

Lack of cellular enzyme triggers switch in glucose processing

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A study investigating how a cellular enzyme affects blood glucose levels in mice provides clues to pathways that may be involved in processes including the regulation of longevity and the proliferation of tumor cells. In their report in the January 22 issue of *Cell*, a Massachusetts General Hospital (MGH)-based team of researchers describes the mechanism by which absence of the enzyme SIRT6 induces a fatal drop in blood sugar in mice by triggering a switch between two critical cellular processes.

"We found that SIRT6 functions as a master regulator of [glucose levels](#) by maintaining the normal processes by which cells convert glucose into energy," says Raul Mostoslavsky, MD, PhD, of the MGH Cancer Center, who led the study. "Learning more about how this protein controls the way cells handle glucose could lead to new approaches to treating [type 2 diabetes](#) and even cancer."

SIRT6 belongs to a family of proteins called sirtuins, which regulate important biological pathways in organisms from bacteria to humans. Originally discovered in yeast, sirtuins in mammals have been shown to have important roles in metabolic regulation, programmed [cell death](#) and adaptation to stress. SIRT6 is one of seven mammalian sirtuins, and Mostoslavsky's team previously showed that mice lacking the protein die in the first month of life from acute hypoglycemia. The current study was designed to investigate exactly how lack of SIRT6 causes this radical drop in blood sugar.

Normally cells convert glucose into energy through a two-step process.

The first stage called glycolysis takes place in the [cytoplasm](#), where glucose is broken down into an acid called pyruvate and a few molecules of ATP, the enzyme that provides the energy to power most biological processes. Pyruvate is taken into cellular structures called mitochondria, where it is further processed to release much greater amounts of ATP through a process called cellular respiration.

In a series of experiments in mouse cells, the researchers showed that SIRT6-deficiency [hypoglycemia](#) is caused by increased cellular uptake of glucose and not by elevated insulin levels or defects in the absorption of glucose from food. They then found increased levels of glycolysis and reduced mitochondrial respiration in SIRT6-knockout cells, something usually seen when cells are starved for oxygen or glucose, and showed that activation of the switch from [cellular respiration](#) to glycolysis is controlled through SIRT6's regulation of a protein called HIF1alpha. Normally, SIRT6 represses glycolytic genes through its role as a compactor of chromatin - the tightly wound combination of DNA and a protein backbone that makes up chromosomes. In the absence of SIRT6, this structure is opened, causing activation of these glycolytic genes. The investigators' finding increased expression of glycolytic genes in living SIRT6-knockout mice - which also had elevated levels of lactic acid, characteristic of a switch to glycolytic glucose processing - supported their cellular findings.

Studies in yeast, worms and flies have suggested a role for sirtuins in aging and longevity, and while much of the enzymes' activity in mammals is unclear, SIRT6's control of critical glucose-metabolic pathways could signify a contribution to lifespan regulation. Elevated glycolysis also is commonly found in tumor [cells](#), suggesting that a lack of SIRT6 could contribute to tumor growth. Conversely, since knocking out SIRT6 causes blood sugar to drop, limited SIRT6 inhibition could be a novel strategy for treating type 2 diabetes.

"There's a lot we still don't know about SIRT6," adds Mostoslavsky, who is an assistant professor of Medicine at Harvard Medical School. "We need to identify the factors that interact with SIRT6 and determine how it is regulated; investigate whether it acts as a tumor suppressor and how it might help lower [glucose](#) levels in diabetes; and determine its target organs in living animals, all of which we are investigating."

Provided by Massachusetts General Hospital

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