Biologists identify a new clue into cellular aging

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The ability to combat some age-related diseases, such as cancer and diabetes, may rest with scientists unlocking clues about the molecular and cellular processes governing aging. The underlying theory is that if the healthy portion of an individual's life span can be extended, it may delay the onset of certain age-related diseases. In the search to understand these molecular processes, researchers at the University of Massachusetts Medical School have uncovered an important new DAF-16 isoform - DAF-16d/f - that collaborates with other DAF-16 protein isoforms to regulate longevity.

Part of the insulin signaling pathway, DAF-16 plays a critical role in a number of biological processes in C. elegans, including longevity, lipid metabolism, stress response and development, and is the center of a complex network of genes and proteins. Previous studies have identified the isoform - a different form of the same protein - DAF-16a as a regulator of longevity; genetically knocking down the DAF-16a isoform shortens C. elegans' life span. In a new study appearing in the July 7, advanced online edition of *Nature*, Heidi A. Tissenbaum, PhD, associate professor of molecular medicine, and colleagues in the Program in Gene Function and Expression at UMass Medical School, show that the newly discovered isoform DAF-16d/f works in concert with DAF-16a to promote organismal life span.

"Up until now, research has focused on the DAF-16a and DAF-16b isoforms," said Dr. Tissenbaum. "What we're able to show is that DAF-16a alone is insufficient for lifespan regulation. Moving forward,

any discussion about the process of aging will have to include this new protein isoform."

To see the effect of DAF-16d/f on life span, lead author Dr. Eun-soo Kwon, a post-doctoral fellow in the Tissenbaum laboratory, increased expression of the DAF-16d/f and DAF-16a in C. elegans. These studies showed that worms with the overexpressed DAF-16d/f lived longest. Additional experiments reveal that worms expressing DAF-16d/f were also more tolerant to heat stress during development and store more fat.

Because the DAF-16 gene in C. elegans is homologous to the FOXO gene in mammals, it may provide clues to longevity in humans. "Understanding the molecular pathways of DAF-16 and other genes will give us insight into aging at both the cellular and organism levels," said Tissenbuam. "As we age, at a certain point, something happens that triggers age-related disease. If we can learn what these signals are, it's possible we can find a way to extend the healthy portion of a person's life span and potentially delay the onset of age-related diseases such as cancer, diabetes and Alzheimer's."

The next line of inquiry will explore whether an increase in life span correlates to the health of the worm. "It's possible that we're restoring life span, but we don't know the effect of doing so," said Tissenbaum. "We have to explore whether this increased lifespan is of the healthy portion of the lifespan."

Graduate student Sri Devi Narasimhan and post-doctoral fellow Dr. Kelvin Yen also contributed to this study.

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