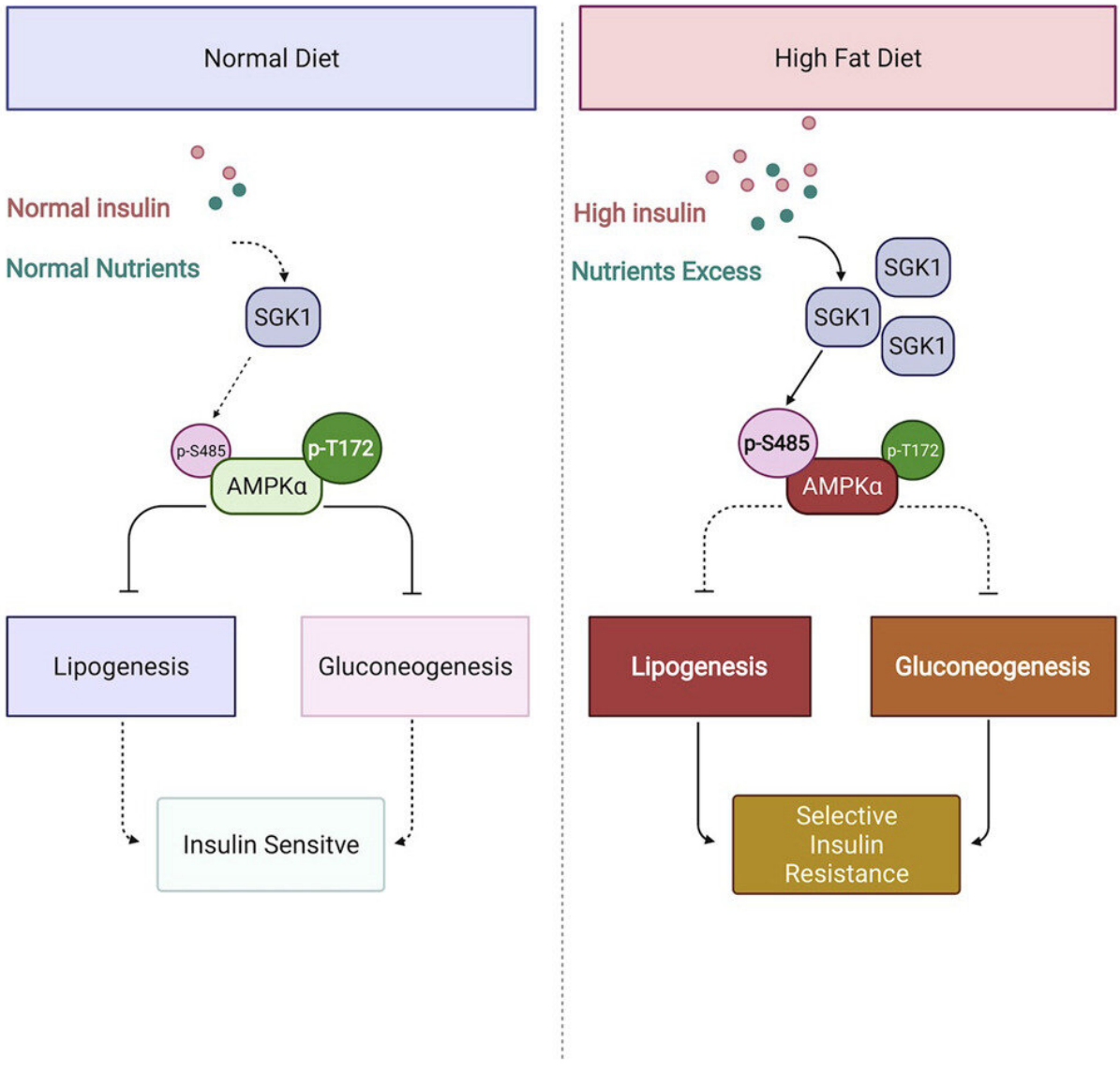
Enzyme driving insulin resistance in liver and may represent promising therapeutic target

October 13 2021, by Marcela Quintanilla Dieck



Graphical abstract. Credit: DOI: 10.1016/j.celrep.2021.109785

A central feature of type 2 diabetes is an inability of the body's cells to respond to insulin, a hormone that keeps blood glucose levels normal. Critical to this balance is the liver, which both stores and manufactures glucose depending on the body's need. New research published in *Cell Reports* that was led by investigators at Massachusetts General Hospital (MGH) indicates that an enzyme called serum- and glucocorticoid-regulated kinase (SGK) drives insulin resistance in the liver and therefore may represent a promising therapeutic target for type 2 diabetes.

"We decided to study the role of SGK in insulin action and metabolism because the field has assumed, since it looks very similar to another insulin-activated kinase called Akt, that SGK would do the same thing as Akt," says senior author Alexander A. Soukas, MD, Ph.D., a principal investigator in MGH's Center for Genomic Medicine and Diabetes Unit and an associate professor of medicine at Harvard Medical School. "We had the idea, based upon some early experiments, that it might actually be working in opposition to Akt, and that it might represent a way to target insulin resistance in diabetes in a very different way, promoting metabolic health and insulin sensitivity."

Indeed, the team's experiments revealed that when mice ate an unhealthy diet, Sgk (the mouse version of SGK) hindered the action of insulin by inhibiting the beneficial metabolic effects of a liver molecule called AMP-activated protein kinase (AMPK). Blocking Sgk activity released the brakes on AMPK, causing the liver to be more sensitive to insulin and to burn fat in the process. "In this way, targeting Sgk may be a way

to target metabolic changes in type 2 diabetes in a way not previously thought possible," says Soukas.

The findings indicate that inhibiting SGK activity in the liver might prevent the insulin resistance that is typical of type 2 diabetes. "In essence, blocking SGK in the liver restores more normal insulin action, in the process helping to block the buildup of fat in the liver and the weight gain that so frequently accompany eating a Western diet," explains Soukas. "While we wouldn't expect this to give people the power to eat fast food with impunity, when combined with exercise and attempts to eat more healthily, treatments like this could revolutionize the way we treat type 2 diabetes."

More information: Ben Zhou et al, Serum- and glucocorticoid-induced kinase drives hepatic insulin resistance by directly inhibiting AMP-activated protein kinase, *Cell Reports* (2021). DOI: 10.1016/j.celrep.2021.109785

Provided by Massachusetts General Hospital