4 and DNA mismatch repair proteins.

Analysis of the TCGA data showed that SMAD4 loss occurred in 87 percent of tumors originating in the hindgut and 50 percent of tumors originating in the midgut. The significant association of SMAD4 loss with tumors originating in the hindgut persisted after adjusting for the presence of mutations in genes involved in DNA mismatch repair. Smith explained that this is important because the biology of tumors with mutations in genes involved in DNA mismatch repair is different from the biology found in sporadic colorectal cancers. Therefore, it was important to show that the findings persisted even when mismatch repair tumors were excluded and that SMAD4 loss was not simply a downstream effect of defective DNA mismatch repair.

The same DNA mismatch repair–independent association between SMAD4 loss and hindgut tumors was also seen with the immunohistochemistry analysis.

Further analysis revealed that among patients with tumors originating in the hindgut, those whose tumors had SMAD4 loss had significantly worse recurrence-free survival compared with those whose tumors had normal SMAD4 levels: 47 months versus 231 months. The same trend persisted when hindgut tumors with SMAD4 loss and no DNA mismatch repair gene mutations were analyzed: median recurrence-free survival of 36 months versus not yet reached at 140 months for the tumors originating in the hindgut with normal SMAD4 levels.

According to Smith, a major limitation of the current study is that complete data on patient outcomes were not available for all the TCGA and tissue samples so the statistical analysis for outcome

measures is limited in its power. He also noted that the analysis was retrospective and that prospective analysis should be performed to validate the findings.

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