The MicroRNA *mir-71* Promotes Longevity through Multiple Neurotransmitters

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A fundamental question in the field of aging is how different tissues communicate with each other to coordinate the rate of aging of the entire organism. Recent work has underscored the importance of the interplay between the nervous system and the intestine in the regulation of *C. elegans* lifespan by the gonad-dependent and the mitochondrial respiratory signaling pathways (Boulias and Horvitz, 2012; Durieux et al., 2011). Which specific neurons participate in this interaction, which neuroendocrine molecules are secreted, which downstream signaling effectors are used and whether these components are shared among the different longevity pathways (Insulin/IGF-1, gonad-dependent, mitochondrial, etc.) are questions that remain to be addressed.

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. Our previous studies identified the microRNA *mir-71* as a novel component of a DAF-16-dependent pathway by which the germ cells regulate lifespan (Boulias and Horvitz, 2012). We showed that *mir-71* acts in neurons to promote the localization and activity of DAF-16 in the intestine, suggesting that signaling among the gonad, the nervous system and the intestine coordinates organismal lifespan.

We are now seeking to identify the neuronal networks, signaling molecules (neurotransmitters and/or neuropeptides) and downstream effectors (ion channels, G protein-coupled receptors, etc.) that function to transduce the effects of germ cells on lifespan. To this end, we have started a systematic analysis of neural synaptic function mutants for defects in their lifespan response to germ cell loss. Our preliminary results suggest that *mir-71*-mediated lifespan extension in animals lacking germ cells depends on acetylcholine signaling, G protein signaling and synaptic release via dense core vesicles, whereas GABA signaling functions antagonistically to *mir-71* in mediating the effects of germline on lifespan. We are currently testing whether specific neuromodulators function to promote germline-mediated longevity by regulating the localization and activity of DAF-16, and we are performing site-of-action studies to help identify the specific neurons involved in the communication between the germline and the somatic tissues of *C. elegans*.

Poster
Aging, Metabolism, Stress, Pathogenesis and Small RNAs Meeting
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