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Pittsburgh scientists find protein may be key to new therapies for elevated triglycerides

High triglycerides common in people who are obese and/or diabetic, at risk for heart disease

Diabetes researchers at the John G. Rangos Sr. Research Center at Children's Hospital of Pittsburgh of UPMC have identified a potential target for the development of new therapies to treat hypertriglyceridemia, a lipid disorder commonly seen in people who are obese and diabetic. Results of their study are published in the June issue of the Journal of Clinical Investigation.

Scientists in the Division of Immunogenetics at Children's Hospital studied the role of a protein known as Forkhead Box O1 (FoxO1) that mediates the metabolism of glucose and cholesterol. In the laboratory, the researchers were able to curb the secretion of triglycerides in animals that were obese and diabetic by inhibiting the production of FoxO1 in the liver. Elevated triglyceride levels have been identified as a risk factor for heart disease.

Our latest findings suggest that we may eventually be able to develop drug therapies that inhibit FoxO1, which would thereby inhibit the production of proteins that lead to elevated triglyceride levels in people who are obese and/or who suffer from type 2 diabetes," said Henry Dong, PhD, a diabetes researcher in the Division of Immunogenetics at Children's and senior author of the study. Hypertriglyceridemia is a known risk factor for developing heart disease, the leading cause of death in the United States.'

The research team was led by Dr. Dong, who has been studying the role of FoxO1 for the last seven years. Adama Kamagate, PhD, is the lead author in the study. Dr. Dong is an assistant professor of Pediatrics at the University of Pittsburgh School of Medicine.

Their research suggests that FoxO1 is vital to the regulation of a protein known as microsomal triglyceride transfer protein (MTP). MTP facilitates the production of very low-density

lipoproteins (VLDL), which are produced in extreme excess in people with hypertriglyceridemia. The study found that FoxO1 mediates insulin action on the production of MTP in the liver. Augmented production of MTP, caused by the inability of insulin to regulate the activity of FoxO1, led to the overproduction of VLDL and hypertriglyceridemia in mice. Mice that were made to be deficient in FoxO1 in the liver experienced reduced MTP and VLDL production.

Having determined FoxO1's role in the liver, Children's researchers now are studying its function in other tissues and organs to determine what an impact such therapies might have on children and adults who are obese and/or have type 2 diabetes, which put a person at risk for heart disease.

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Heart disease is the leading cause of death in the United States and is a major cause of disability, according to the Centers for Disease Control and Prevention. Almost 700,000 people die of heart disease in the United States each year, which is about 29 percent of all U.S. deaths.

For more information about diabetes research at Children's, visit www.chp.edu.