Gene signature may improve colon cancer treatment

February 26 2010

A gene signature, first identified in mouse colon cancer cells, may help identify patients at risk of colon cancer recurrence, according to a recent study by Vanderbilt-Ingram Cancer Center researchers.

The findings, published in the March issue of *Gastroenterology*, could help personalize treatments for colon cancer — the second leading cause of cancer-related deaths in the United States — by identifying patients most likely to benefit from chemotherapy.

In its early stages, colorectal cancer is treated with surgery only. However, between 20 percent and 25 percent of patients with Stage II disease (when the tumor has penetrated the muscular wall of the colon) will experience metastatic recurrence after surgical resection alone.

For stage III, when the cancer has spread to the lymph nodes, surgery is generally followed by chemotherapy — despite research showing that about 40 percent of stage III patients treated by surgery alone do not have a recurrence of disease in five years.

This suggests that identifying stage II patients at the greatest risk for recurrence — and targeting adjuvant chemotherapy to them — could decrease recurrences in that group. In addition, those stage III patients at lowest risk, if prospectively identified, could avoid having potentially toxic chemotherapy.

Using a mouse colon cancer cell line, R. Daniel Beauchamp, M.D., the

John Clinton Foshee Distinguished Professor of Surgery and chair of the Section of Surgical Sciences, and colleagues identified 300 genes that showed distinct patterns of expression related to their ability to invade into a gel-like matrix, a test that reflects the aggressiveness of cancer cells.

Statistical analysis, led by Yu Shyr, Ph.D., the Ingram Professor of Cancer Research and professor of Biostatistics, helped refine the initial set of 300 genes into a set of 34 genes that were most closely associated with metastasis and death in a set of human colon cancer samples from Vanderbilt patients.

The researchers then examined whether this 34-gene signature could predict recurrence and death in a larger patient population.

In colon cancer tissue samples from 177 patients from the H. Lee Moffitt Cancer Center in Tampa, Fla., the signature identified in the highly invasive mouse cells — the "high recurrence" (or "poor prognosis") signature — was associated with increased risk of recurrence and death across all stages of disease.

Among patients with stage II disease, those with the "poor prognosis" signature had a five-year mortality rate of 31 percent. However, no stage II patients with a "low recurrence" (or "good prognosis") signature died within the five-year period.

In patients with stage III disease, 38 percent of those with a "poor" signature died of their disease within five years, whereas only 10.7 percent of those with a "good" prognosis signature died within that time period.

"Across all stages, if patients had a 'poor' prognosis signature, then they would be five times more likely to have a recurrence of cancer than

those with a 'good' prognosis signature," said Beauchamp.

But the most interesting finding, Beauchamp says, is the ability of this gene signature to identify the patients most likely to benefit from chemotherapy.

Among stage III patients with a "poor" prognosis signature, those who had received chemotherapy had a 36 percent cancer-related death rate. Those who did not receive chemotherapy had an 86 percent death rate.

"That tells us that patients with the ('poor' prognosis signature) probably benefited from chemotherapy," Beauchamp said. "And (patients with a 'good' prognosis signature) appeared to get no benefit from chemotherapy."

"This really feeds right into personalized cancer medicine…in identifying subgroups of patients that will benefit from one treatment versus another treatment modality, trying to target those patients that are most likely to benefit…and not exposing patients who are less likely to benefit with potentially toxic treatments," Beauchamp said.

"Ultimately this should lead to more individualized therapy for cancer patients."

Provided by Vanderbilt University Medical Center