Unlocking the metabolic secrets of the microbiome

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The number of bacterial cells living in and on our bodies outnumbers our own cells ten to one. But the identity of all those bugs and just what exactly our relationship to all of them really is remains rather fuzzy. Now, researchers reporting in the May issue of *Cell Metabolism,* have new evidence showing the metabolic impact of all those microbes in mice, and on their colons in particular.

"We point out one relatively general metabolite in the colon that has profound effects—it does a lot to keep things running smoothly," said Scott Bultman of the University of North Carolina at Chapel Hill. And, he says, that single metabolite, known as butyrate, surely isn't all that unique. It is but one example of the complex interactions between mammals and their microbial inhabitants among many more yet to be defined.

There were already clues that the microbiome had significant effects on metabolism. For instance, earlier studies showed that "germ-free" mice have to consume 10%□□% more food to maintain their body weights compared to normal mice. Bultman's group wanted to look a little closer at where in the body those metabolic effects might be most important.

They suspected those influences might be stronger in the colon relative to other tissues, where microbes are represented in the greatest numbers. Indeed, that's exactly what they found.

Those effects were explained by the fact that cells known as colonocytes

are literally fueled by bacteria-produced butyrate as their primary energy source, in place of the glucose burned by other cell types. Colonocytes taken from germ-free mice are found in an energy-deprived state, showing lower levels of important metabolic enzymes and the molecular energy currency known as ATP. Those cells manage to survive that way by digesting some of their own components in a process known as autophagy.

When the researchers added butyrate to germ-free colonocytes, it rescued their energy deficit and prevented them from undergoing autophagy, they report.

The findings come at an important time, just as efforts are underway to sequence the genomes of each and every microbe represented in the human microbiome. "As important as the Human Microbiome Project is, it is really just a launching-off point," Bultman said. "A 'parts list' of bacterial genes won't be enough. We'll need to know about the metabolites they make and their effects on energy, the immune system," and other functions.

The new insight into the important role of butyrate may also have dietary and clinical implications, the researchers say.

"Dietary factors known as prebiotics promote the growth of certain bacteria at the expense of others and have implications for human health and disease," they wrote. "As our diets have shifted away from fiber and other complex carbohydrates toward processed, simple carbohydrates, the incidences of colorectal cancer and inflammatory bowel diseases such as ulcerative colitis and Crohn's disease have increased. It is possible that increasing butyrate levels in the lumen and in colonocytes could help reverse this trend. In fact, butyrate enema therapy has been shown to ameliorate the inflammation associated with colitis in mouse models and in human clinical trials."

More information: Donohoe et al.: "The Microbiome and Butyrate Regulate Energy Metabolism and Autophagy in the Mammalian Colon." *Cell Metabolism* May 4, 2011

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