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Explaining How Mitochondrial Aging Leads to Diabetes

As we age, the mitochondrial motors that power our cells start to lose their horsepower. This drop-off in mitochondrial activity predisposes us to accumulate intracellular fat in muscle and liver cells, which can lead to insulin resistance and type 2 diabetes. A new study directed by Howard Hughes Medical Institute investigator Gerald I. Shulman has shown how changes in an enzyme known to be vital to the body's energy levels may lead to a decreasing ability to stave off diabetes as we get older.

Type 2 diabetes is a major problem for us as we age, says Shulman, pointing to the 40 percent of people over age 65 who suffer from type 2 diabetes or impaired glucose tolerance. Hoping to unravel how aging affects the components of the cell's energy production system, Shulman and colleagues at Yale University studied the effects of aging on the activity of AMP-activated protein kinase (AMPK).

"As we age, we may actually have to work harder to maintain the same level of AMPK activity."

— **Gerald I. Shulman**

AMPK is a chief regulator of whole-body energy balance, which governs the activity and number of mitochondria, which produce energy by oxidizing fatty acids and glucose. Numerous pharmaceutical companies are developing drugs that target AMPK in hopes of preventing or reversing the insulin resistance seen in type 2 diabetes. Given the key role of AMPK in regulating mitochondrial fatty acid oxidation and mitochondrial biogenesis, we wanted to determine if our earlier observations in healthy, lean, elderly volunteers — reductions in mitochondrial function and increases in the level of triglycerides within the liver and muscle cells — might be explained by alterations in AMP kinase activity, Shulman said.

A single muscle cell can contain as many as 10,000 mitochondria. Previous studies by Shulman's group have demonstrated a key role for AMPK in promoting mitochondrial biogenesis in response to exercise, which, in turn, boosts the muscle's metabolic capacity.

In a study published in the February 6 issue of the journal *Cell Metabolism*, Shulman's lab examined how aging affects the AMPK signaling pathway and the creation of new mitochondria in laboratory rats. Their findings, Shulman said, suggest that as we age we may actually have to work harder to maintain the same level of AMPK activity.

In three sets of experiments, Shulman and colleagues compared AMPK and mitochondria in healthy, 3-month-old laboratory rats to those in healthy, elderly (28-month-old) rats.

The scientists first infused both groups of animals with AICAR — a drug known to acutely activate AMPK activity. When the young animals were infused with the drug, the AMPK activity in their muscle increased by 44 percent.

Once AMPK becomes activated, it exerts its metabolic control in part by transferring a chemical group called a phosphate to acetyl CoA carboxylase 2 (ACC2), an enzyme involved in fatty acid synthesis. Phosphorylation by AMPK inhibits ACC2's activity, which in turn slows fatty acid synthesis and enhances mitochondrial fatty acid oxidation. When Shulman and colleagues analyzed the young, AICAR-treated rats, they saw that the increase in AMPK activity was associated with an increase in phosphorylation of acetyl CoA carboxylase 2 (ACC2).

By contrast, the old rats showed no increase in AMPK activity or ACC2 phosphorylation in their limb muscle, demonstrating that aging reduces AICAR induced activation of AMPK and mitochondrial fatty acid oxidation.

The scientists then examined the effect of exercise on AMPK activity in young and old animals. When energy stores in the muscle are depleted through exercise, healthy cells respond by activating AMPK to help replenish that energy by promoting increased glucose transport and fatty acid oxidation. Putting the rats on a 5-day treadmill exercise regimen more than doubled the AMPK activity and ACC2 phosphorylation in the young animals, but resulted in much less change in these parameters in the skeletal muscle of the old rats.

A final set of experiments looked at how chronic activation of AMPK triggers the creation of new mitochondria in young and old rats. For these experiments, the scientists fed the rats another chemical known to stimulate AMPK activity, β -guanidinopropionic acid (β -GPA) for two months. Again, they saw a large increase in AMPK activity, which was associated with an approximately 40 percent increase in the density of mitochondria in the muscle cells of the young β -GPA-fed rats, but the old rats showed no increase in AMPK activity or mitochondrial biogenesis. These changes were also associated with an increase in intramuscular triglyceride content.

Shulman believes the results suggest that aging-associated reductions in AMPK activity are likely important factors contributing to the observed reductions in mitochondrial function and increases in triglycerides inside muscle cells associated with aging. This decline in AMPK activity and

mitochondrial biogenesis predisposes older adults to insulin resistance and type 2 diabetes. Shulman plans to carry out related studies of AMPK activity in humans, comparing older to younger adults, to understand better the factors underlying the increased prevalence of type 2 diabetes and impaired glucose tolerance associated with aging.