FASEB
Federation of American Societies for Experimental Biology
Science Research Conferences

STABLE ISOTOPE TRACING IN VIVO REVEALS A METABOLIC BRIDGE LINKING THE MICROBIOTA TO HOST HISTONE ACETYLATION

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The gut microbiota, a community of resident microbes in the intestinal lumen, influences host epigenetics by processing dietary fiber into butyrate and other short-chain fatty acids. Although butyrate is thought to promote histone acetylation primarily by acting as a histone deacetylase inhibitor, it may also undergo oxidation to acetyl-CoA, a necessary cofactor for histone acetyltransferases. Consistent with the microbiota supporting histone acetylation, we find that epithelial cells from germ-free mice harbor a loss of histone H4 acetylation across the genome except at promoter regions as assessed by ChIP-seq. Using stable isotope tracing in vivo with 13C-labeled fiber, we demonstrate that the microbiota supplies carbon for histone acetylation. Subsequent metabolomic profiling by mass spectrometry revealed hundreds of labeled molecules and supported a microbial contribution to host fatty acid metabolism, which declined in response to intestinal inflammation and correlated with reduced expression of genes involved in fatty acid oxidation. These results illuminate the flow of carbon from the diet to the host via the microbiota, disruptions to which may affect energy homeostasis in the distal gut and contribute to the development of inflammatory diseases, such as ulcerative colitis.

This research was funded by the Crohn's and Colitis Foundation (RFA 598467 and the Microbiome Initiative), the PennCHOP Microbiome Program, the Shapiro-Silverberg Fund for the Advancement of Translational Research at The Rockefeller University, the St. Jude Children's Research Hospital Chromatin Consortium, the Host-Microbial Analytic and Repository Core of the Center for Molecular Studies in Digestive and Liver Diseases (P30 DK050306), and the National Institutes of Health (T32CA009140, F32GM134560, P01CA196539, R01AI118891, R01GM40922).