Changes in the diet affect epigenetics via the microbiota

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Nacho Vivas, lab manager at the Rey Lab in the Bacteriology Department at the University of Wisconsin-Madison, checks on a group of germ-free mice inside a sterile lab environment on June 22, 2015. Credit: Bryce Richter/UW-Madison

You are what you eat, the old saying goes, but why is that so? Researchers have known for some time that diet affects the balance of microbes in our bodies, but how that translates into an effect on the host has not been understood. Now, research in mice is showing that microbes communicate with their hosts by sending out metabolites that act on histones—thus influencing gene transcription not only in the colon but also in tissues in other parts of the body. The findings publish November 23 in *Molecular Cell*.

"This is the first of what we hope is a long, fruitful set of studies to understand the connection between the microbiome in the gut and its influence on host health," says John Denu, a professor of biomolecular chemistry at the University of Wisconsin, Madison, and one of the study's senior authors. "We wanted to look at whether the gut microbiota affect epigenetic programming in a variety of different tissues in the host." These tissues were in the proximal colon, the liver, and fat tissue.

In the study, the researchers first compared germ-free mice with those that have active gut microbes and discovered that gut microbiota alter the host's epigenome in several tissues. Next, they compared mice that were fed a normal chow diet to mice fed a Western-type diet—one that was low in complex carbohydrates and fiber and high in fat and simple sugars. Consistent with previous studies from other researchers, they found that the gut microbiota of mice fed the normal chow diet differed from those fed the Western-type diet.

"When the host consumes a diet that's rich in complex plant polysaccharides (such as fiber), there's more food available for microbes in the gut, because unlike simple sugars, our human cells cannot use them," explains Federico Rey, an assistant professor of bacteriology at UW-Madison and the study's other senior author.

Furthermore, they found that mice given a Western diet didn't produce certain metabolites at the same levels as mice who ate the healthier diet. "We thought that those metabolites—the short-chain fatty acids acetate, propionate, and butyrate, which are mostly produced by microbial fermentation of fiber—may be important for driving some of the epigenetic effects that we observed in mouse tissues," Denu says.

The next step was to connect changes in metabolite production to epigenetic changes. When they looked at tissues in the mice, they found differences in global histone acetylation and methylation based on which diet the mice consumed. "Our findings suggest a fairly profound effect on the host at the level of chromatin alteration," Denu explains. "This mechanism affects host health through differential gene expression."

To confirm that the metabolites were driving the epigenetic changes, the investigators then exposed germ-free mice to the three short-chain fatty acids via their drinking water to determine if these substances alone were enough to elicit the epigenetic changes. After looking at the mice's tissues, they found that the epigenetic signatures in the mice with the supplemented water mimicked the mice that were colonized by the microbes that thrive on the healthy diet.

Additional work needs to be done to translate these findings from mice into humans. "Obviously that's a complex task," Denu says. "But we know that human microbial communities also generate these short-chain fatty acids, and that you find them in the plasma in humans, so we speculate the same things are going on."

Rey adds that butyrate-producing bacteria tend to occur at lower levels in people with diabetes and cardiovascular disease, and butyrate is also thought to have anti-inflammatory effects in the intestine.

But the investigators don't advocate supplementing the diet with short-chain fatty acids as a way around eating healthy. "Fruits and vegetables are a lot more than complex polysaccharides," Rey says. "They have many other components, including polyphenols, that are also metabolized in the gut and can potentially affect chromatin in the host in ways that we don't yet understand. Short-chain fatty acids are the tip of the iceberg, but they're not the whole story."

More information: Krautkramer et al: *Molecular Cell* "Diet-microbiota interactions mediate global epigenetic programming in multiple host tissues." www.cell.com/molecular-cell/fu … 1097-2765(16)30670-0 , DOI: 10.1016/j.molcel.2016.10.025

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