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Cynthia Kenyon's Lecture Part 2: Genes that Control Aging

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1. Recommended Reading

1. Hubbard E. J. A. and Greenstein D., Introduction to the germline (September 1, 2005), review of *C. elegans* biology. WormBook, ed. The *C. elegans* Research Community.
(http://www.wormbook.org/chapters/www_introgermline/introgermline.html)
2. Apfeld, J., and Kenyon, C. (1999). Regulation of lifespan by sensory perception in *Caenorhabditis elegans*. *Nature* 402, 804-809.
3. Arantes-Oliveira, N., Berman, J.R., and Kenyon, C. (2003). Healthy animals with extreme longevity. *Science* 302, 611.
4. Alcedo, J., and Kenyon, C. (2004). Regulation of *C. elegans* Longevity by Specific Gustatory and Olfactory Neurons. *Neuron* 41, 45-55.
5. Hsin, H., and Kenyon, C. (1999). Signals from the reproductive system regulate the lifespan of *C. elegans*. *Nature* 399, 362-366.

6. Lin, K., Hsin, H., Libina, N., and Kenyon, C. (2001). Regulation of the *Caenorhabditis elegans* longevity protein DAF-16 by insulin/IGF-1 and germline signaling. *Nat Genet* 28, 139-145.
7. Pinkston, J., Garigan, D., Hansen, M., and Kenyon, C. (2006). Mutations that increase the life span of *C. elegans* inhibit tumor growth. *Science* 313(5789), 971-975.

2. Review Questions

1. What pathways regulate aging in *C. elegans*?
2. What kinds of sensory system mutations affect aging in *C. elegans*?
3. What is required for sensory system mutants to live long?
4. What does laser ablation of the germ cell precursors do to lifespan in *C. elegans*?
What does laser ablation of the somatic gonad precursors as well as the germ line do to lifespan?
5. What signaling pathway is required for the extended lifespan of animals lacking a germ line?
6. Which diseases have been shown to be regulated by the insulin/IGF-1 pathway in model organisms?
7. What happens in the *gld-1* mutant that mimics a tumor model?
8. How does the *gld-1* mutation cause tumors?

3. Answers to Review Questions

1. Insulin/IGF-1/FOXO signaling; caloric restriction; sensory perception; mitochondrial dysfunction; reproductive pathway. (There are actually additional pathways that weren't mentioned in the lecture, such as the TOR signaling pathway.)

2. Mutations in structure of the sensory neurons and mutations that affect specific chemosensory receptors expressed on the neurons.
3. DAF-16 is required. Sensory mutations don't extend lifespan if daf-16 is not present. Two further points of evidence that daf-2 signaling pathway is important: 1) A single mutation in a sensory neuron causes all DAF-16 to go into the nucleus. 2) Sensory mutations do not further extend the lifespan of long-lived daf-2 mutants.
4. Killing the germ cells extends lifespan by 60% in *C. elegans*. Killing the somatic gonad has no effect on lifespan – the lifespan of these animals is the same as that of wild type.
5. Steroid hormone signaling pathways are needed to promote DAF-16 nuclear accumulation and extend lifespan.
6. Huntington's Disease, Alzheimer's Disease, sarcopenia, heart failure, cancer.
7. In these animals, oocytes become like the germ line stem cells and begin to proliferate. They keep dividing until the whole animal is filled with these mitotic tumor cells and eventually dies.
8. By inhibiting apoptosis and promoting cell division.

4. Discussion Questions

1. Why would mutations in the sensory system regulate aging? Could this be tied to the dauer pathway?
2. One theory of aging is that longevity evolved as a trade-off for progeny production. If resources are limited, most of an organism's energy/resources are invested in producing progeny, not in maintenance of older post-reproductive individuals. One extreme example is a salmon species that undergoes rapid aging immediately after spawning. What is implied by this theory? How does regulation of aging by the reproductive tissue in *C. elegans* argue against this?

5. Answers to Discussion Questions

1. As mentioned in the lecture, the *daf-2* pathway is needed for regulation of aging by the sensory system. As we heard in the last lecture, the *daf-2* pathway is important not only for lifespan regulation, but for control of dauer formation – an alternative developmental state chosen for survival in harsh conditions. *C. elegans* may sense cues in the environment that tell the animal whether conditions are good or bad. The ability to both smell and taste these cues could give the animal a head-start on implementing the processes necessary for their survival.
2. This theory implies that decreasing reproduction would increase longevity. Indeed, some long-lived mutants do produce less progeny than wild type. Ablation of the germ line precursor cells seems to agree with this theory. This system may allow coordination between rate of aging and reproduction. In other words, if germ cell production is delayed, aging will be delayed as well, thus allowing time for the animal to produce progeny at a later time point. However, if the longevity-progeny trade-off were true, ablation of the entire gonad (germline as well as somatic gonad) would also extend lifespan. Animals lacking the entire gonad are obviously sterile, but they are not long-lived.

6. Explain or Teach These Concepts to a Friend

1. Explain the model for how the sensory system regulates aging in *C. elegans*
2. Describe how changes in the reproductive system in *C. elegans* lead to changes in lifespan.
3. Explain the tumor model in *C. elegans*.

7. Research the Literature on Your Own

1. Sensory perception of smell and taste can affect lifespan in *C. elegans*. What about thermosensory perception? Could temperature affect lifespan? (Hint: Look for Lee and Kenyon, 2008)
2. Is there evidence for regulation of aging by the reproductive system in model organisms other than *C. elegans*? (Hint: Look for Flatt *et al.*, 2008 and Cargill *et al.*, 2003)

8. Papers for Journal Club

1. Pinkston, J., Garigan, D., Hansen, M., and Kenyon, C. (2006). Mutations that increase the life span of *C. elegans* inhibit tumor growth. *Science* 313(5789), 971-975.
2. Pinkston-Gosse, J. and Kenyon, C. (2007). DAF-16/FOXO targets genes that regulate tumor growth in *Caenorhabditis elegans*. *Nature Genetics* 39(11), 1403-1409.

These two papers explore the link between tumorigenesis and aging in *C. elegans*. The first paper describes the *gld-1(-)* tumor model and its regulation by the insulin/IGF-1 pathway. In the second paper, the authors examine the activity of DAF-16 target genes, and test whether these genes affect lifespan and tumor size in the *gld-1(-)* tumor model. They find that a subset of genes regulates both lifespan and tumor growth, underscoring the link between cancer and aging. Furthermore, the genes identified in this study provide clues as to a mechanism of tumor suppression.