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Colon Cancer's Potential for Metastasis Determined Early

Some colon cancers are destined to spread to the liver and other parts of the body, whereas others are successfully treated by surgical removal of the tumor. Now, Howard Hughes Medical Institute investigators have found that the ability of a colon tumor to metastasize arises early in its development.

Those colon cancers that spread carry the ability to metastasize from the time they become cancerous, the researchers found. They don't need to acquire any new genetic mutations to become metastatic. The research also suggests that once a colon carcinoma develops, if it is going to spread outside the colon, it will do so in less than two years.

"The ability to metastasize is hard-wired into this group of tumors in the colon," said Sanford Markowitz, a Howard Hughes Medical Institute investigator at Case Western Reserve University. "It isn't something that happens after a cancer cell wanders off and leaves the colon."

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- Sanford Markowitz

Markowitz and his colleagues published their findings in the *Proceedings of the National Academy of Sciences* on March 3, 2008.

Colon cancer is the second leading cause of cancer mortality in the United States, causing about 60,000 deaths annually. But there are many more cases of colon cancer that are cured by surgical removal of the tumor. Markowitz and his team wanted to understand the genetic differences between the two types.

"It's clear that colon cancer comes in two very different varieties," said Markowitz, who led the study. "With one variety, the surgeon cuts it out and the individual is cured. With the other variety, the surgeon cuts it out but the

disease still spreads, and despite our best efforts the individual succumbs to the disease. So you have two hugely different biological behaviors that are literally the difference between life and death. And we wanted to know if we could find a genetic basis for that difference.”

To do so, the team compared the DNA of primary colon tumors to the DNA of tumors in the liver that had spread from the colon - the metastases. Markowitz said he was shocked to discover that, in 7 of 10 patients, there were no new mutations in the liver tumors. That means the ability of those tumors to spread from the colon was hard-wired from their inception.

In the tumors from the other three patients, a few new genetic mutations appeared in the liver metastases. But none of the mutations appeared in more than one patient. “My guess is that these mutations are noise, that they aren't responsible for the metastases,” said Markowitz.

The project drew on advances in DNA sequencing technology and collections of tumor samples from patients treated by Markowitz. The DNA sequencing was begun in the laboratory of Bert Vogelstein, a Howard Hughes Medical Institute investigator at the Kimmel Cancer Center at Johns Hopkins. Vogelstein's laboratory sequenced all of the DNA of more than 18,000 genes in each of the tumor samples. The sequenced genes were drawn from RefSeq, a compendium of 18,191 genes that represents the gold-standard in the field and is estimated to contain more than 90 percent of the coding information in the human genome.

Last October, the same team published a landmark paper in *Science* that surveyed all of the genetic mutations in samples of colon and breast tumors. That study found that approximately 280 candidate genes give rise to colon and breast cancer.

The new research focused exclusively on metastatic colon cancer. The study examined point mutations - single letter changes in DNA base-pair sequences - in the tumor samples.

Because the researchers know how quickly such random mutations accumulate, they could estimate how long it took each colon tumor to develop and metastasize. “We can use the mutations as a molecular clock,” said Markowitz. The clock ticks at a rate of about one mutation every two years.

Markowitz and his team discovered that it takes about 17 years for a small colon polyp - also called an adenoma, the first, non-deadly stage of colon cancer - to develop into a more dangerous advanced carcinoma. The team determined this by comparing, within individual patients, the DNA of adenomas to the DNA of adjacent carcinomas that developed later. “The adenomas just kind of percolate along,” said Markowitz. “It takes them a good while to figure out how to become a carcinoma, which is a cancer that

can metastasize.”

But if a tumor develops into a carcinoma with the ability to metastasize, it will progress to metastasis quickly. This transformation occurs within about two years, before another mutation can develop.

The next stage of the project will compare the DNA of colon tumors in patients with metastatic disease to colon tumors from patients who don't experience metastases. “Our research implies that the genetic machinery that causes metastases is hard-wired into the tumor from the beginning. We now want to find out what that genetic machinery looks like,” said Markowitz.

Understanding the hard-wired genetic defects that cause metastases could have implications for patient care. Once such mutations are known, testing for them could highlight patients at high-risk of metastases and help guide treatment decisions.