Muscling toward a longer life: Genetic aging pathway identified in flies

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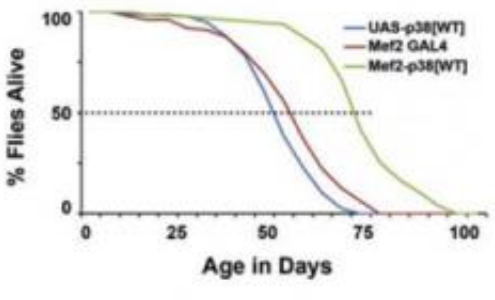

Flies with an extra copy of the p38 MAP kinase gene (green), turned on in muscles only, live significantly longer than regular flies. Credit: Subhabrata Sanyal

Researchers at Emory University School of Medicine have identified a set of genes that act in muscles to modulate aging and resistance to stress in fruit flies.

Scientists have previously found mutations that extend fruit fly lifespan, but this group of genes is distinct because it acts specifically in muscles. The findings could help doctors better understand and treat muscle degeneration in human aging.

The results were published online this week by the journal *Developmental Cell.*

The senior author is Subhabrata Sanyal, PhD, assistant professor of cell biology at Emory University School of Medicine. The first author of the paper is postdoc Alysia Vrailas-Mortimer. Collaborators from Howard University and the University of Athens contributed to the paper.

Vrailas-Mortimer, Sanyal and colleagues started investigating a pair of genes called "p38 MAP kinase" in fruit flies with the expectation that they could play a role in learning and memory. Along the way, they discovered that mutations in these genes speed up the process of aging and make the flies more sensitive to oxidative stress.

"It was really just dumb luck, because we found a mutant that had almost completely lost gene activity, but had enough activity to be born," Sanyal says.

If both genes are defective in the same fly, the flies die very early. They begin to develop motor problems, becoming unable to fly and climb, a few days after birth. The mutant flies are also more sensitive to heat, being deprived of food and water, and exposure to oxidative stress. The researchers could correct the effects of the mutations by restoring the genes' activity in muscles, but not nerve cells.

"The experiment that made us nervous was when we asked whether having more p38 could increase lifespan," Sanyal says. "You can make flies sick and shorten their lives in a hundred different ways easily, but finding one gene that makes a big change in lifespan is more significant."

Fruit flies normally live about fifty days in Sanyal's laboratory, depending on temperature and conditions. Some strains of fly that overproduce p38 MAP kinase live on average about 75 days, 50 percent longer than regular flies (green line in graph below). For this effect, it is sufficient that p38 is overproduced in muscles only.

Vrailas-Mortimer showed that a protein that protects cells against oxidative stress that is found in mitochondria, superoxide dismutase (MnSOD), is responsible for at least some of p38 MAP kinase's effects on aging. A third gene called MEF2 is also involved, in between p38 MAP kinase and MnSOD. Mitochondria are cells' miniature power plants and are more abundant in muscle.

Giving flies more MnSOD can restore a more normal lifespan to the p38 mutants. Other types of antioxidant enzymes don't rescue lifespan in flies with p38 mutations, the researchers found.

P38, MEF2 and MnSOD's action in muscles distinguishes them from a well-studied genetic circuit regulating aging in the worm C. elegans as well as flies and mice, which appears to work through insulin-like hormone responses in the brain and other tissues. Caloric restriction (consistently eating less), an established way of lengthening lifespan, acts through this insulin-like signaling pathway.

"It may be that oxidative stress is especially important in flies' muscles because flies' energy use is so high," Sanyal says. "The role oxidative stress plays in aging is well-known, so its involvement here was not a surprise. I think what's new here is finding a genetic pathway regulating aging that is specific to muscles and separate from insulin signaling."

Sanyal says he and his team plan to examine what kinds of dietary antioxidants can extend lifespan in flies without p38. They also plan to probe how caloric restriction interacts with p38 deficiency.

More information: A. Vrailas-Mortimer et al. A muscle-specific p38 MAPK/Mef2/MnSOD pathway regulates stress, motor function and lifespan in Drosophila. Dev Cell 21, 783-795 (2011).

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