Receptor protein in adipose tissue plays a role in controlling blood sugar levels

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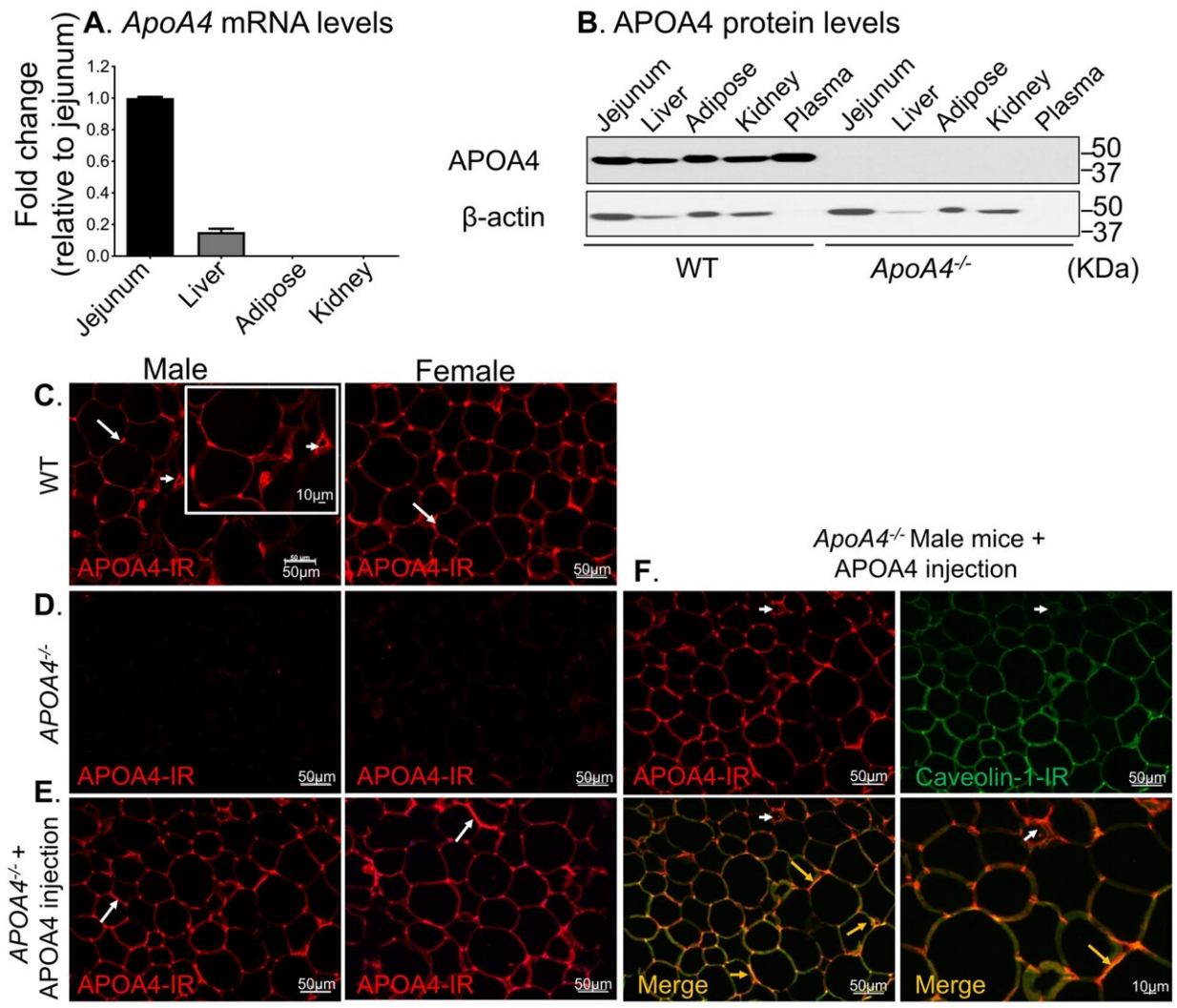

APOA4 is transcribed and translated primarily in the gut and transported to adipose tissue via circulation. (A) APOA4 gene was expressed in mouse jejunum and liver tissues, but not in gonadal adipose tissue and kidney. RT-PCR for

ApoA4 and β-actin was performed on total mRNA isolated from jejunum, liver, gonadal fat, and kidney tissues from male and female 129X1/SvJ WT mice (n = 3 for each sex). ApoA4 levels were normalized with β-actin levels and data was presented as fold change over normalized ApoA4 mRNA levels in jejunum. See Supplemental Fig. S1. (B) Presence of APOA4 protein in tissues of WT but not of ApoA4−/− mice. Total protein (40 μg) from jejunum, liver, epididymal fat and kidney tissues and plasma (10 μg) were separated by SDS-PAGE and probed with anti-APOA4 antibody. The blot was stripped and probed with anti-β-actin for loading control and used for normalization. A representative western blot image shows the presence of APOA4 protein in all tissues from WT, but not ApoA4−/− mice (n = 3/group); these findings also confirmed specificity of the antibody used. (C-E) Representative immunofluorescence confocal images of APOA4 immunoreactivity (IR) in mouse gonadal fat tissues. Epididymal fat from male and periovarian fat from female mice were harvested, fixed, paraffin embedded, sectioned and stained with anti-APOA4 and anti-caveolin-1 (n = 2 technical and 3 biological replicates). Scale bar: 50 μm. (C) APOA4 immunoreactivity (APOA4-IR) was present at the cell surface of adipocytes in a discrete manner in male and female WT mice (arrows) and in the vasculature (inset: arrowhead), (D) no APOA4-IR was detected in ApoA4−/− mice, thereby also confirming specificity of the antibody used. (E) I.p. injection of r-m-APOA4 (5 μg/g body weight) in ApoA4−/− mice resulted in APOA4 uptake in gonadal fat tissues with similar pattern of localization of APOA4-IR in adipocytes as that in WT mice (arrows show discrete cell surface expression). (F) Apo-A-IV-IR co-localized with the adipocyte cell surface marker caveolin-1 (Merge, yellow arrows), but not in the vasculature (white arrowhead), confirming that exogenous APOA4 is targeted to the appropriate cell types. Scale bar: 50 μm and 10 μm. Credit: DOI: 10.1038/s41598-021-92711-0

Researchers at the University of Cincinnati College of Medicine have identified a receptor protein found in adipose tissue that may play a role in controlling blood sugar and could offer an important therapeutic pathway for tackling diabetes and obesity.

The receptor is called LRP1 and it can bind with a protein called

apolipoprotein A4 (APOA4), which helps with sugar uptake in fat cells and also stimulates insulin secretion. Previously, scientists didn't know much about the mechanism involved in regulating blood sugar levels because no one knew which receptor was used by APOA4.

The study findings by the researchers are available online in the Nature journal *Scientific Reports*.

"There are many clinical studies that show that APOA4 can serve as a biomarker for pre-diabetes and also related to coronary artery disease in patients," says Jie Qu, Ph.D., postdoctoral fellow in the UC Department of Pathology and Laboratory Medicine and lead author of the study. "We are trying to understand the molecular mechanisms of how apolipoprotein A4 plays such an important role in diabetes, obesity and cardiovascular disease."

Qu and her colleagues were able to inactivate LRP1 in mouse fat cells and found that APOA4 was no longer able to stimulate sugar uptake by cells. It offers convincing evidence that this is a receptor responsible for APOA4's blood sugar lowering properties.

Patrick Tso, Ph.D., professor emeritus in the UC Department of Pathology and Laboratory Medicine and a study co-author, says scientists have long been convinced of APOA4's importance because it constitutes 3% of all the protein produced by the small intestine and the lack of this protein results in glucose intolerance, a hallmark of pre-diabetes.

"That's a lot of protein made by the small intestine," says Tso. "If we know how APOA4 interacts with LRP1, it is possible to make a drug that resembles a certain part of APOA4 that will interact with LRP1. That offers a possible therapeutic option for disease. Over the years my laboratory has published over 70 papers on this protein. APOA4 is an

important protein."

More information: Jie Qu et al, Low-density lipoprotein receptor-related protein 1 (LRP1) is a novel receptor for apolipoprotein A4 (APOA4) in adipose tissue, *Scientific Reports* (2021). DOI: 10.1038/s41598-021-92711-0

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