People at risk of diabetes offer clues toward novel drugs

February 14 2011

Once people develop type 2 diabetes, high blood glucose levels alter their metabolism so much that it becomes difficult to sift through all the clues to find what might enable the disease. "To identify factors that play a primary role in disease susceptibility, we want to investigate people before they get to that point," says Mary-Elizabeth Patti, M.D. of Joslin Diabetes Center. By examining people across the spectrum of diabetes—from healthy to the full-blown disease—scientists in her lab have found a molecular pathway that offers novel targets for drugs.

People develop type 2 diabetes over time as their bodies become more and more resistant to the hormone insulin, which is necessary to process the glucose in blood that provides energy for cells, explains Dr. Patti, who is also an Assistant Professor at Harvard Medical School.

In research reported online in the *Journal of Clinical Investigation* on February 14, Joslin clinical researchers, led by Dr. Allison Goldfine, took tiny samples of muscles from three categories of people: some who were healthy, some with a family history of diabetes who showed signs of insulin resistance although their blood glucose levels were normal, and some with full-blown type 2 diabetes.

They found that among the latter two groups, a gene known as STARS was expressed more than twice as much as in healthy people. STARS activates another gene known as SRF, and a group of genes regulated by SRF along with a co-activator protein called MKL1 showed the most increase in expression in the cells of those with type 2 diabetes. When

scientists cultivated those cells in vitro, the same results appeared.

Examining the muscles of insulin-resistant mice, the scientists found similar boost in the expression of those key genes.

But was this molecular pathway helping to trigger insulin resistance or just showing up at the scene of the crime?

To find out, the scientists next took muscle cells derived from rodents, reduced the expression of STARS and found that glucose uptake climbed in the cells. They then examined the effect of a chemical that inhibits SRF and found that glucose uptake rates increased in both mice and human cells—and that the effects were greater in cells from patients who were insulin resistant or had type 2 diabetes. Finally, the investigators showed that giving the chemical inhibitor to mice with high glucose levels also boosted glucose uptake in muscles.

"This pathway holds promise as a target for novel diabetes therapies, and it also gives us tools to understand the pathways of progression to diabetes," concludes Dr. Patti.

Provided by Joslin Diabetes Center