The HIRA histone chaperone complex maintains normal cellular function in adult animals and protects against late-onset pleiotropic defects

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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 cellular functions. The molecular mechanisms by which cells preserve their functions throughout an organism's lifespan are unclear. Here we report an essential role for HIRA-1 in maintaining normal cellular function in adult *C. elegans*. HIRA is an evolutionarily conserved histone chaperone that facilitates the deposition of the histone variant H3.3. We characterized mutants lacking *hira-1* (the sole *HIRA* ortholog encoded in the *C. elegans* genome). Loss of *hira-1* results in age-dependent pleiotropic defects: whereas *hira-1(-)* larvae are healthy, *hira-1(-)* adults have defects in body size, pigmentation, feeding, and defecation. HIRA-1 localizes to nuclei, is broadly expressed, and functions in multiple cell types to protect against these age-dependent pleiotropic defects. *hira-1* mutants also display a progressive decay in intestinal nuclear architecture and stage-specific misregulation of gene expression. We designed a mutagenesis screen to identify factors that function similarly to *hira-1*. In addition to identifying alleles of *hira-1*, this screen identified *pqn-80*. PQN-80 is the *C. elegans* ortholog of a core member of the HIRA complex (UBN-1 in humans and HPC2 in yeast), strongly suggesting that PQN-80 is a core member of the *C. elegans* HIRA complex. We posit that the *C. elegans* HIRA complex maintains normal nuclear architecture and gene expression to preserve normal cellular function in adult animals.