Stanford researchers uncover link between 2 aging pathways in mice

January 8 2009

Two previously identified pathways associated with aging in mice are connected, say researchers at the Stanford University School of Medicine. The finding reinforces what researchers have recently begun to suspect: that the age-related degeneration of tissues, organs and, yes, even facial skin with which we all struggle is an active, deliberate process rather than a gradual failure of tired cells. Derailing or slowing this molecular betrayal, although still far in the future, may enable us to one day tack years onto our lives -- or at least delay the appearance of that next wrinkle.

"There is a genetic process that has to be on, and enforced, in order for aging to happen," said Howard Chang, MD, PhD, associate professor of dermatology at the school and a member of Stanford's Cancer Center. "It's possible that those rare individuals who live beyond 100 years have a less-efficient version of this master pathway, just as children with progeria — a genetic aging disease — may have components of this pathway that are more active."

The study, which will be published in the Jan. 9 issue of *Cell*, grew out of a three-year collaboration between Chang and Katrin Chua, MD, PhD, assistant professor of endocrinology, gerontology and metabolism at Stanford and member of the Stanford Cancer Center and the Veterans Affairs Palo Alto Health Care System. Chang and Chua are co-senior authors of the research.

The researchers focused their investigation on two seemingly separate

pathways linked to aging. One involved a molecule known as SIRT6 — a member of the sirtuin family of proteins that modulate life span in organisms such as yeast and worms — that Chua's laboratory has been studying for several years. She and her lab members have previously shown that SIRT6 is involved in genomic stability and the protection of chromosomal ends called telomeres. Telomeres, which grow shorter with each cell division, are thought to function as a kind of internal molecular clock associated with aging. Furthermore, mice lacking SIRT6 are born normally but die within a few weeks because of a rapid, multi-organ degeneration that somewhat resembles premature aging.

"Sirtuin family members have been implicated in aging and age-related diseases," said Chua, "but very little was known about how SIRT6 worked on a molecular level until recently. Our new study reveals that SIRT6, in addition to its role in genomic stability and telomere protection, also regulates gene expression."

The other pathway involved a more well-known protein called NF-kappa B, or NF-kB, that binds to and regulates the expression of many genes, including those involved in aging. The expression of many of these genes increases with age, and blocking the activity of NF-kB in the skin cells of elderly mice causes them to look and act like younger cells.

The researchers wondered if NF-kB and SIRT6 somehow work together to help cells age appropriately. They found that, in human and mouse cells, SIRT6 binds to a subunit of NF-kB and modifies components of a nearby DNA packaging center, called histones. This modification makes it more difficult for NF-kB to trigger the expression of the downstream gene — perhaps by causing the DNA to twist in such a way to boot off the protein.

"It seems that an important job of SIRT6 is to restrain NF-kB and limit the expression of genes associated with aging," said Chang. "We've been

interested in the activity of regulatory genes such as NF-kB during aging for several years now, and we were quite happy to find this very clear biochemical connection between these two pathways."

Young mice lacking the SIRT6 protein displayed elevated levels of NF-kB-dependent genes involved in immune response, cell signaling and metabolism — all potentially involved in the uniformly fatal aging-like condition that killed them within four weeks of birth. Tamping down the expression of the gene for NF-kB's SIRT-binding subunit allowed some of the mice to escape this fate.

"Mice lacking SIRT6 seem to hit some kind of a wall at around four weeks of age," said Chua, "when their blood sugar drops to a level barely compatible with life. Reducing NF-kB activity somehow allows the mice to get over this critical period and to live much longer. These mice provide a great new tool to study the effect of SIRT6-deficiency in much older animals than was possible before."

The researchers are now working to understand how NF-kB knows when and to what extent during an organism's lifetime to initiate the degenerative process and what role SIRT6 may play.

"It's a very provocative question," said Chang. "We've tied together two previously separate pathways in aging. Now we'd like to better understand what regulates that pathway."

Source: Stanford University Medical Center