Tether Mutations that Restore Function and Suppress Pleiotropic Phenotypes of the *C. elegans isp-1(qm150)* Rieske Iron-sulfur Protein

Mitochondria play an important role in numerous diseases as well as normative aging. Severe reduction in mitochondrial function contributes to childhood disorders such as Leigh Syndrome, whereas mild disruption can extend the lifespan of model organisms. The *Caenorhabditis elegans isp-1* gene encodes the Rieske iron-sulfur protein subunit of *cytochrome c* oxidoreductase (complex III of the electron transport chain). The partial loss of function allele, *isp-1(qm150),* leads to several pleiotropic phenotypes. To better understand the molecular mechanism of ISP-1 function, we sought to identify genetic suppressors of the delayed development of *isp-1(qm150)* animals. Here we report a series of intragenic suppressors, all located within a highly conserved six amino acid tether region of ISP-1. These intragenic mutations suppress all of the evaluated *isp-1(qm150)* phenotypes, including developmental rate, pharyngeal pumping rate, brood size, body movement, activation of the mitochondrial unfolded protein response reporter, CO_2 production, mitochondrial oxidative phosphorylation and lifespan extension. Furthermore, analogous mutations show a similar effect when engineered into the budding yeast Rieske iron-sulfur Rip1, revealing remarkable conservation of the structure-function relationship of these residues across highly divergent species. The focus on a single subunit as causal both in generation and in suppression of diverse pleiotropic phenotypes points to a common underlying molecular mechanism, for which we propose a “spring-loaded” model. These observations provide insights into how gating and control processes influence the function of ISP-1 in mediating pleiotropic phenotypes including developmental rate, movement, sensitivity to stress and longevity.