

## **HIRA-1 maintains neuromuscular function throughout the lifespan of *C. elegans***

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Individual cells can function for remarkably long periods of time. For example, retrospective birth dating of human cells suggests that muscle cells can function for up to 15 years and that neurons can function for an entire lifetime. Aging and many aging-associated diseases are characterized by a progressive decline in physiological functions. Nonetheless, the molecular mechanisms by which cells preserve their functions throughout an organism's lifespan are still unclear. The broad goal of this project is to understand the molecular mechanisms by which cells maintain their functions over animal lifespan. Specifically, I focus on epigenetic mechanisms.

I hypothesize that cells possess epigenetic factors that are dedicated to the maintenance of their function throughout animal lifespan. To test this hypothesis, I screened mutants lacking chromatin-associated factors for defects in the maintenance of neuromuscular function throughout the lifespan of *C. elegans*. This screen identified the evolutionarily conserved histone chaperone HIRA-1. Mutant animals lacking *hira-1* are healthy at larval stages but display a rapid decline in both defecation and feeding behaviors as adults. *hira-1* is therefore dispensable for the establishment of these neuromuscular functions but is required for their maintenance in the adult. Consistent with *hira-1* functioning to actively maintain cellular function throughout *C. elegans* lifespan, *hira-1* expression is enriched in the adult tail (the region of the worm where most of the cells that control defecation are positioned) and the adult pharynx (the organ that controls feeding). HIRA, the ortholog of HIRA-1 in other organisms, has a well-established function in the deposition of the histone variant H3.3. In mammalian cells, HIRA is required for the changes in chromatin state that occur during senescence. Therefore, HIRA-1 might have a conserved role in maintaining stable cellular states throughout animal lifespan. My screen also identified four other factors, all of which are conserved in mammals. Thus, the genes and pathways discovered by my screen might reveal fundamental mechanisms that are broadly important for the maintenance of cellular function throughout animal lifespan.