

Joslin researchers discover new effect for insulin

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Researchers at the Joslin Diabetes Center have shown that insulin has a previously unknown effect that plays a role in aging and lifespan, a finding that could ultimately provide a mechanism for gene manipulations that could help people live longer and healthier lives.

The paper, published in the March 21st issue of *Cell*, reports that insulin inhibits a master gene regulator protein known as SKN-1, and that increased SKN-1 activity increases lifespan. SKN-1 controls what is called the Phase 2 detoxification pathway, a network of genes that defends cells and tissue against oxidative stress – damage caused by elevated levels of free radicals (byproducts of metabolism) – and various environmental toxins. The new finding was demonstrated in experiments on the digestive system of *C. elegans*, a microscopic worm often used as a model organism.

“We’ve found something new that insulin does and it has to be considered when we think about how insulin is affecting our cells and bodies,” said Dr. T. Keith Blackwell, senior investigator at Joslin and author of the paper. “This has implications for basic biology since under some circumstances insulin may reduce defense against the damaging effects of oxidative stress more than we realize.”

The idea down the line is that fine-tuning the activity of SKN-1 may lead to increased resistance to chronic diseases and influence longevity, he said. The work could be important as it relates to diabetes and the many problems associated with the disease, particularly vascular and renal

complications.

But, today's finding may be most important for what it teaches about aging in general, he said.

“The major implication is that we have found something new that affects lifespan and aging, and an important new effect that insulin and/or a related hormone called insulin-like growth factor-1 may have in some tissues,” said Blackwell. “The implications go far beyond diabetes.”

It has been known since the 1990s that insulin inhibits a gene regulator protein known as FOXO, important in diabetes metabolism, tumor suppression and stem cell maintenance. FOXO controls a number of genes, including many involved in stress resistance. Studies in *C. elegans* showed that reduced insulin signaling boosted activity of a FOXO protein known as DAF-16, leading to greater stress resistance and longer life.

The new work places SKN-1 alongside FOXO as a second master gene regulator that is inhibited by insulin signaling and adds to the body of knowledge about insulin and its effects on gene pathways, stress resistance and aging. According to the paper, insulin's effect on SKN-1 occurs independently of its effect on DAF-16.

“You can manipulate the expression of SKN-1 and the worms live longer,” said Blackwell, an Associate Professor of Pathology at Harvard Medical School and faculty member at the Harvard Stem Cell Institute.

The experiments will have to be repeated in mammals, where insulin and insulin-like growth factor-1 have a complex array of effects in different tissues. But, according to Blackwell, other findings in the *C. elegans* model have generally turned out to be applicable to mice and humans.

Blackwell's lab at Joslin is focusing on mechanisms of free radical resistance and aging, and on gene regulation mechanisms in *C. elegans* stem cells with the idea of using this knowledge towards reprogramming human stem cells into insulin-producing cells.

Source: Joslin Diabetes Center

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