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Team identifies key protein causing excess liver production of glucose in diabetes

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Researchers at the John G. Rangos Sr. Research Center at Children's Hospital of Pittsburgh of UPMC and the University of Pittsburgh School of Medicine have identified a powerful molecular pathway that regulates the liver's management of insulin and new glucose production, which could lead to new therapies for diabetes. The findings were published online this week in *Diabetes*, a journal of the American Diabetes Association.

Usually, the liver stores excess blood sugar as glycogen, which it doles out overnight during sleep and other periods of fasting to keep glucose levels within a normal physiological range, explained H. Henry Dong, Ph.D., associate professor of pediatrics, Pitt School of Medicine. But in diabetes, the liver continues to pump out glucose even when insulin is provided as a treatment.

"Scientists have been trying to find the factors that contribute to this liver overproduction of glucose for decades," Dr. Dong said. "If we can control that pathway, we should be able to help reduce the abnormally high blood sugar levels seen in patients with diabetes."

He and his team have been studying a family of proteins called Forkhead box or FOX, and for the current project focused on one called FOX06. They found that mice engineered to make too much FOX06 developed signs of metabolic syndrome, the precursor to diabetes, including high blood sugar and high insulin levels during fasting as well as impaired glucose tolerance, while mice that made too little FOX06 had

abnormally low blood sugars during fasting.

"In a normal animal, a glucose injection causes blood sugar level to rise initially and then it goes back to normal range within two hours," Dr. Dong said. "In animals that made too much FOX06, blood sugar after a glucose injection doesn't normalize within two hours. They have lost the ability to regulate the level while the liver keeps making unneeded glucose."

Other experiments showed that diabetic mice have abnormally high levels of FOX06 in the liver, he added. Blocking the protein markedly reduced liver production of glucose, although blood sugar did not completely normalize. Within two weeks of treatment, there was significant improvement in blood sugar and glucose metabolism in diabetic mice.

Tests with human liver cells echoed the importance of FOX06's role in glucose production.

"These findings strongly suggest that FOX06 has potential to be developed as a therapeutic target," Dr. Dong said. "If we can inhibit its activity, we can possibly slow the liver's production of glucose in patients with diabetes and better control blood sugar levels."

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