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Researchers identify new vitamin B3 pathway

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Researchers at Beth Israel Deaconess Medical Center (BIDMC) have identified a new vitamin B3 pathway that regulates liver metabolism. The discovery provides an opportunity to pursue the development of novel drug therapies to address obesity, type 2 diabetes and related metabolic diseases.

Published in the August 2015 issue of *Nature Medicine*, the new findings show that a small molecule called N1-methylnicotinamide prevents metabolic complications caused by a high-fat diet.

"Our laboratory investigates the metabolic effects of nicotinamide adenine dinucleotide [NAD+], a metabolite derived from a form of vitamin B3 called nicotinamide," explained senior author Pavlos Pissios, PhD, an investigator in the Division of Endocrinology, Diabetes and Metabolism at BIDMC and Assistant Professor of Medicine at Harvard Medical School. NAD+ is central to intermediary metabolism, the intracellular process by which food is converted into cellular components in the body.

"Like reservatrol, which is found in red wine, NAD+ boosts the effects of the protein sirtuin 1 [Sirt1], which is known to provide many health benefits," said Pissios. "Interest in the metabolic effects of NAD+ has spurred the production of several new dietary supplements to improve metabolic health and delay aging. While these results have yet to be demonstrated in humans, recent research has shown that boosting tissue levels of NAD+ can improve health and reduce metabolic complications in mice that have been fed a high-fat diet."

The liver plays a central role in all metabolic processes, including breaking down fats to produce energy. Because a number of different proteins are involved in the metabolic effects of NAD+, Pissios and his colleagues hypothesized that there might be an as-yet-unidentified vitamin B3 pathway that was directly regulating liver metabolism. "We thought that, in addition to boosting NAD+, vitamin B3 might be positively impacting liver metabolism by acting directly on another pathway," he explained.

To test this hypothesis, the researchers conducted a variety of experiments that assessed these proteins. Their results showed that nicotinamide N-methyltransfersase (NNMT), a "clearance" enzyme that helps the body excrete excess vitamin B3, also plays a more prominent metabolic role.

"Our lab had been gathering evidence that NNMT not only functions to clear nicotinamide from the liver, but is also involved in the regulation of liver metabolism," said Pissios. "We confirmed this in our new study, which found that N1-methylnicotinamide, the product of nicotinamide methylation by NNMT, increases Sirt1 protein levels and improves metabolism."

In subsequent experiments, Pissios and colleagues found that NNMT correlated positively with Sirt1 and a healthy metabolic profile in mice, and also showed that humans with low cholesterol and low triglycerides exhibited high levels of NNMT and Sirt1 in their livers.

"Since N1-methylnicotinamide is a small molecule, we were able to feed it directly to mice to find out if it would prevent the metabolic complications caused by a high-fat diet," said Pissios. As predicted, N1-methylnicotinamide increased liver Sirt1 protein and suppressed triglyceride and cholesterol synthesis resulting in a healthier liver—with fewer inflammatory markers, less liver fat and lower cholesterol

compared to control groups.

"We have now identified a new vitamin B3 pathway that regulates liver metabolism and provides us with an opportunity to pursue development of novel treatments for metabolic diseases," said Pissios.

More information: Nicotinamide N-methyltransferase regulates hepatic nutrient metabolism through Sirt1 protein stabilization, *Nature Medicine* 21, 887–894 (2015) DOI: 10.1038/nm.3882

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