New Functional and Biophysical Insights into the Mitochondrial Rieske Iron-Sulfur Protein from Genetic Suppressor Analysis

Several intragenic mutations suppress the *C. elegans isp-1 (qm150)* allele of the mitochondrial Rieske iron-sulfur protein (ISP), a catalytic subunit of Complex III of the respiratory chain. These mutations were located in a helical region of the "tether" span of ISP-1, distant from the primary mutation in the extrinsic head, and suppressed all pleiotropic phenotypes associated with the *qm150* allele. Analysis of these suppressors revealed control of electron transfer into Complex III through a "spring-loaded" mechanism involving a binding force for formation of enzyme-substate complex, counterbalanced by forces (a chemical "spring") favoring helix formation in the tether. The primary P→S mutation results in inhibition of electron flow into the Q-cycle by decreasing the binding force, and the tether mutations relieve this inhibition by weakening the "spring." In this commentary we discuss additional control features and relate the primary inhibitions to outcomes at the organismal level. In particular, the sensitivity to hyperoxia and the elevated reactive oxygen species (ROS) seen in *isp-1 (qm150)*, likely reflect over-reduction of the quinone pool, which is upstream of the inhibited site; at high O_2, this would lead to increased ROS production through complex I. We speculate that alternative NADH:ubiquinone oxidoreductase activity in *C. elegans* from the worm apoptosis inducing factor (AIF) homolog (WAH-1) might also be involved, and that WAH-1 might have a "canary" function in detection of this adverse state (high O_2/reduced pool), and a role in protection of the organism by transformation to AIF-like products, and apoptotic recycling of defective cells.