Immune protein may link chronic inflammation and frailty in older adults

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Johns Hopkins Medicine researchers have identified an immune system protein called interleukin-6 as a possible link between chronic inflammation and frailty in older adults. Credit: Public domain image

Chronic inflammation in people age 65 and older may be marked by frequent infections, pain, injuries and slow healing wounds. To make matters worse, the negative impact of chronic inflammation on older adults is often compounded by frailty—the state of aging characterized

by weakness, weight loss, poor balance and other symptoms that makes older adults among the most vulnerable for accidents, mobility issues, poor outcomes following illnesses, and death.

In recent years, medical researchers have proposed that the dangerous connection between chronic inflammation and frailty may be due to a protein called interleukin-6 (IL-6). IL-6 is a cytokine, a molecule produced by immune system cells to help regulate the body's response to injury or infection. It is one of the main stimulators of inflammation and fever, two of the mechanisms the immune system uses to restore health.

What isn't known is how IL-6 contributes to the loss of physical ability commonly associated with increasing frailty during aging. To better understand this role, a Johns Hopkins Medicine research team genetically engineered a new mouse model that develops chronic inflammation but lacks IL-6. The model can be used to determine if the absence of IL-6 during uncontrollable chronic inflammation is enough to protect against the physical and functional decline observed with age.

The team's findings were published in the February 2021 issue of the *Journals of Gerontology, Series A*.

To characterize their new mouse model, the researchers used a state-of-the-art metabolomic profiling assay that enabled them to define the unique chemical fingerprints involved in the development of chronic inflammation without IL-6.

They also used an advanced dynamic positron emission tomography–computed tomography (PET-CT) system to determine how the absence of IL-6 (with presence of inflammation) impacts energy production by mitochondria (the cell's "energy factory") in the hearts of the mice. Decline in energy production during aging is considered a major contributor to many age-related illnesses including heart failure

and Alzheimer's disease.

What the researchers found in frail mice lacking IL-6 were increases in circulating fat compounds—lysolecithins—that are important in maintaining healthy mitochondria function and decrease with age in humans. The frail mice lacking IL-6 also had increased heart energy production compared to the frail mice that produced IL-6. Together, these findings show that improvements in mitochondrial function occurred in frail mice when IL-6 was not present.

To determine if the enhancements in mitochondrial function translated to improvements in physical performance, the researchers used functional assessment tools commonly reserved for humans, such as running on a treadmill and grip strength. Treadmill running was chosen because of its similarity to human cardiac stress tests and because it assesses several systems at once: cardiovascular, skeletal muscle and pulmonary.

"Frail mice without IL-6 had short term improvements in running and fewer falls off the treadmill, but this improvement disappeared after three days," says study senior author Peter Abadir, M.D., associate professor of medicine at the Johns Hopkins University School of Medicine. "Surprisingly, and perhaps counterintuitively, we observed dramatically higher mortality in these mice in the presence of chronic inflammation—as high as a fourfold increase compared with nonmodified mice and with mice that developed chronic inflammation but could still produce IL-6."

The researchers say these results suggest multiple impacts for IL-6. While the deletion or absence of IL-6 may improve some molecular and physical functions, its absence in the context of stress or chronic inflammation also may precipitate a quick decline in health and eventually, death.

Hints of similar effects can be gleaned from clinical studies of human patients with autoimmune disorders who were taking treatments with antibodies against TNF alpha, a cytokine similar to IL-6. When these patients develop fever or signs of infection, clinicians often withhold their medication to allow the body to mount an immune response.

The researchers say their findings in frail mice suggest a delicate balance exists between aging and chronic inflammation, and that IL-6 may be needed to maintain long-term exercise ability and prevent premature death. Therefore, they caution physicians to keep this balance in mind when prescribing drugs to reverse age-related increases in IL-6 levels.

More information: Lina Ma et al. Targeted Deletion of Interleukin-6 in a Mouse Model of Chronic Inflammation Demonstrates Opposing Roles in Aging: Benefit and Harm, *The Journals of Gerontology: Series A* (2020). DOI: 10.1093/gerona/glaa156

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