Blocking a tiny RNA may forestall age-related bone and muscle loss, inflammation

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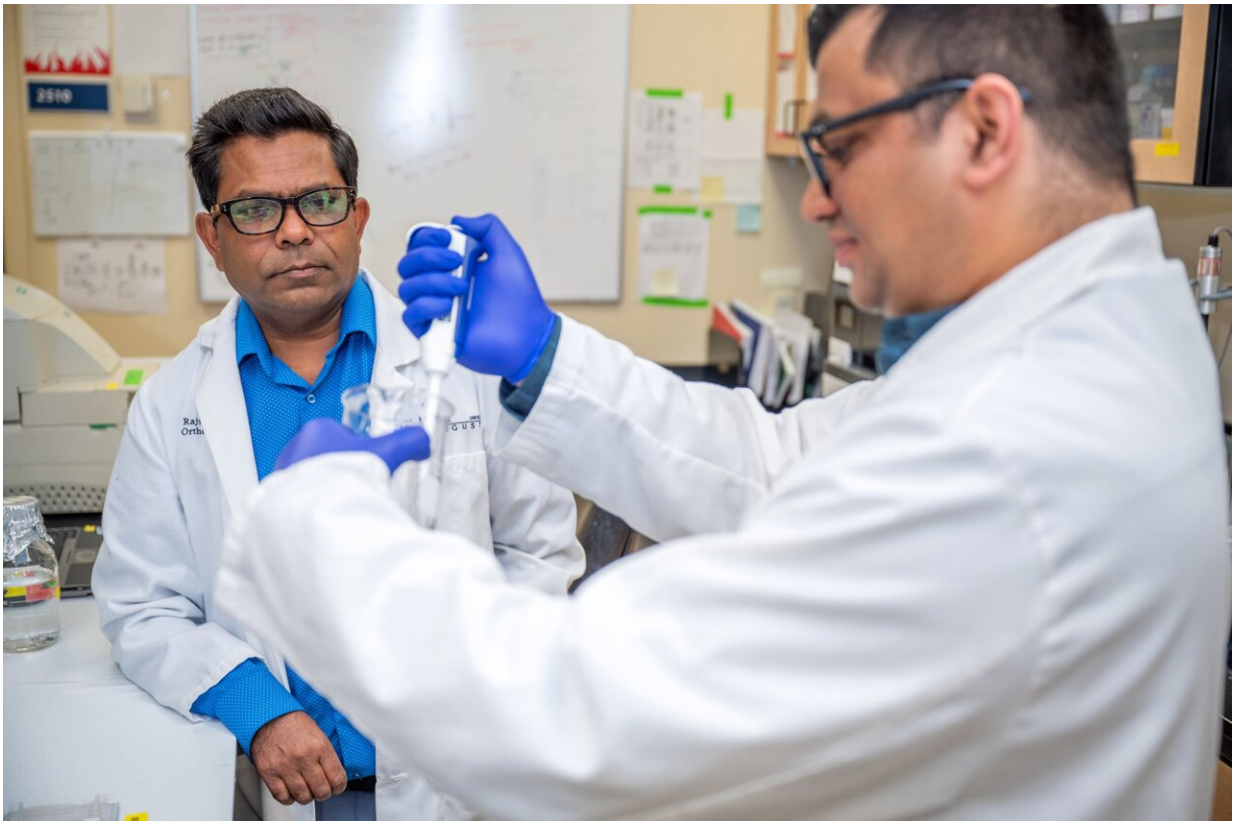

Sadanand Fulzele, DVM, PhD, and first author and postdoctoral fellow Sagar Vyavahare, PhD. Credit: Michael Holahan, Augusta University

Inhibiting a tiny RNA whose levels significantly increase with age, along with problems like weaker bones and sagging muscles, may be a way to

keep our bodies more youthful and healthy, scientists say.

MicroRNAs help regulate gene expression and consequently the function of our cells, and several, including one called microRNA-141-3p, have been implicated in the ills of aging, like increasing levels of potentially damaging chronic inflammation and that shrinking muscle mass.

"When we age in all these complications like chronic inflammation, muscle loss, bone loss, this microRNA is elevated," says Sadanand Fulzele, DVM, Ph.D., aging researcher in the Department of Medicine at the Medical College of Georgia at Augusta University. "We wanted to suppress it."

In what appears to be the first study of its kind, Fulzele and his colleagues used an inhibitor he had specifically designed to block microRNA-141-3p in aged mice. These types of engineered molecules are called antagomirs, and while at the moment restricted to research, could one day have therapeutic value for patients, says Fulzele, corresponding author of the study in the journal *Aging and Disease*.

The mice, who would equate to humans in their 60s, were treated for three months with twice-weekly subcutaneous injections of this antagomir, a regimen that could be easily adapted for humans.

The scientists then looked at changes that occurred in the blood, the spleen whose tasks include regulating levels of infection-fighting white blood cells, as well as the bone and muscle. They found a more youthful profile everywhere they looked.

In the spleen, for example, they saw more inflammation-reducing immune cells called macrophages (M2) rather than their inflammation-promoting counterpart (M1). M2s also have been reported to support tissue repair. The blood had lower levels of inflammation-promoting

proteins called cytokines, and the microstructure of the bone was more solid and muscle fiber size was bigger.

They found that microRNA-141-3p regulates expression of AUF1, a "good" gene whose many jobs include regulating the stability of messenger RNA, which plays a role in the proteins DNA ultimately makes. AUF1 helps protect younger people from making so many proinflammatory products like IL-6 which contribute to chronic, damaging inflammation. It does the same for cell senescence when cells become less able to function normally and divide but typically don't die. Higher levels of microRNA-141-3p mean less of the protective AUF1 and blocking the microRNA enabled higher levels and consequently less inflammation and senescence.

Fulzele notes that like with everything else in the body, the effect of microRNA-141-3p has to do with its level of expression and in aging its high. Their latest findings point toward reducing its expression as a possible strategy to improve immune, bone and muscle health with age, Fulzele says.

Levels of inflammation and oxidative stress are an indicator of overall health at any age. Chronic inflammation and chronic oxidative stress are hallmarks of an aging body and important players in the negative changes that can result.

With age, the repair/replacement capacity of cells is known to decrease so that, for example, bone loss begins to outpace new bone formation. Meanwhile inflammation, essential to healing but destructive at chronic, high levels, creeps upward. Resulting problems can range from increasing physical frailty to an increased incidence of diseases like cancer, cardiovascular disease and dementia.

Fulzele notes that his research is geared toward finding ways to prevent

damage, rather than trying to restore a healthy normal. Some of his next steps include looking at how blocking the microRNA impacts other age-related concerns like cognition and giving the microRNA-141-3p-specific antagomir for a longer timeframe. He noted they did not identify any overt side effects over the three months of the study.

Fulzele and his colleagues reported in 2018 evidence that with age, expression of microRNA-141-3p went up while the key signaling molecule stromal cell derived factor 1, or SDF-1, that helps stem cells make healthy bone and muscle, goes down in the mesenchymal stem cells that are responsible for making bone and muscle as well as fat. SDF-1 helps regulate the differentiation into different cell types. In both human and mouse mesenchymal stem cells the scientists found levels of microRNA-141-3p were low in younger cells and tripled or greater in older cells. Levels of SDF-1 in these cells were directly opposite. With age, mesenchymal stem cells also make more fat, rather than bone or muscle, which they are inclined to do because fat's easier to make.

More information: Inhibiting MicroRNA-141-3p Improves Musculoskeletal Health in Aged Mice, *Aging and Disease* (2023). DOI: 10.14336/AD.2023.0310-1.
www.aginganddisease.org/EN/10.14336/AD.2023.0310-1

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