

## **The microRNA *mir-71* Acts in the Ectoderm to Promote Germline-Mediated Longevity by Regulating DAF-16 Activity**

**Konstantinos Boulas and Bob Horvitz**

HHMI, Dept. Biology, MIT, Cambridge, MA 02139 USA

The reproductive systems of worms, flies and mammals control aging of the entire organism. When the germline of *C. elegans* is removed, either by laser microsurgery or by mutations that block germ-cell proliferation, animals live up to 60% longer than controls. This lifespan extension requires the activities of the FOXO family transcription factor DAF-16 and of the steroid hormone receptor DAF-12. In animals lacking germ cells, DAF-16 accumulates specifically in the intestinal nuclei and activates the transcription of stress-related and metabolic genes.

microRNAs, a class of small non-coding RNAs, have emerged as critical post-transcriptional regulators of gene expression in diverse biological processes. *C. elegans* microRNAs have been shown to play critical roles in the control of developmental timing, cell-fate specification, embryonic development, neural synaptic activity and longevity.

We performed a comprehensive search for microRNA genes that regulate *C. elegans* aging by determining the lifespans of deletion mutants for most of the 115 known microRNA genes. We found that the microRNA *mir-71* promotes longevity and stress resistance and mediates the effect of germ cell loss on lifespan. *mir-71* is required for the lifespan extension caused by germline removal, and overexpression of *mir-71* further extends the lifespan of animals lacking germ cells. Genetic epistasis analysis indicated that *mir-71* functions upstream of or in parallel to DAF-16 to promote germline-mediated longevity. Through a series of mosaic analysis and tissue-specific rescue experiments, we found that *mir-71* functions cell non-autonomously in the ectoderm of germline-less animals to promote the activity of DAF-16 in the intestine. Our findings reveal a novel microRNA-dependent mechanism of lifespan regulation by the germline and support a model in which signaling among the ectoderm, the intestine and the gonad coordinates the rate of aging of the whole organism.

Talk

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