Prevailing theory of aging challenged in Stanford worm study

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Age may not be rust after all. Specific genetic instructions drive aging in worms, report researchers at the Stanford University School of Medicine. Their discovery contradicts the prevailing theory that aging is a buildup of tissue damage akin to rust, and implies science might eventually halt or even reverse the ravages of age.

"We were really surprised," said Stuart Kim, PhD, professor of developmental biology and of genetics, who is the senior author of the research.

Kim's lab examined the regulation of aging in C. elegans, a millimeter-long nematode worm whose simple body and small number of genes make it a useful tool for biologists. The worms age rapidly: their maximum life span is about two weeks.

Comparing young worms to old worms, Kim's team discovered age-related shifts in levels of three transcription factors, the molecular switches that turn genes on and off. These shifts trigger genetic pathways that transform young worms into geezers. The findings will appear in the July 24 issue of the journal *Cell*.

The question of what causes aging has spawned competing schools of thought. One side says inborn genetic programs make organisms grow old. This theory has had trouble gaining traction because it implies that aging evolved, that natural selection pushed older organisms down a path of deterioration. However, natural selection works by favoring genes that

help organisms produce lots of offspring. After reproduction ends, genes are beyond natural selection's reach, so scientists argued that aging couldn't be genetically programmed.

The alternate theory holds that aging is an inevitable consequence of accumulated wear and tear: Toxins, free-radical molecules, DNA-damaging radiation, disease and stress ravage the body to the point it can't rebound. So far, this theory has dominated aging research.

But the Stanford team's findings told a different story. "Our data just didn't fit the current model of damage accumulation, and so we had to consider the alternative model of developmental drift," Kim said.

The scientists used microarrays - silicon chips that detect changes in gene expression - to hunt for genes that were turned on differently in young and old worms. They found hundreds of age-regulated genes switched on and off by a single transcription factor called elt-3, which becomes more abundant with age. Two other transcription factors that regulate elt-3 also changed with age.

To see whether these signal molecules were part of a wear-and-tear aging mechanism, the researchers exposed worms to stresses thought to cause aging, such as heat (a known stressor for nematode worms), free-radical oxidation, radiation and disease. But none of the stressors affected the genes that make the worms get old.

So it looked as though worm aging wasn't a storm of chemical damage. Instead, Kim said, key regulatory pathways optimized for youth have drifted off track in older animals. Natural selection can't fix problems that arise late in the animals' life spans, so the genetic pathways for aging become entrenched by mistake. Kim's team refers to this slide as "developmental drift."

"We found a normal developmental program that works in young animals, but becomes unbalanced as the worm gets older," he said. "It accounts for the lion's share of molecular differences between young and old worms."

Kim can't say for sure whether the same process of drift happens in humans, but said scientists can begin searching for this new aging mechanism now that it has been discovered in a model organism. And he said developmental drift makes a lot of sense as a reason why creatures get old.

"Everyone has assumed we age by rust," Kim said. "But then how do you explain animals that don't age?"

Some tortoises lay eggs at the age of 100, he points out. There are whales that live to be 200, and clams that make it past 400. Those species use the same building blocks for their DNA, proteins and fats as humans, mice and nematode worms. The chemistry of the wear-and-tear process, including damage from oxygen free-radicals, should be the same in all cells, which makes it hard to explain why species have dramatically different life spans.

"A free radical doesn't care if it's in a human cell or a worm cell," Kim said.

If aging is not a cost of unavoidable chemistry but is instead driven by changes in regulatory genes, the aging process may not be inevitable. It is at least theoretically possible to slow down or stop developmental drift.

"The take-home message is that aging can be slowed and managed by manipulating signaling circuits within cells," said Marc Tatar, PhD, a professor of biology and medicine at Brown University who was not involved in the research. "This is a new and potentially powerful circuit

that has just been discovered for doing that."

Kim added, "It's a new way to think about how to slow the aging process."

Source: Stanford University