Researchers flip the switch between development and aging in C. elegans

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When researchers at the Buck Institute dialed back activity of a specific mRNA translation factor in adult nematode worms they saw an unexpected genome-wide response that effectively increased activity in specific stress response genes that could help explain why the worms lived 40 percent longer under this condition. The study, appearing in the July 6, 2011 edition of *Cell Metabolism*, highlights the importance of mRNA translation in the aging process. mRNA translation occurs after genetic messages have been transcribed in cells, when the encoded messages of genes are actually translated into functional proteins.

"This study gives us a much more comprehensive picture of the aging process," said Buck faculty Pankaj Kapahi, PhD, the principle investigator of the study. "Our work may help explain the relationship between development and aging."

Scientists have identified a number of so-called "longevity" genes active in many species. However, the mechanisms by which those genes impact lifespan remain poorly understood. According to Kapahi, the majority of research involving those genes has focused on transcription, the first level of cellular activity whereby DNA produces RNA. This research focuses on translation, whereby RNA specifies the production of proteins.

First-author Aric N. Rogers, Ph. D., a Buck Institute postdoctoral fellow, inhibited expression of the mRNA translation factor, IFG-1, in adult worms. IFG-1 is important for growth and development, and has a

homolog (eIF4G) in humans.. According to Rogers turning down IFG-1 right after the animals reached maturity set off a genome-wide change in the type of messages that were being translated. He said this causes a shift towards increased somatic maintenance by increasing the activity of genes involved in stress responses thereby enhancing longevity. Rogers said. "Turning down ifg-1 expression flips a switch that turned down growth and reproduction, but increased their healthspan as well as their lifespan."

Analysis of genes that were upregulated and downregulated pointed to processed transcript length as a determinant of altered translation. The next phase of the research will involve a closer look at small conserved sequences within the genetic code that may also contribute to changes in protein expression"Our primary interest is to understand the biological basis of aging," said Kapahi. "This will help identify molecular targets that can be used to develop therapeutics that would slow age-related diseases and extend the healthy years of life."

More information: Lifespan extension via eIF4G inhibition is mediated by post-transcriptional remodeling of stress response gene expression in C. elegans, *Cell Metabolism*.

Provided by Buck Institute for Age Research