BIOLOGICAL SCIENCES

Mitochondrial DNA copy number in *Caenorhabditis elegans* is regulated by a functional output of the electron transport chain

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Within mitochondria reside semi-autonomous genomes called mitochondrial DNA (mtDNA). mtDNA is multi-copy per cell and cells contain hundreds to thousands of mtDNA molecules. mtDNA copy number varies between cell types and within an individual over developmental time, but it is not yet known how copy number is regulated. Since incorrect copy number is correlated with detrimental outcomes such as cancer and infertility, it is important to understand copy number regulation. It has long been postulated that a sensing mechanism exists to effectively count mtDNA molecules, but it is not understood what is being counted by the cell. Importantly mtDNA can exist in a state of heteroplasmy, wherein two types of mtDNA (haplotypes) co-exist in the same cell or organism. Copy number analyses were conducted in various heteroplasmic strains to determine the minimal genic region required for the sensing mechanism. Our data suggest that not all mtDNA mutations disrupt copy number regulation and we infer that a functional output of the electron transport chain is required for mtDNA to be counted. Given these data, we explored a candidate gene (*clk-1*) that may serve to count mtDNA molecules by this functional output. Consistent with this hypothesis, we found that *clk-1* null mutants exhibit elevated copy number.

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