OXIDATIVE STRESS AND RESPIRATORY MITOCHONDRIAL FUNCTION IN COENZYME Q MUTANTS.

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Coenzyme Q (CoQ) , or ubiquinone, is a lipid-soluble component of mitochondrial inner membrane, involved in the transport of electrons from complex I and II to complex III in mitochondrial respiratory chain, it's also a well known antioxidant and involved in other aspects of cellular metabolism. In human, CoQ deficiency can cause encephalomyopathy, cerebellar ataxia, or even Leigh syndrome. CoQ biosynthesis, in yeast, involves nine gene products (coq1- 9), and the lack of any of these genes result in the total absence of mature ubiquinone. Patients with recessive ataxia were identified harboring mutations of ADCK3/COQ8 , We analyzed these mutations pathogenicity in yeast cells, considering their respiratory capacity and oxidative stress. We also have identified a new gene necessary for fully functional expression of coenzyme Q, which was named COQ10. Curiously, even though coenzyme Q is present in yeast mitochondria of coq10 mutants, the respiratory electron transport chain is severely affected, and it can be rescued with the addition of exogenous coenzyme Q, a hallmark phenotype of coenzyme Q biosynthetic mutants. Furthermore, respiratory growth of coq10 mutants is partially reestablished with the over expression of COQ2, COQ7 and COQ8 , and in the last case the endogenous amount of coenzyme Q was duplicated. Altogether our previous results showed that Coq10p may direct coenzyme Q function. Two additional observations corroborate it: Coq10p and coenzyme Q can bind to each other, and Coq10p homologous have a typical tunnel domain, present in cholesterol binding domain of StAR proteins. We have hypothesized that Coq10p may function in helping negative charged semiquinone radical in diffusing through the matrix side of Q cycle, until its protonation. In the absence of Coq10p an increase of "free" semiquinone level would result in an elevation of oxidative stress. And that's exactly what we observed in coq10 mutants: an elevation of H2O2 release, a higher sensitivity to lipid peroxidation, and increment in mt-DNA damage.