Calorie reduction lowers protein linked to the aging process

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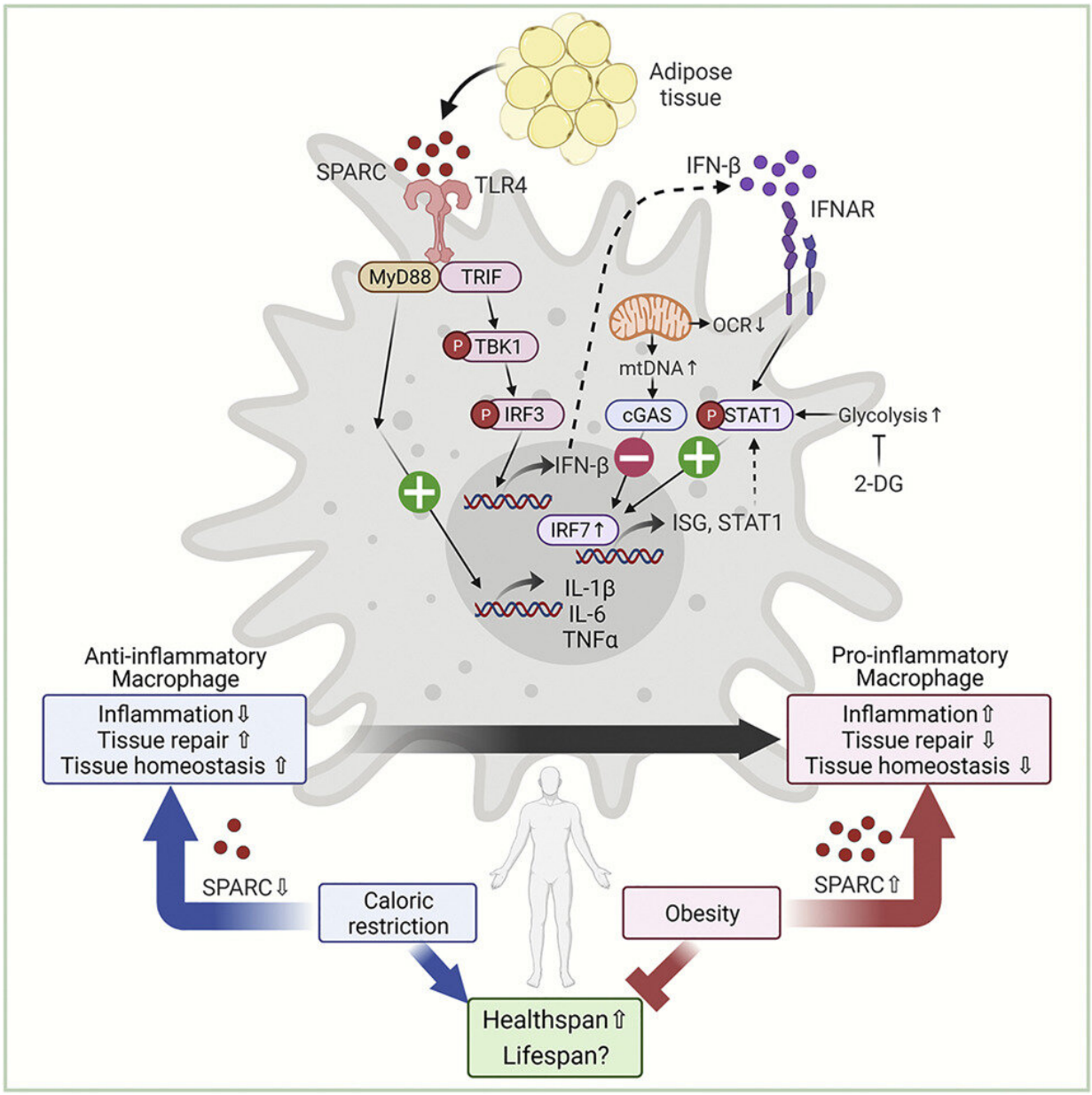
Reduced calorie intake has been shown to improve health and lifespan in laboratory animals, and recent research shows these benefits may extend to humans as well.

In a new study, Yale researchers show that moderate calorie restriction in people reduces the production of a protein called SPARC, which then reins in harmful inflammation and improves health in the aged. It could be a target for extending human health span, they report Aug. 12 in the journal *Immunity*.

The study, led by Vishwa Deep Dixit, the Waldemar Von Zedtwitz Professor of Pathology, professor of immunobiology and comparative medicine, and director of the Yale Center for Research on Aging, follows a study published earlier this year that identified key health benefits of moderate calorie reduction in humans.

In the new study, Dixit and his co-authors further analyzed data from a clinical trial funded by the National Institutes of Health. In the trial, known as Comprehensive Assessment of Long-term Effects of Reducing Intake of Energy (CALERIE), some participants reduced their calorie intake by 14% for two years, while others ate as usual; researchers then tracked the long-term health effects.

Specifically, Dixit and his colleagues analyzed trial data to identify molecules that are responsible for the positive effects of calorie reduction and could be targets for therapeutic treatment.



Graphical abstract. Credit: *Immunity* (2022). DOI: 10.1016/j.immuni.2022.07.007

Looking for genetic changes in participants' fat tissue after one and two years, they found that those who consumed fewer calories had reduced amounts of a protein called SPARC—or secreted protein acidic and rich

in cysteine—which has been linked to obesity, diabetes, and inflammation.

"Because inflammation plays such a big role in age-related decline, we wanted to better understand whether a pro-longevity intervention like calorie restriction works through SPARC in controlling inflammation and immune responses," said Dixit. So, to dig deeper into SPARC's contributions to inflammation they studied what effects the protein had on mouse immune cells and mouse health.

The researchers found that SPARC triggered inflammation by converting anti-inflammatory immune cells called macrophages into a pro-inflammatory state. However, lowering SPARC production by fat cells in mice reduced inflammation, improved metabolism, and extended their health span as they aged.

The findings could lead to preventions for age-related decline, said Dixit.

"We now have a better understanding of how SPARC affects inflammation and health span by acting on macrophages," he added. "And it may be a useful target for inducing the health benefits of calorie restriction without having to actually alter calorie intake."

More information: Seungjin Ryu et al, The matricellular protein SPARC induces inflammatory interferon-response in macrophages during aging, *Immunity* (2022). DOI: 10.1016/j.immuni.2022.07.007

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