Good for the goose, not so great for the gander

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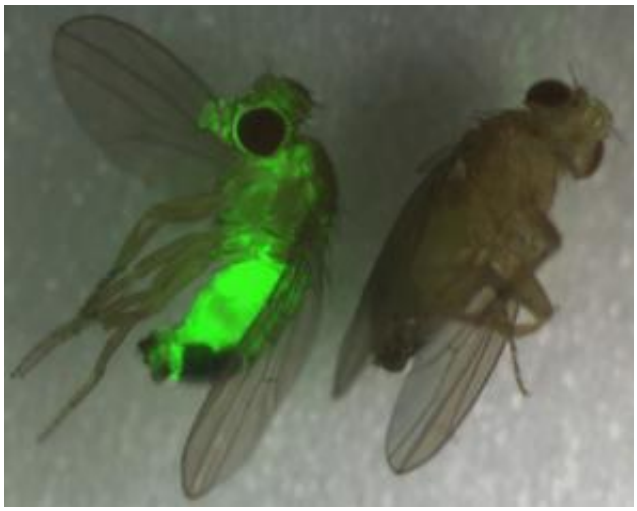

John Tower, associate professor of biological sciences in USC College, studies the genetics of aging in the fruit fly Drosophila melanogaster. Photo credit: Nicholas Hoe

A provocative new model proposed by molecular biologist John Tower of the University of Southern California may help answer an enduring scientific question: Why do women tend to live longer than men? That tendency holds true in humans and many other mammals as well as in the much-studied fruit fly Drosophila melanogaster.

In genetic studies of Drosophila, Tower and his team have shown that genes known to increase longevity always affect male and female flies differently.

“For a long time, we only did experiments in one sex or the other, depending on what was convenient,” said Tower, an associate professor of biological sciences in the USC College of Letters, Arts & Sciences who has studied the genetics of aging in Drosophila for the last two decades. “I thought if it was truly a gene fundamental to the aging process, it would be important in both sexes.”

Instead, genetic effects on longevity were highly sex-specific, research by Tower and USC postdoctoral researcher Morris Waskar, as well as a group led by Stephen Helfand at Brown University, revealed. In 1999, Tower’s graduate student, Jingtao Sun, showed that a gene for the antioxidant enzyme Cu/Zn-superoxide dismutase (SOD) led to a longer life span in male flies, but had a less dramatic impact in females. In later studies, both Waskar and Helfand’s group reported different effects in male and female flies in their work with the p53 gene, which encodes a protein that suppresses cancerous growth but also shortens life span.

Scientists’ initial surprise at these results was rooted in the assumption that aging was biologically identical in male and female. It’s an assumption Tower began to seriously question about a year and a half ago, eventually deciding to include both male and female flies in all of his experiments. It also made him consider just how aging might differ in the two sexes. Intrigued, he began to read widely, scouring the scientific literature and postulating how it might all work.

“I wanted to figure out a model to explain the sex-specific effects we saw in the antioxidant and p53 gene studies,” Tower said.

Based on his work and an extensive review of scientific reports from labs studying organisms ranging from alga to mice, Tower developed a new model suggesting how, on a genetic level, the evolution of aging and sex may be inextricably linked.

Tower published the theoretical model in the September Mechanisms of Ageing and Development, the journal of the British Society for Research on Ageing, and presented it at the 2006 meeting of the American Federation for Aging Research.

The model offers a new way to link the regulation of

life span to the biological mechanisms that trigger a fertilized egg's development into a male or female. The model suggests that sexual differentiation may exact a high biological cost — reduced function of the cell's mitochondria, the energy-producing components of the cell that are of intense interest to longevity researchers.

On a more practical level, the model predicts which genes and molecular processes are most likely to regulate the functional life span of an organism. And, as with any good model, it suggests testable hypotheses and new approaches to explore one of the biggest questions in the field of aging — why sex matters.

Gender differences in life span "is a topic worth deep thought," said USC's Caleb Finch, a University Professor and the ARCO/William F. Kieschnick Chair in the Neurobiology of Aging. "It's quite remarkable that women tend to survive better than men. It's not only hormones. The differences are present at birth [in humans], with boys more vulnerable to infant mortality up to age 1. There's something really different about how we [males and females] are built from the very beginning. And it's something that is still not well understood."

"With this model, Tower has made a significant contribution by suggesting new avenues to probe the biological basis of sex differences in aging," said Finch, a professor of gerontology, biological sciences and psychology. "He's suggested mechanisms that deserve experimental testing."

Trudy Mackay, a distinguished fruit fly geneticist at North Carolina State University, also finds the work compelling. "I certainly agree with the general argument" outlined in Tower's article, she said. "The two sexes represent completely different environments for expression of genes affecting life span. The challenge for the future is to understand this at a mechanistic level, and John's review is a significant step in that direction."

Looking to the Mitochondria

In recent years, much of Tower's research on aging has focused on extending life span by manipulating genes that produce the cell's most powerful and ancient antioxidants — the superoxidase dismutase (SOD) enzymes. Antioxidants protect cells from the toxic effects of oxygen free radicals, which are produced when cells burn their oxygen fuel during normal metabolism. Free radicals are destructive to DNA, protein and the other complex, delicate molecules that carry out life's every function.

In the so-called "oxidative stress" theory of aging, biologists surmise that the whips and scorns of time — arthritis, dementia, cancer and all the rest — are caused in part by a steady accumulation of such damage.

Anyone thinking about how oxidative stress might promote aging would be drawn to the mitochondria, the metabolic powerhouses of the cell. So would anyone thinking about sex differences and genetics. The mitochondria, thousands of which populate every cell, are the body's largest producers of free radicals. The mitochondria also are unique in that they evolved from free-living bacteria and contain their own complete set of genes, or genome, which has remained distinct from the cell's genome (stored in the nucleus) over millions of years of evolution.

While both parents contribute to their offspring's cellular genetic inheritance, only the female passes on the mitochondrial genome to the next generation. Why, and how, this asymmetrical inheritance happens is not clear, but Tower thinks understanding it may be key to understanding sex differences in aging.

Genetic Battle of the Sexes?

One expected effect of maternal inheritance of the mitochondrial genome, Tower suggests, might be a kind of Darwinian battle of the sexes played out on the genetic level called sexual antagonistic pleiotropy.

Because the mitochondrial genome (as well as the X chromosome) is inherited from the mother, evolutionary pressures might have selected for versions optimized for the female body. If the mitochondrial genome is better adapted to the female environment, the mitochondria in females

just may work better, and longer, than those in males.

This, Tower posits, might explain the longevity differences seen in the two sexes.

Tower suggests a novel way this might occur. Mitochondria play a key role in regulating the programmed cell death pathway, or apoptosis. In flies and humans, apoptosis works during normal embryonic development and sexual differentiation, sculpting the body by killing unwanted cells.

But the cell death pathway, in which the p53 gene is a central player, also appears to malfunction more frequently over an organism's lifetime, thereby contributing to aging and aging-related diseases like Parkinson's.

This might happen more often or differently in males, Tower speculates, leading to a shorter life span.

Tower's far-reaching model leads to "a list of predictions," which his lab has already started testing in experiments with Drosophila. One that he's particularly interested in following up on is the idea that the human Xist gene may control sex determination and be very much involved in regulating human life span, he said.

His team aims to find out how manipulating the activity of the analogous gene in the fruit fly, called Sxl or sex lethal gene, influences Drosophila life span.

"If my model is correct, Sxl in Drosophila and Xist genes in humans should be involved in sending a signal to the mitochondria that will make them viable longer and thereby make the organism live longer," he said.

Most scientists who have reviewed the model have been intrigued by the idea that sexual differentiation might limit life span. And, so far, no one has challenged his fundamental proposal describing how the mitochondrial genome has continued to exist independently of the cellular genome. This mechanism, Tower said, may inadvertently result in the molecular processes of aging.

The model, if correct, could alter scientists' fundamental understanding of cancer, Alzheimer's disease and other aging-related maladies.

George Martin, an expert on the genetics of longevity at the University of Washington School of Medicine in Seattle, calls Tower's model "very provocative and original."

"[The model] has enough to keep a small army of graduate students busy for many years," Martin said. "Some [predictions] should be quickly amenable to testing, such as the prediction that female life span may be more limited by the insulin-like signaling pathway and dietary restriction, while male life span may be more limited by stresses such as oxidative stress. Some [other predictions]… already are supported by preliminary data."

Tower cautions that only experimental data will determine the longevity of his model. But, he said, "If I'm right, this is big news."

Source: University of Southern California