

Maternal H3.3 nucleosome assembly complexes prevent late-onset defects and chronic mitochondrial stress

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Many disease phenotypes manifest as late-onset, not presenting for years to decades. The molecular defects that lead to many of these disorders are unknown. We have discovered that *C. elegans* mutants lacking components of H3.3-assembly complexes have late-onset defects and chronic mitochondrial stress. HIRA is an evolutionarily conserved histone chaperone that facilitates the deposition of the histone variant H3.3. Mutants lacking *hira-1*, the sole *HIRA* ortholog encoded in the *C. elegans* genome, have defects in body size, pigmentation, pharyngeal pumping, and defecation. These pleiotropic defects are minor or undetectable until adulthood. These late-onset defects can be maternally rescued, likely by the persistence of maternally-derived HIRA-1 into the adult. Tissue-specific rescue experiments indicate that loss of *hira-1* has a systemic effect, as neuron-, muscle-, or intestine- specific expression is sufficient to rescue *hira-1* mutant defects. Loss of *hira-1* results in gene expression profiles similar to those of animals undergoing mitochondrial stress and chronic systemic activation of the mitochondrial stress response suggesting that mitochondrial stress might contribute to *hira-1* mutant defects. A screen for mutants that mimic the late-onset defects and mitochondrial stress of *hira-1* mutants identified *PQN-80/UBN1*, a core HIRA complex component, and *XNP-1/ATRX*, an H3.3 chaperone that functions in a complex distinct from that of the HIRA complex. Mutants lacking H3.3 are superficially wild-type but have a late-onset defect in defecation similar to that of *hira-1*, *pqn-80*, and *xnp-1* mutants, strongly suggesting that the HIRA complex and XNP-1 assemble H3.3-containing chromatin to prevent this late-onset defect. We hypothesize that H3 can compensate for loss of H3.3, explaining why H3.3 mutants share only one of the pleiotropic defects of *hira-1*, *pqn-80*, and *xnp-1* mutants. Indeed, RNAi of H3 mimics the small and pale aspects of the *hira-1* phenotype in H3.3 mutants but not in wild-type animals, supporting our hypothesis that H3 can compensate for loss of H3.3 and that this compensation is executed by the HIRA complex and XNP-1. We propose that HIRA- and ATRX- mediated assembly of H3.3-containing chromatin plays an essential role in preserving normal organismal physiology across the lifespan of many organisms and that perturbations of these pathways might underlie some late-onset human diseases.