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AGE, FAT, DNA

NEWLY UNVEILED LINKS TO GERIATRIC DISEASES

BY ASHER JONES

Older adults are highly prone to frailty, cardiovascular disease, cancer, arthritis, neurodegeneration and other maladies. Exactly why age makes people more susceptible to these disorders isn't yet clear, but findings by Pitt's Aditi Gurkar, an assistant professor of medicine, may explain how shedding pounds with age can lead to development of these types of diseases.

"People typically think that aging is linked with putting on fat, which is true, but there's a tipping point when weight gain switches to weight loss. People seem to lose weight about nine to 10 years before they develop age-related diseases," explains Gurkar, a PhD who is a member of the University of Pittsburgh/UPMC's Aging Institute.

"However," she adds, "there hasn't been a mechanistic understanding of the connection."

At least not until now. Gurkar and her research team may have found that connection. Their findings were recently published in Science Advances.

They used a grain-of-sand-size worm, Caenorhabditis elegans, to show that DNA damage—a hallmark of aging—rewires metabolism, triggering the breakdown of fat deposits and production of inflammatory compounds that drive age-related disorders.

"DNA damage happens to all of us, all of the time," says Gurkar. "Even sitting in the sun or eating that burger last night generates compounds that damage DNA. But with age, our DNA repair pathways become less efficient and damage accumulates."

To understand how persistent DNA damage drives aging, Gurkar and her team used C. elegans. The worm's 20-day lifespan allows scientists to study aging without gaining too many gray hairs themselves. C. elegans shares many cellular features and molecular pathways with mammals, making insights potentially relevant to humans.

The researchers compared normal C. elegans to mutants that lacked key DNA repair genes. Unable to fix DNA lesions, the mutants accumulate damage faster than usual and experience premature aging and shortened lifespans.

By nematode "middle age," the mutant worms had elevated expression of genes involved in lipid breakdown and depleted fat stores compared with their normal peers. When the researchers did the same experiments in "young adults," they didn't observe these differences. These results indicate that accumulation of DNA damage with age rewires cellular metabolism to break down fat deposits.

Looking more closely, the researchers found that lipid breakdown led to elevated levels of omega-6 polyunsaturated fatty acids in the mutant C. elegans. These fatty acids are precursors for compounds called lipid mediators, which promote inflammation, a known driver of age-related diseases.

Gurkar says that the findings, in addition to possibly explaining how shedding pounds with age can lead to development of disease, may also reveal that DNA damage is more than just a consequence of getting old—it may actually drive aging.

"When cells recognize DNA damage, they sound an alarm, and if the damage isn't resolved, the siren never shuts off. It's not the damage itself, but the noise that seems to be driving aging," she says.

When the researchers reduced fatty acid oxidation in mutant worms, they no longer lost fat stores and normal lifespan was restored.

"We can inhibit inflammation and excessive fat loss," says Gurkar. "It's about calming the cell down so it's no longer screaming SOS all the time."

Lipid metabolism pathways in C. elegans are shared by mice and humans, suggesting that the findings could help identify therapeutic targets for age-related diseases and accelerated aging disorders. The research could also explain why people who were treated successfully with chemotherapy or radiotherapy for pediatric cancer as children often become frail and have accelerated aging by their mid-40s.

"We plan to partner with pediatric doctors to follow chemotherapy patients over time," says Gurkar. "By measuring their DNA repair proteins, we hope to identify patients who might be more susceptible to frailty and age-related disorders later in life. This could inform tailored, or precision medicine, approaches to chemotherapy dose." ■