



A GUT CHECK FOR BETTER AGING

How the gut changes with age could affect not only our susceptibility to digestive diseases, but also the aging process itself **By Sandeep Ravindran**

WHETHER IT'S A FEW MORE GRAY HAIRS or a wrinkle or two, the outward signs of aging are hard to miss. But the changes taking place inside our bodies are just as significant—not least to our gut. How the gut ages doesn't just affect gastrointestinal health and disease, but also has broader ramifications for overall wellness.

The human body tends to slow down and become less efficient as it ages, and that includes the digestive system. "Older people will often report constipation or diarrhea or bloating, and the motility of their guts"—that is, how quickly food moves through the body—"can often be a little bit slower," says Dawn Bowdish, a professor of medicine at McMaster University in Canada.

Aging is complex, and there's still a lot scientists don't know about how and why getting older affects a person's gut or their susceptibility to particular digestive diseases. Some, such as colorectal cancer, occur mainly in people over 50. But others, including Crohn's disease and other types of inflammatory bowel disease (IBD), do not seem to be associated with older age. "People get it fairly consistently throughout their life," says Bowdish.

What's clear is that many of the factors typically brought on by aging—such

as a weaker immune system, increased medication use, poorer diet and reduced physical activity—can adversely affect gut health. "There's a lot happening all at the same time," says Bowdish.

But aging-related changes to the immune system and gut microbiota, the 100 trillion or so microbes that live in the gut, appear to powerfully affect gut health and disease—and may even hold the key to healthier aging overall. Understanding these changes also opens up the possibility of using diet or other methods to improve both gut health and aging.

How aging changes the gut

One of the key characteristics of aging is an increase in chronic inflammation. Inflammation isn't a bad thing in itself; inflammatory responses can help protect against pathogens. But if these responses are not appropriately regulated and extinguished, they can play a role in causing autoimmune diseases such as multiple sclerosis or IBD. "Aging is associated with low-grade inflammation, and this low-grade inflammation is one of the strongest predictors of adverse health outcomes," says Thomas Buford, associate professor of medicine at the University of Alabama at Birmingham.

Aging and gut health go hand in hand, and a plant-filled diet seems to help both

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Inflammation happens more frequently as people get older, and a main reason is what goes on in their gut. A healthy gut microbiota is diverse, housing a mix of microbes that help strengthen the gut mucosal barrier to keep harmful microbes and toxins from entering the blood. Over time, though, this microbial community becomes less diverse, and a less-diverse gut produces lower levels of short-chain fatty acids. “Short-chain fatty acids play a large number of roles in our immune system and have an important impact on gut integrity,” says Buford. These changes can result in a gut barrier that’s more “leaky.”

In some older adults, a leaky gut that allows in bacteria that the immune system sees as infectious can kick-start an inflammatory response, says Bowdish. This leakiness can also result in more gastrointestinal infections that can cause fever, diarrhea, nausea and abdominal pain.

One way that scientists explore how the microbiota affect the aging gut is to use germ-free mice lacking any microbiota. “One of the things that’s really fascinating is that our old germ-free mice don’t ever develop inflammation; their organs look young, and most of their inside and their outside tend to look very, very young for their age,” says Bowdish. “This was the first hint that the microbiome might play a causal role in inducing some age-associated inflammation, which is a feature of just about every aspect of unhealthy aging.”

There are also signs that the gut microbiota might play a role in the development of age-associated brain disorders such as Parkinson’s disease, Alzheimer’s disease or dementia. Links between the gut microbiome and such diseases are still very preliminary in humans, but researchers have studied the relationship in animal models.

“In mice we do see that there are some cognitive issues, and the immune system seems to be the middleman,” says Bowdish. “Basically [if] you have a bad microbiome, you get this inflammation. Inflammation is bad for cognition, so there likely is a link,” she says.

Growing old with your gut bacteria

That’s not the only link among microbial diversity, aging and health. The relationship begins in the first few years

of life, during which the gut microbiota change dramatically. Starting around age three or four, it remains remarkably stable through most of adulthood. But as the microbiome shifts again around 50 or 60 years of age, it seems to diverge based on how healthfully a person ages.

The microbiomes of frail older adults and those in long-term-care facilities tend to be less diverse and contain fewer beneficial microbes. Along with chronic inflammation, a less-diverse microbiome is associated with increased frailty, gastrointestinal disease and systemic diseases such as IBD, autoimmune diseases and Type 2 diabetes.

However, when researchers examined the microbiomes of centenarians—people over 100 years old—they found that they contained more beneficial microbes than those of the average elderly population. “There have been studies done on extremely long-lived individuals, including centenarians in Italy, China and Korea, and their gut microbiomes do not look anything like adult microbiomes, but

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they also don’t look like microbiomes of older frail individuals,” says Tomasz Wilmanski, a research scientist at the Institute for Systems Biology in Seattle. This suggests that the gut microbiome might have different patterns of aging, with some patterns associated with a healthier and longer life and others with age-associated decline and frailty.

In a recent study published in February 2021 in the journal *Nature Metabolism*, Wilmanski and his colleagues found that people’s microbiome composition can start diverging by around 40 or 50 years of age. “Their microbiome is more of a unique fingerprint to them and them alone, and this continues to increase well into your 80s,” he says.

Whether the microbiome continues to change and adapt with age may influence how well we age. “People who are healthy into older age—who remain independent, have better physical function and higher walking speed, who perceive their health as excellent and better than their peers—they continue on this trajectory of increasing divergence in their [gut microbial] ecosystem,” says Wilmanski. People whose microbiomes continued to diverge into older age also appeared to have healthier metabolisms as measured by their cholesterol and vitamin-D levels.

The microbiome may even be associated with longevity. “People who continued on this trajectory into the latest decades of human life, their 80s and 90s, tended to live significantly longer than people who did not follow the same pattern,” says Wilmanski. “I think that’s very interesting, because it suggests that these patterns that reflect healthy aging in centenarians actually are also predictive of a longer life span, adding further evidence that their gut microbiome may potentially contribute to healthy aging, not just reflect it.”

Promising animal findings

It’s still too early to say whether the microbiome is actually causing these benefits or is just associated with them. What older people eat, the medications they take, how physically active they are and where they live can all affect the composition of their microbiome, which makes it hard to determine cause and effect. But studies in mice, which are able to examine

aging under more controlled conditions, have generated intriguing results.

When Bowdish and her colleagues let mice grow to the ripe old age of 2, they noticed that mice in one cage looked older and more sick, while those in another cage looked young and healthy. “The interesting thing was the two cages came from the same parents, so they were effectively siblings,” says Bowdish.

But what could make a whole cage of genetically similar mice look so different in age? “Ultimately it came down to their gut microbiome,” says Bowdish. “Mice are coprophagic, meaning they eat their own poop, so all you have to do is stick two mice in the same cage, and eventually they’ll share each other’s microbiome,” she says.

Over their two years of life, the mice’s gut microbiota would subtly change in ways that increased gut leakiness, inflammation, immune dysfunction and the risk of developing serious pneumonia. “Our mice don’t smoke, they don’t have medications, they don’t have diet changes, they don’t have any changes other than aging, and we definitely see that how the microbiome changes with age seems to have a feedback loop where it does contribute to unhealthy aging,” says Bowdish.

Bowdish then looked at the effects of housing old germ-free mice, which do not have age-associated inflammation, in the same cage as old mice, and therefore giving them the corresponding microbiome. “We can see that when we give them the microbiome of an old mouse, they get very inflamed and they have some health issues, and this helped us understand that there was a causal role between the microbiome and unhealthy aging,” says Bowdish. If the same is true in humans, this suggests that altering the microbiome in just the right way could potentially change how healthfully people age.

How to influence aging through the gut

“Many of the things that we already know are good for health are also good for the microbiome,” says Buford. That includes physical activity. Regular physical activity is associated with increased life expectancy and a reduced risk of chronic diseases and cognitive decline as we age. “Exercise is nature’s anti-inflammatory, and by reducing inflammation, we can



improve the health of our gut microbiome,” says Bowdish.

A healthy diet provides many of the same benefits as exercise to aging, as well as to the gut. Fiber-filled diets rich in fruits and vegetables, such as the Mediterranean diet, appear to be particularly helpful. “High-fiber diets generally correspond to beneficial shifts in the gut microbiome,” says Wilmanski. In contrast, eating a Western diet—with a lot of red and processed meats, fried foods, high-fat dairy products and sweetened drinks—is associated with an unhealthy gut environment.

A Mediterranean-type diet seems to also have beneficial effects on metabolism and cognition, as well as on preventing diabetes and heart disease. “It looks like the diet that’s good for your microbiome is also good for you,” says Bowdish.

Probiotic supplementation is another way to modify your microbiome. “Finding the right probiotic could shift your gut microbiome toward what we would want it to do: toward higher fiber

Fibrous foods may help diversify the microbiome, making them great for the gut and for the aging process

degradation and increased short-chain fatty acid production, for example,” says Wilmanski.

Probiotics research is still in its infancy, but scientists are trying to develop next-generation versions to help make the gut less leaky, fight off harmful bacteria, enhance the immune system and eventually improve aging. Researchers must first figure out not just which microbes are present in the guts of healthy older adults, but also what they’re doing there. That’s what Wilmanski is working on, by sequencing gut microbial DNA in greater detail. He hopes what he learns will let researchers manipulate the gut microbiome to promote a more robust gut and healthier aging.

What’s clear right now is that the age-old advice—eat healthy and exercise—can benefit both a person’s gut and their journey through life. “Effectively, all the things you need to do to take care of yourself are also things you need to do to take care of your microbes,” says Bowdish. □