MedicalXpress

New culprit in muscle defects, insulin resistance that come with age

May 4 2010

Type 2 diabetes is a widespread problem for many people these days, and our risk for insulin resistance and diabetes only grows as we age. Now, a new report in the May issue of *Cell Metabolism* reveals a new contributor to the problem: The muscles of elderly people and of people with type 2 diabetes contain lower concentrations of a protein known as PARL (short for "presenilin-associated rhomboid-like").

PARL plays an important role within cells in remodeling power-generating mitochondria. It's PARL's job to oversee mitochondria's quality control, specifically by maintaining their integrity as the cellular components undergo normal processes of fission and fusion.

The findings provide yet another link between insulin resistance and the function of mitochondria, the researchers say.

When mitochondria aren't functioning properly, food doesn't get metabolized to the level that it should, explained Anthony Civitarese of Pennington Biomedical Research Center. Instead of getting burned, fats accumulate in cells where they impair insulin's action. As mitochondria fail to work efficiently, they also produce more damaging free radicals.

In the new study, Civitarese's team wanted to follow up on previous clues that PARL might play a role in mitochondrial abnormalities and insulin resistance. To do that, they examined PARL expression levels in the muscles of healthy young people compared to elderly people. Importantly, they specifically compared young and elderly people who

were similar to one another in other respects, including their body composition, fatty acid and glucose levels, and physical activity levels.

Relative to younger people, older people showed signs of insulin resistance. They also had fewer numbers of mitochondria and lower expression of the PARL gene.

Follow-up studies in mice showed that treatments designed to lower PARL levels in muscle led to fewer mitochondria, reductions in other important mitochondrial proteins, and reduced insulin sensitivity. Studies in human muscle cells showed essentially the same thing, the researchers report.

"These overlapping answers point to a common mechanism for insulin resistance and the defects that come with aging," Civitarese said.

Together with earlier evidence, the findings show "that lower PARL expression is an early defect altering mitochondrial function and insulin resistance in response to a metabolic challenge," the researchers wrote. "We hypothesize that impaired PARL function is an important risk factor for the development of insulin resistance in skeletal muscle by decreasing mitochondrial mass and energetics and increasing oxidative stress, thus contributing to impaired glucose metabolism. As insulin resistance continues to develop, mitochondrial function, oxidative damage, and PARL activity may decline further, leading to a vicious cycle that eventually contributes to the development of T2DM or other age-associated diseases, including sarcopenia," a loss of muscle mass and strength.

Civitarese said it's not clear why PARL levels decline with age, but the findings suggest that increasing PARL levels may bring metabolic benefits. There is some possibility that PARL could be used as a drug or drug target, but he cautions that such a path would likely be difficult.

That's because PARL does its work in a hard-to-reach place-- inside mitochondria, which are encapsulated in a double membrane.

More information: Ravussin et al.: "Regulation of Skeletal Muscle Oxidative Capacity and Insulin Signaling by the Mitochondrial Rhomboid Protease PARL." Publishing in Cell Metabolism 11, 412-426, May 5, 2010. DOI:10.1016/j.cmet.2010.04.004

Provided by Cell Press