# Study sheds new light on role of genetic mutations in colon cancer development

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In exploring the genetics of mitochondria – the powerhouse of the cell – researchers at Fred Hutchinson Cancer Research Center have stumbled upon a finding that challenges previously held beliefs about the role of mutations in cancer development.

For the first time, researchers have found that the number of new mutations are significantly lower in cancers than in normal cells.

"This is completely opposite of what we see in nuclear DNA, which has an increased overall mutation burden in cancer," said cancer geneticist Jason Bielas, Ph.D., whose findings are published in the June 7 issue of *PLoS Genetics.*

Mutations are changes in the genetic sequence of a cell's genome and can occur as a result of environmental exposure to viruses, radiation and certain chemicals, or due to spontaneous errors during cell division or DNA replication.

Mitochondria, which are primarily responsible for the cell's energy production, are semi-autonomous; similar to the nucleus, they have their own set of DNA, which encodes genes critical for the functioning of the cell. While the role of genomic instability has been well characterized in nuclear DNA, this is the first attempt to determine whether instability in mitochondrial DNA may play a similar role in cancer growth and metastasis.

"We were surprised to find that the frequency of new mutations in mitochondrial DNA from tumor cells is decreased compared to that of normal cells," said Bielas, an assistant member of the Public Health Sciences and Human Biology divisions at the Hutchinson Center. "By extension, this suggests, somewhat counterintuitively, that higher mitcochondrial mutation rates may actually serve as a barrier to cancer development, and drugs that focus directly on increasing mitochondrial DNA damage and mutation might swap cancer's immortality for accelerated aging and tumor-cell death."

For the study, the researchers used using an ultra-sensitive test to detect mutations in mitochondrial DNA from normal and cancerous colon tissue resected from 20 patients prior to chemotherapy.

Bielas and colleagues first set out to analyze mutation rates in mitochondrial DNA because they wanted to see if it could act as a surrogate for nuclear DNA as a cancer biomarker. "Cells contain a thousandfold more mitochondrial genetic material than nuclear DNA, so theoretically you'd need a thousand times less tissue to get the same genetic information to predict clinical outcomes such as how fast a tumor would progress or whether it would be resistant to therapy," Bielas said.

While mitochondrial DNA proved to be an unreliable stand-in for nuclear DNA as a cancer biomarker, it offers promise as a new drug target.

"If we could increase DNA damage and mutation within the mitochondrial genome, theoretically we could decrease cancer," Bielas said. "That's what we're testing now. This is a whole new hypothesis."

The way mitochondria maintain genetic stability in the face of cancer, Bielas suggests, may be because unlike normal cells, cancer cells do not

need oxygen to survive. In fact, cancer cells decrease the process by which they get energy from the mitochondria and rely instead on a process called glycolysis, which is a form of energy production in the absence of oxygen.

"We believe less damage occurs to mitochondrial DNA of cancer cells because they no longer need oxygen," he said. "If we could program a cancer cell to once again need oxygen, we expect it would die – with minimal side effects."

Bielas and colleagues are now testing this theory in the laboratory, seeing whether cancer cells that are reprogrammed to utilize oxygen and/or are targeted for mitochondrial DNA damage respond better to certain therapeutic agents.

"This finding is a game-changer because it challenges previous notions about the role of mutations in cancer development," said Bielas, who is also an affiliate assistant professor of pathology at the University of Washington, where the ultra-sensitive mutation-detection technology, called Random Mutation Capture, was developed. The test is so sensitive that it can detect the mutational equivalent of one misprinted letter in a library of a thousand 1,000-page books.

"This work started with the idea that there would be a huge mutation burden in the mitochondrial DNA, but our findings were completely opposite of what we had expected. Hopefully our discovery will open up new avenues for treatment, early detection and monitoring treatment response of colon cancer and other malignancies," he said.

**More information:** "Decreased Mitochondrial DNA Mutagenesis in Human Colorectal Cancer," *PLoS Genetics*.

Provided by Fred Hutchinson Cancer Research Center