High-fat diet and lack of enzyme can lead to heart disease in mice

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It's no secret that a high-fat diet isn't healthy. Now researchers have discovered a molecular clue as to precisely why that is.

Writing in the Journal of Biological Chemistry, Mitchell Lazar, MD, PhD, the Sylvan Eisman Professor of Medicine and director of the Institute for Diabetes, Obesity, and Metabolism at the Perelman School of Medicine at the University of Pennsylvania, and colleagues, describe that mice lacking a gene-expression-controlling enzyme fed a high-fat diet experience rapid thickening of the heart muscle and heart failure. This molecular link between fat intake and an enzyme tasked with regulating gene expression - at least in mice - has implications for people on so-called Western diets and combating heart disease. Modulating the enzyme's activity could be a new pharmaceutical target.

The team found that the engineered mice without the enzyme HDAC3 tended to underexpress genes important in fat metabolism and energy production. Essentially, when fed a high-fat diet, these animals' hearts cannot generate enough energy and thus cannot pump blood efficiently.

These same mice tolerate a normal diet as well as non-mutant, normal animals. "HDAC3 is an intermediary that normally protects mice from the ravages of a high-fat diet," says Lazar.

HDAC enzymes control gene expression by regulating the accessibility of chromatin - the DNA and protein structure in which genes reside. Within chromatin, DNA is wound around proteins called histones. Genes in tightly wound chromatin areas are generally inaccessible and suppressed, whereas those in loosely packed areas can be activated.

When an animal eats, its metabolism changes, but food doesn't change a cell's genome. Instead, food modulates the "epigenome," molecular markers on the chromatin that influence gene expression by affecting how tightly DNA is wrapped around its protein scaffolding.

Previously, researchers at the University of Texas Southwestern Medical Center showed that if HDAC3 were deleted in heart tissue in the middle of embryonic development, the animals developed severe thickening of the heart walls (hypertrophic cardiomyopathy) that reduces the organ's pumping efficiency. These animals usually died within months of birth.

Lazar and his team wanted to know what would happen if the gene was inactivated in heart tissue after birth. To their surprise, they found that these animals were essentially normal.

On a diet of regular chow, the engineered mice lived as long as their normal littermates, although they did tend to accumulate fat in their heart tissue. On a high-fat diet, however, these animals deteriorated rapidly, dying within a few months of hypertrophic cardiomyopathy and heart failure.

To understand why, Lazar's team compared the gene expression patterns of young mutant mice to their normal siblings. They found that the mutant mice tended to underexpress genes important in fat metabolism and energy production. Essentially, on a high-fat diet, these animals' hearts cannot generate enough energy and thus cannot pump blood efficiently.

According to Lazar, this study identifies an "interesting and dramatic example" of the link between diet and epigenetics. Now his team is working to identify the molecular nature of that link. They are also investigating whether the same pathway and interaction occurs in humans since it may contribute to the increased heart disease associated with Western diets.

Whatever the outcome of those studies, says

Lazar, there is one sure-fire intervention people can always use to stave off the ravages of over-nutrition: Changing your diet. "We don't want to forget that that's still a noble thing to strive for," he says.

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