Q&A: Demystifying the biology of growing older

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Exercise. Social connections. Sunscreen. It seems there is no shortage of advice on how to stay young, but among scientists, the exact physiology behind aging remains unknown. Tufts Now asked biology professor Mitch McVey to decode the latest and most popular explanations for why all living species gradually decline, and share his views on the true

aims of aging research. Hint: it's not immortality.

Tufts Now: Before we get into the biology of aging, on a fundamental level, why do humans—and all living things, for that matter—age? Is it genetic programming? Something like built-in obsolescence but for people?

Mitch McVey: Well, that's the million-dollar question, and unfortunately, all I can tell you is that we don't really know the reasons we age. Scientists have come up with many different theories, and right now we're very good with the how, but not with the why.

As for built-in obsolescence, if you think about, for example, a car—various systems within the car are going to break down and wear out. The difference between a car and a living organism is that a living organism has the potential to rejuvenate. Cells can restore themselves. DNA can repair itself. There's some evidence that if we knew how to tweak those repair and rejuvenation pathways, we could actually do that, but we're far from being able to at this point.

As an aging researcher, how do you define aging? How has the concept evolved, and has your own understanding of it changed over time?

There are many ways to define aging. It plays out on multiple levels, including molecular, cellular, tissue, and whole organisms. While there are certainly genetic components to aging, it's remarkably plastic and can be greatly impacted by environmental factors such as diet, chemical exposure, and lifestyle choices. The greatest risk factor for many diseases, including cancer, is advanced age, but healthy people also age. It's a normal process.

When I started research in the field, I was in my mid-20s, and a lot of what I was reading was still abstract for me. Years ago, I started teaching a course called Biology of Aging, and about five years in, I actually began to experience some of the symptoms I was teaching. Which is disconcerting, because in one sense it's very academic, and in another, it's entirely personal because it's happening to you.

For a long time, people have viewed aging as inevitable. Then in the 1990s, research labs published papers showing that they could greatly extend the lifespan of model organisms by making single mutations in their genomes, which led other scientists to jump on the aging bandwagon.

Since then, we've been able to develop drugs that activate or suppress the relevant genetic pathways, impacting lifespan without genetic manipulation. However, neither of these approaches have yet been shown to work in humans, and there are serious ethical concerns associated with manipulating the human genome. Time will tell if the therapeutics that extend lifespan in model organisms have similar effects in humans.

So what is actually happening, biologically speaking, during the aging process? What are some of the more popular theories?

Again, there are quite a few of them. One being the evolutionary theory of aging, which is the idea that the genes that control the aging process are subject to forces of natural selection. To test his, a research group led by scientist and professor Steven Austad of the University of Alabama at Birmingham did an experiment with opossums.

They were looking at a group that lived on an island a few miles off the

coast of Georgia. He proposed that the animals there—as opposed to the ones living on the mainland—were less subject to forces like predation or even just being run over by cars. And because it was so much safer for the opossums on the island, they had less selective pressure to reproduce quickly. Austad postulated that this would allow successive generations to live longer, and his team's data showed this was indeed true.

Another group of theories relates to what's going on at the cellular level. The oxidative damage theory, to name one, states that we're exposed to a whole host of things that can do damage to different components within our cells—the DNA, the proteins, the lipids, and so on. If we could find a way to minimize oxidative damage, the theory supposes that we could potentially slow the rate of aging, either through less exposure to detrimental things or by jump-starting the repair process within our cells.

Are there newer theories, more recent developments in the field, that you're excited by?

The genome maintenance theory is one I find intriguing. Think of the fact that in each of our cells, there is a bunch of DNA containing instructions for everything that's going to happen with that cell, from development to survival to reproduction. Because cells are continually dividing, each time they divide, they have to make an exact copy of all of that DNA. Over time, the integrity of the DNA can become compromised. Basically, the genome maintenance breaks down.

There's a new direction that we've started to take in the lab, and we're not sure how it ties into genome maintenance, if at all, but it's following up on some studies that originated at the USDA Human Nutrition Research Center On Aging at Tufts. We collaborated with a scientist named Jimmy Crott who found a particular bacterium that could slow

the development of colon cancer in mice.

You might ask, what does this have to do with aging? Well, often, as you get older, your chances of developing cancer substantially increase. We thought, if we fed this particular bacterium to fruit flies, would it not only help them not develop cancer, but possibly extend their lifespan? We were flabbergasted to find out that it extended the lifespan of the fruit flies by 30%–40%.

One of the things we discovered is that as the flies got older, their digestive systems tended to become leakier. Over time, in the flies that were fed the bacterium, that leakiness was suppressed. With less leaky gut, there was less inflammation. Inflammation, it's important to note, has been shown to be a very bad thing for aging. There is even a term coined for this, called "inflammaging."

Does this mean the secret to controlling aging might have less to do with our genes than with other living things inside us?

That's the idea. There may be things not within our own cells that are having a big impact on the aging process. That 30%–40% increase in lifespan, while happening in fruit flies, is intriguing, because many of the genes that are found in fruit flies are also found in people.

And while the specific species of bacteria that we tested isn't found in the fruit fly microbiome, it is a normal component of the human microbiome. So it's possible that these bacteria might impact the aging process in people. We think this is linked to an anti-inflammatory property of the bacteria and are testing this now.

Comparing the lifespan of a fruit fly—about 40 to 50

days—to that of a human being, I'm curious why different species age at different rates. Is it size-related?

There seem to be two trends. First, for mammals, the trend is that larger animals tend to have longer average lifespans, although there are certainly outliers in both directions. For example, the naked mole rat lifespan lies well above the trendline. Second, within a single species, smaller animals tend to live longer than their larger counterparts. A common example is dogs, although again, outliers are common.

Humans live longer than would be predicted based on their size, and this is likely a result of their ability to manipulate their environments. Whether or not taller humans have shorter lifespans is still debated, although several analyses published in the past 20 years suggest that shorter stature may promote longer life.

After reflecting on all the research that has been done, how far do you think we are from a truly major breakthrough in the science of aging?

My students ask this question every day. I wish I could read the tea leaves and know. While it's possible that we might be within a decade or two of something that could fundamentally change the rate of aging for people, I think the more important goal is finding ways to promote increases in healthspan. We want to make sure that individuals develop fewer cases of osteoporosis, heart disease, and Alzheimer's—age-related diseases that affect quality of life in our later years.

The goal would be to lengthen the amount of time that we live in a healthy state, where we can take care of ourselves and continue to live

independently, for as long as possible, getting maximum enjoyment out of life. That's why I'm in this field. For me and many of my colleagues, it's to find ways to increase the healthspan, and not simply the lifespan, of people.

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