Jekyll-Hyde microRNA binding variant linked to improved outcome in early-stage colorectal cancer

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A variant site linked to poor outcome in advanced colorectal cancer has now been found to predict improved prognosis in early stages of cancer, according to research presented at the American Association for Cancer Research special conference on Colorectal Cancer: Biology to Therapy, held Oct. 27-30, 2010.

Researchers said they don't know why this variant site, a microRNA binding site that should allow appropriate regulation of the KRAS gene, exhibited a Dr. Jekyll and Mr. Hyde duality. Further study could show that patients with this miRNA variant might benefit from therapy early-on to forestall aggressive tumor behavior.

"Our results suggested that patients with this variant have a good prognosis, but only in early stages. We need to make sure we identify them in an early stage before the cancer progresses," said lead researcher Kim M. Smits, Ph.D., a molecular biologist and epidemiologist in the GROW-School for Oncology and Developmental Biology at Maastricht University Medical Center, in the Netherlands.

The binding site responds to a molecule that belongs to the lethal-7 (let-7) family of microRNAs that has been linked to control the KRAS gene, which, if unregulated or mutated, can lead to growth of colorectal cancers. But the "G" variant at this site has been shown to lead to poorly regulated KRAS because it does not allow appropriate binding of let-7 to

the gene, thus leading to increased KRAS expression. The G variant has previously been associated with an increased risk of lung cancer in moderate smokers, increased risk of ovarian cancer, reduced survival among patients with oral cancers and reduced survival in late-stage colorectal cancer independent of KRAS mutations.

In this study, the researchers evaluated the effect the G variant had on early-stage colorectal cancer compared to the more common "wild type" T variant.

Researchers examined preserved tissue from 409 early-stage colorectal cancer patients who were part of the Netherlands Cohort Study from 1989 to 1994. Median survival was 7.6 years, but patients with the G variant had a 54 percent improved survival compared to patients with T variant. This survival benefit was enhanced if KRAS mutations were taken into account, Smits said.

"None of the patients with a KRAS mutation and the T variant died," she said.

In later stages of the cancer, this survival advantage was reversed, which Smits said was unexpected.

"You would intuitively think that the G variant would be associated with a poorer prognosis, as it is in late-stage colorectal cancer, but that is not the case," said Smits.

Smits believes that in patients with the G variant, "KRAS control has been taken over by another, still unidentified pathway. These patients may be born with reduced KRAS control and I think the body has taken action on this, and another pathway controlling KRAS is overexpressed or activated to compensate for the imbalance."

"This would explain why these patients have a good prognosis, even if KRAS has an activating mutation - KRAS is controlled by another pathway," she said. "In late-stage patients, this alternative pathway might be impaired, thereby losing KRAS control."

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