Tale of 2 mice pinpoints major factor for insulin resistance

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The road to type 2 diabetes is paved with insulin resistance, a condition often associated with obesity in which the hormone begins to fail at its job helping to convert sugars to energy. Researchers at Joslin Diabetes Center have now identified an enzyme called PKC-delta as an important molecular modifier for development of insulin resistance, diabetes and fatty liver in mice. They also have found evidence suggesting a similar role for the enzyme in humans, making PKC-delta a promising new target for drugs for diabetes and related ailments.

Investigators in the laboratory of C. Ronald Kahn, M.D., began with two existing strains of mice that are on opposite sides of the spectrum for insulin resistance.

"The 'B6' mouse is very prone to develop both obesity and diabetes, and the '129' mouse is quite protected from both, even if it possesses a genetic defect in insulin signaling," says Dr. Kahn, who is the Mary K. Iacocca Professor of Medicine at Harvard Medical School. "Comparing the two models, it's as if there's an on/off switch for insulin resistance and diabetes between them. We reasoned that if we could find out the differences between B6 and 129 mice, we could identify a factor that could be a major modifier of insulin resistance, and a good drug target for treatment of type 2 diabetes."

In previous work, the Kahn lab created a genetic cross between these two mice models, did a genome-wide screening and found an area on mouse chromosome 14 that appeared to be important for insulin sensitivity. In

the latest paper, published online in the Journal of Clinical Investigation, they followed up and found that PKC-delta stood out in activity among the genes in that region.

The researchers then showed that levels of the PKC-delta enzyme were about two times as high in the liver and other tissues in the B6 as in the 129 mouse. When both types were put on high-fat diets, levels of the enzyme stayed the same in the 129 mouse but rose to three times higher in the B6 mouse.

Could these differences be enough to make the profound change in insulin sensitivity? The scientists next created three new mice models to check.

In one model, they removed one of the two normal copies of the PKC-delta gene from B6 mice, thus cutting production of the enzyme in half, and the mice became much more insulin sensitive. In a second effort, they removed the gene entirely from the livers of B6 mice, and again the resulting mice were more insulin sensitive. In a third model, they inserted an extra copy of the PKC-delta gene in the liver of 129 mice, which became much more insulin resistant and diabetic.

In short, PKC-delta levels correlated closely with insulin resistance and the abnormalities in glucose tolerance in all three cases of mice. In addition, the insulin resistance correlated with increased fat in the liver, an increasing problem in people with insulin resistance.

Biopsies of human liver tissue, Dr. Kahn says, also showed that levels of the enzyme are heightened in people who are obese or have diabetes. "People with diabetes tend to get fatty liver and that also seems to correlate with the activity of PKC-delta," he adds.

Overall, "drugs that inhibit the activity of PKC-delta in the liver and

other tissues potentially could aid treatments for diabetes and fatty liver disease, which is second only to alcohol as a cause of liver failure," Dr. Kahn says.

Provided by Joslin Diabetes Center