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Protein may play role in obesity, diabetes, aging

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(Medical Xpress) -- Researchers at Washington University School of Medicine in St. Louis have identified a potent regulator of sensitivity to insulin, the hormone that controls blood sugar levels. The new findings may help scientists find better treatments for type 2 diabetes, obesity and other health problems caused by the body's inability to properly regulate blood sugar.

The research is published online Feb. 13 in *PLoS ONE.*

Fat and muscle cells in patients with type 2 diabetes become resistant to insulin, which normally causes them to take in glucose from the blood. The protein studied by the researchers, known as TBC1D3, keeps the insulin pathway open, so the cells can continue to take up glucose. TBC1D3 is found only in humans and certain other primates.

"When cells made more of the TBC1D3 protein, they had a much bigger response to insulin," says senior author Philip Stahl, PhD, professor of cell biology and physiology. "We found that TBC1D3 significantly slows the deactivation of a molecule that relays signals from the insulin receptor. This enhances the cells' response to insulin."

Stahl studies G proteins, which help convert signals from hormones like insulin into specific actions within cells. He became interested in TBC1D3 because part of it binds to some G proteins.

In the new study, Stahl and his colleagues showed that higher levels of

TBC1D3 impede a feedback loop that normally deactivates the insulin signal into the cell from receptors on the cell membrane.

“There are quite a few regulatory pathways like this in biology,” Stahl says. “To make sure the signal doesn’t stay on indefinitely, there are factors built into the signaling pathway that reach back to the origin of the signal and attempt to shut it off.”

More active TBC1D3 impedes that feedback process, keeping the insulin signaling pathway turned on longer, Stahl explains.

Stahl and his colleagues tracked the effects of TBC1D3 to a cluster of proteins that control some of the cell’s most important functions, including nutrient uptake, cell growth and proliferation, and aging.

“We found that TBC1D3 activates a protein called PP2A,” Stahl says. “Flies had shorter lifespans when the PP2A gene was knocked out. This suggests that TBC1D3 also may influence the aging process.”

The researchers are now investigating the factors that regulate the activity of TBC1D3. One such influence may be the number of copies of the TBC1D3 gene in a person’s DNA.

TBC1D3 is one of the most duplicated genes in humans, appearing anywhere from five to more than 50 times in an individual’s DNA. The scientists plan to compare cells with many copies of the gene to others with fewer copies to see whether the number of copies is linked to changes in the cells’ response to insulin.

More information: Wainszelbaum MJ, Liu J, Kong C, Srikanth P, Samovski D, Su X, Stahl PD. TBC1D3, a hominoid-specific gene, delays IRS-1 degradation and promotes insulin signaling by modulating p70 S6 kinase activity. *PLoS ONE*, online Feb. 13, 2012.

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