Scientists discover mechanism that could reduce obesity

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Approximately 68 percent of U.S. adults are overweight or obese, according to the National Cancer Institute, which puts them at greater risk for developing cancer, cardiovascular disease, diabetes and a host of other chronic illnesses. But an international team of scientists led by Virginia Commonwealth University Massey Cancer Center researcher Andrew Larner, M.D., Ph.D., has successfully reversed obesity in mice by manipulating the production of an enzyme known as tyrosine-protein kinase-2 (Tyk2). In their experiments, the scientists discovered that Tyk2 helps regulate obesity in mice and humans through the differentiation of a type of fat tissue known as brown adipose tissue (BAT).

Published today in the online edition of the journal Cell Metabolism, the study is the first to provide evidence of the relationship between Tyk2 and BAT. Previous studies by Larner and his team discovered that Tyk2 helps suppress the growth and metastasis of breast cancer, and now the current study suggests this same enzyme could help protect against and even reverse obesity.

The scientists were able to reverse obesity in mice that do not express Tyk2 by expressing a protein known as signal transducer and activator of transcription-3 (Stat3). Stat3 mediates the expression of a variety of genes that regulate a host of cellular processes. The researchers found that Stat3 formed a complex with a protein known as PR domain containing 16 (PRDM16) to restore the development of BAT and decrease obesity.

"We discovered that Tyk2 levels in mice are regulated by diet. We then tested tissue samples from humans and found that levels of Tyk2 were more than 50 percent lower in obese humans," said Larner, Martha Anne Hatcher Distinguished Professor in Oncology and co-leader of the Cancer Cell Signaling program at VCU Massey Cancer Center. "Our findings open new potential avenues for research and development of new pharmacological and nutritional treatments for obesity."

There are two different types of fat – white adipose tissue (WAT) and BAT. WAT is the primary site of energy storage. BAT is responsible for energy expenditure in order to maintain body temperature. BAT deposits are present in all mammals, but until recently, scientists thought BAT was only active in infants and not in adult humans. Only in the last four years have scientists realized that BAT is present in adults and helps to regulate energy expenditure. Additionally, research has shown that diminished BAT activity is associated with metabolic syndrome, a combination of medical disorders that increase the risk of developing cardiovascular disease and diabetes. Researchers estimate metabolic syndrome could affect as much as 25 percent of the U.S. population.

"We have made some very interesting observations in this study, but there are many questions left unanswered," said Larner. "We plan to further investigate the actions of Tyk2 and Stat3 in order to better understand the mechanisms involved in the development of brown adipose tissue. We're hopeful this research will help lead to new targets to treat a variety of obesity-related diseases such as cancer, cardiovascular disease and diabetes."

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