Removing a protein could prevent aging and obesity from evolving into metabolic diseases, research suggests

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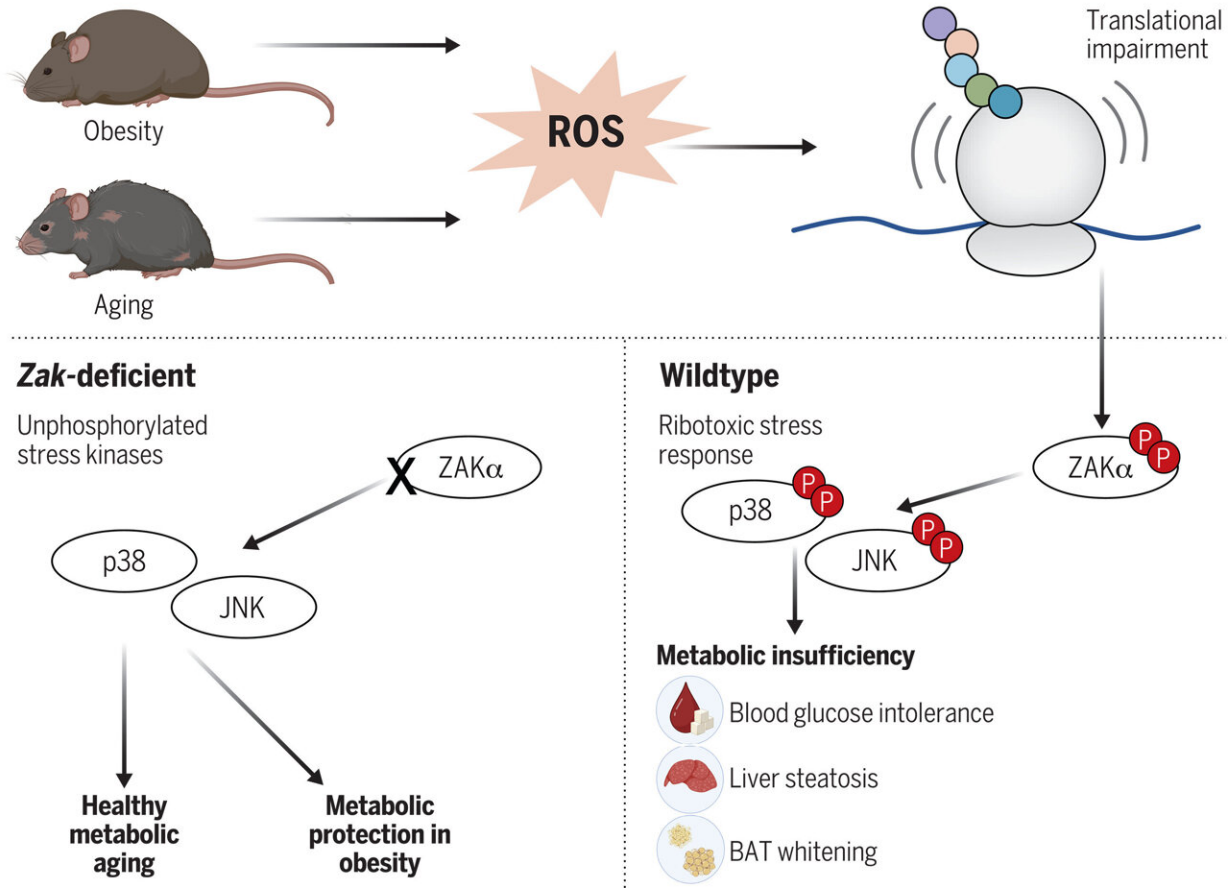

The ribotoxic stress response drives metabolic maladaptation in obesity and aging. ROS are a physiologically relevant source of translational impairment and activation of the stress kinases ZAKα, p38, and JNK. In obese and aging mice, this RSR drives metabolic maladaptation manifested by blood glucose

intolerance, liver steatosis, and whitening of brown adipose tissue (BAT). Figure created with BioRender. Credit: *Science* (2023). DOI: 10.1126/science.adf3208

As we age and gain excess weight, our body's cells undergo stress. This stress is marked by an overproduction of a chemical compound known as ROS (reactive oxygen species), adversely affecting the cells.

This stress elevates the risk of diabetes and leads to the conversion of the body's "brown" fat into "white" fat, contributing to obesity. Moreover, it increases the likelihood of accumulating excess fat in the liver. Notably, 25% of the Danish population has fatty liver, a prevalent cause of later liver failure and death in Western countries like Denmark.

In a recent study, Professor Simon Bekker-Jensen from the Department of Cellular and Molecular Medicine at the University of Copenhagen identified the factors triggering this negative progression.

The article, "ROS-induced ribosome impairment underlies ZAKα-mediated metabolic decline in obesity and aging" is published in *Science*.

"There is a protein called ZAK-alpha that signals the rest of the metabolism system about the cells being stressed. This triggers a chain reaction leading to, among other things, fatty liver," he explains.

Fatty liver is the most widespread liver disease globally. While fatty liver itself is not immediately dangerous, it can progress to cirrhosis and eventual liver failure. Cirrhosis can only be addressed through a liver transplant, and in Denmark, about 700 people die annually from this condition.

Simon Bekker-Jensen and his colleagues demonstrated that by removing

the ZAK-alpha protein, one can prevent aging and obesity from evolving into metabolic diseases.

This prevents the protein from "signaling" the rest of the metabolism system. Experiments with mice and zebrafish showed promising results.

"Mice in which we deactivated the ZAK-alpha protein were much healthier than those with it. In old age, they were more active, had stronger muscles, and, importantly, did not develop various metabolic diseases," says Simon Bekker-Jensen.

Addressing skepticism about the relevance of mouse experiments to humans, he emphasizes, "Mice are a very good model for the human metabolism system. In the laboratory, we can closely simulate the modern human lifestyle, including a lack of exercise and an unhealthy, calorie-rich diet. When mice become overweight, they develop largely the same metabolic diseases as seen in humans."

The findings from this study hold potential for new medicines that could treat and prevent metabolic diseases resulting from aging and obesity.

"While there is already effective and affordable medicine for diabetes, I see great potential for fatty liver, which remains one of the most significant unresolved medical problems today," Simon Bekker-Jensen notes. "ZAK-alpha is a well-established drug target that can be inhibited with small molecules. Therefore, we anticipate that this new knowledge will attract interest from numerous companies actively working on developing and testing drugs against metabolic diseases, including fatty liver."

The next step involves clinical studies, and there is already significant interest from various clinicians.

More information: Goda Snieckute et al, ROS-induced ribosome impairment underlies ZAKα-mediated metabolic decline in obesity and aging, *Science* (2023). DOI: 10.1126/science.adf3208