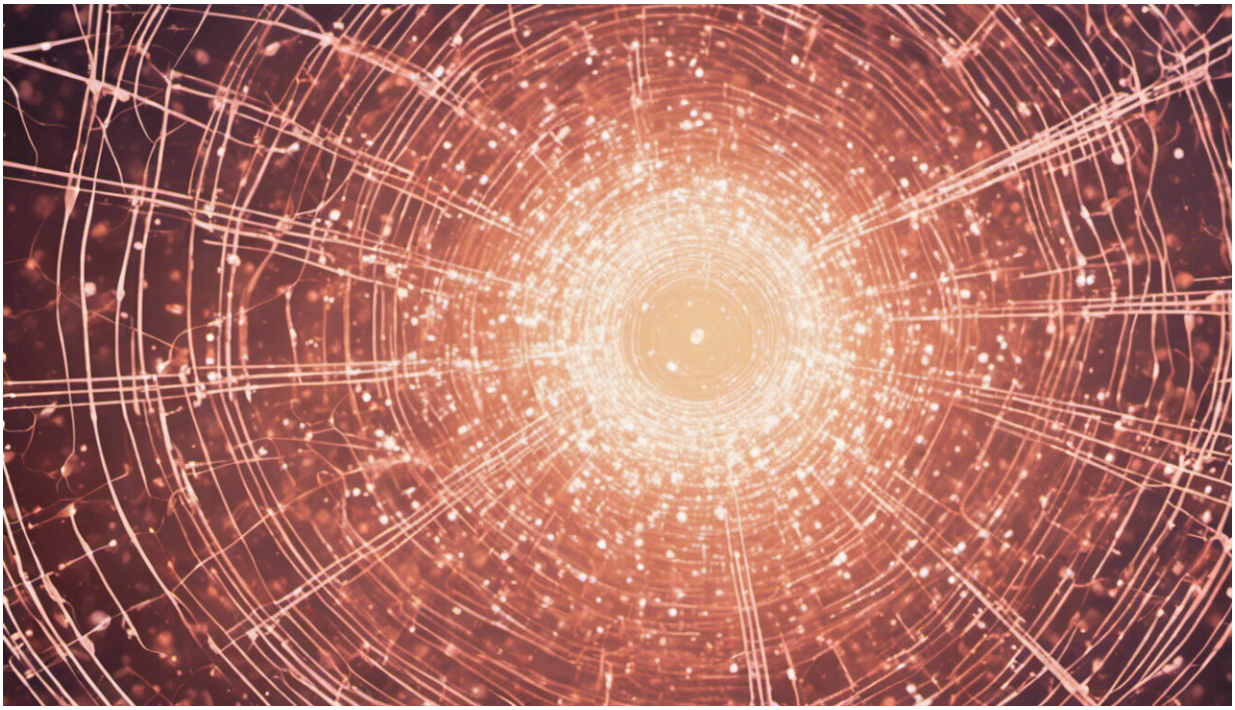
Understanding the role of a little known gene in regulating metabolism

July 24 2019, by Chris Mcintyre



Credit: AI-generated image (disclaimer)

Thousands of genes are involved in the regulation of our day-to-day metabolism and relatively little is understood about their function. One key protein, an ABC Transporter called ABCC5, has recently been predicted to be a susceptibility gene for Type 2 diabetes. In a new study, Associate Professor Heidi de Wet of the Department of Physiology,

Anatomy and Genetics has confirmed ABCC5's role in energy metabolism and identified the mechanism behind its metabolic impact for the first time.

A multitude of physiological signals regulates our appetite and metabolism. An empty stomach triggers the "hunger hormone," Ghrelin, which acts on the brain to stimulate feelings of hunger. When the stomach becomes full, those hunger signals are muted. The arrival of digested food in the small intestine from the stomach engages with hormone-secreting cells known as enteroendocrine cells. These cells are the first point of contact between you and your food: the digested food triggers receptors on these endocrine cells causing them to release hormones into the circulatory system. These hormones have very important downstream effects: they regulate the release of insulin from the pancreas, prompt capillaries to move blood towards the stomach to absorb the food, trigger feelings of satiety in the brain, and interacts with the liver, muscle and fat to enable it to absorb glucose. In essence, "these hormones are spectacularly important because they drive human metabolism in response to food," explains Professor de Wet.

ATP-binding cassette transporters (ABC transporters) are proteins found in cell membranes that transport various substances in and out of the cell. This family of transporters is very well known in the context of certain diseases. Loss of function mutations in the CFTR gene (ABCC8) can cause the respiratory disease cystic fibrosis, while gain of function mutations in the multidrug resistance-associated protein 1 (ABCC1) can cause a tumour to become resistant to chemotherapy. However, the function of one of these transporters, an orphan transporter called ABCC5, was unknown for some time, until a recent study found compelling evidence for its key role in energy metabolism.

The Genome-Wide Association Study used subcutaneous adipose tissue from patients and control subjects stored as part of a diabetes biobank.

The study demonstrated that overexpression of ABCC5 in human adipose tissue would cause their subjects to have a three-fold increased risk of developing type 2 diabetes with age. The individuals with increased levels of ABCC5 had increased visceral fat accumulation and were more insulin resistant. Consequently, the study predicted that ABCC5 may be the new susceptibility gene for Type 2 diabetes. However, the mechanism behind this susceptibility was unknown.

More information: Malgorzata Cyranka et al. Abcc5 Knockout Mice Have Lower Fat Mass and Increased Levels of Circulating GLP-1, *Obesity* (2019). DOI: 10.1002/oby.22521

Provided by University of Oxford