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Study explores how high-fat diet influences colon cancer

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A study published today in *Nature* reveals how a high-fat diet makes the cells of the intestinal lining more likely to become cancerous. It joins a growing body of research that finds obesity and eating a high-fat, high-calorie diet are significant risk factors for many types of cancer.

The new study of mice suggests that a high-fat diet drives a population boom of intestinal stem cells and also generates a pool of other cells that behave like stem cells—that is, they can reproduce themselves indefinitely and differentiate into other cell types, says co-lead author Semir Beyaz, a Harvard Medical School PhD student affiliated with the laboratories of Stuart Orkin, MD, of Dana-Farber/Boston Children's Cancer and Blood Disorders Center and Omer Yilmaz, MD, PhD, of MIT. These stem cells and "stem-like" cells are more likely to give rise to intestinal tumors.

The *Nature* paper builds on previous research that found people who are obese are at greater risk of developing colorectal cancer. Previous research has also shown that intestinal stem cells, which last a lifetime, are the cells most likely to accumulate the mutations that give rise to colon cancer. These stem cells live in the lining of the intestine, known as the epithelium, and generate all of the different cell types that make up the epithelium.

Beyaz and his colleagues, working under study leader Yilmaz, investigated a possible link between these stem cells and obesity-linked cancer by feeding healthy mice a diet made up of 60 percent fat for 9-12

months. A typical American diet usually contains 20-40 percent fat. Mice on the high-fat diet gained 30 to 50 percent more body mass and developed more intestinal tumors than the mice fed a normal diet.

Mice on the high-fat diet also showed distinctive changes in their intestinal stem cells. Not only did they have many more intestinal stem cells than mice on the normal diet but the stem cells were also able to operate without input from neighboring cells, the researchers discovered.

"The epidemiological link between a high-fat diet and colorectal cancer has been reported for many years, but the underlying mechanisms were not known," Beyaz said. "Our study for the first time showed the precise mechanisms of how a high-fat diet regulates intestinal stem cell function and how this regulation contributes to tumor formation."

When the intestinal stem cells were removed from the mice and grown in a culture dish, they gave rise to "mini-intestines" much more readily than intestinal stem cells from mice on a normal diet. The researchers also found that another population known as progenitor cells—differentiated daughter cells of stem cells—started to behave like stem cells: They began to live much longer than their usual lifespan of a few days, and they, too, could generate mini-intestines when grown outside of the body.

"This is really important because it's known that stem cells are often the cells in the intestine that acquire the mutations that go on to give rise to tumors," Yilmaz said. "Not only do you have more of the traditional stem cells (on a high-fat diet), but now you have non-stem-cell populations that have the ability to acquire mutations that give rise to tumors."

Yilmaz, an assistant professor of biology and member of MIT's Koch Institute for Integrative Cancer Research, and David Sabatini, MD, PhD,

an MIT professor of biology and member of the Whitehead Institute, are senior authors of the study. In addition to Beyaz, MIT post-doctoral student Miyeko Mana and MIT visiting scientist Jatin Roper are lead authors.

The researchers also identified a nutrient-sensing pathway that is hyperactivated by the high-fat diet. The fatty acid sensor, known as PPAR-delta, responds to high levels of fat by turning on a metabolic process that enables cells to burn fat as an energy source instead of their usual carbohydrates and sugars. PPAR-delta also appears to turn on a set of genes that are important for stem cell identity. Yilmaz's lab is now investigating how this happens in hopes of identifying possible cancer drug targets for tumors that arise in obesity.

More information: *Nature* (2016). DOI: 10.1038/nature17173

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