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GLADSTONE INSTITUTE OF VIROLOGY AND IMMUNOLOGY NEWS

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GLADSTONE SCIENTISTS IDENTIFY KEY PROTEIN IN ENERGY REGULATION

SAN FRANCISCO—March 3, 2010 -- With obesity and obesity-related diseases epidemic in the developed world, a clear understanding of how metabolism is regulated is crucial. One of the key metabolic pathways involves the oxidation of fat. In the current edition of the journal *Nature*, scientists at the Gladstone Institute of Virology and Immunology report on a new mechanism that governs this pathway and in the process identified a novel potential therapeutic target for controlling fat metabolism. The target is a protein from the mitochondria, or the “power plants” of every cell that are responsible for processing oxygen and converting substances from the foods we eat into energy for essential cell functions.

“Many mitochondrial proteins undergo a small chemical modification known as acetylation, which varies during feeding and fasting conditions,” said Eric Verdin, MD, senior investigator and senior author of the study. “From our previous studies, we knew that the enzyme SIRT3 is involved in removing these modifications, and we speculated that SIRT3 might have a role in regulating metabolism and looked for how it might do this.”

To study the enzyme’s role in mice, the researchers used mice in which both copies of the gene had been deleted. Interestingly, mice that lost both copies of the SIRT3 gene appeared to be completely normal. However, the investigators then tested the mice under fasting conditions. During fasting, expression of SIRT3 was increased in the liver, an organ that helps maintain the body’s energy balance. The livers of mice without SIRT3 had higher levels of fat and triglycerides than normal mice, because the mice could not burn fat.

To determine how SIRT3 controls fat burning, the researchers looked at the mitochondrial proteins. They found that the enzyme called LCAD was “hyperacetylated” and contained even more acetyl groups than usual and the enzyme had reduced activity.

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SIRT 3 and energy

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The mice that lacked SIRT3 also had many of the key markers of fat oxidation disorders, low energy levels and low tolerance to cold. Further investigation showed that higher levels of SIRT3 expression and activity increase the activity of this key enzyme in fat oxidation. However, a number of other proteins are acetylated in the mitochondria, an observation which suggests that other proteins may be involved.

“We conclude that acetylation is a new mechanism for regulating fatty acid oxidation in mitochondria and that SIRT3 mediates the acetylation state,” said Matthew Hirschey, postdoctoral fellow and lead author of the study. “The implication is that SIRT3 may have a pathologic role in some metabolic disorders, such as diabetes, cardiovascular disease, or fatty liver disease. We are excited about exploring these possibilities.”

Additional contributors to the research include C. Ron Kahn of the Joslin Diabetes Center at Harvard Medical School, Robert V. Farese, Jr. of the Gladstone Institute of Cardiovascular Disease, and Chris Newgard of Duke University Medical Center. The work was supported in part by a Senior Scholarship in Aging from the Ellison Medical Foundation and by institutional support from The J. David Gladstone Institutes.

Dr. Verdin’s primary affiliation is with the Gladstone Institute of Virology and Immunology where he is associate director and where his laboratory is located and his research is conducted. He is also professor of medicine at UCSF.

About the Gladstone Institutes. The Gladstone Institutes is a nonprofit, independent research and educational institution, consisting of the Gladstone Institute of Cardiovascular Disease, the Gladstone Institute of Virology and Immunology, and the Gladstone Institute of Neurological Disease. Independent in its governance, finances and research programs, Gladstone shares a close affiliation with UCSF through its faculty, who hold joint UCSF appointments.

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