

In vivo mitochondrial matrix proteome profiling reveals RTN4IP1/OPA10 as an antioxidant NADPH oxidoreductase

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Targeting proximity labeling enzymes to specific cellular locations is a viable strategy for profiling subcellular proteomes. Here, we generated transgenic mice (MAX-Tg) expressing a mitochondrial matrix-targeted ascorbate peroxidase (MTS-APEX2) to analyze tissue-specific matrix proteomes. Desthiobiotin-phenol labeling of muscle tissues from MAX-Tg mice allowed for the efficient profiling of tissue-specific matrix proteome. Comparative analysis of matrix proteomes from MAX-Tg muscle tissues revealed differential enrichment of mitochondrial proteins related to energy production. We identified that Reticulon 4 interacting protein 1 (RTN4IP1), also known as Optic Atrophy-10 (OPA10), is highly enriched in the mitochondrial matrix of muscle tissues and is an NADPH oxidoreductase. Interactome analysis and in vitro enzymatic assays revealed an essential role for RTN4IP1 in coenzyme Q (CoQ) biosynthesis by regulating the O-methylation activity of COQ3. Rtn4ip1 knockout C2C12 myoblasts had markedly decreased CoQ9 levels and impaired cellular respiration, which was rescued by exogenous CoQ treatment. Muscle-specific knockdown of the drosophila Rnt4ip1 ortholog resulted in impaired muscle function which was reversed by dietary supplementation with soluble CoQ. Collectively, RTN4IP1 is a mitochondrial antioxidant NAD(P)H oxidoreductase supporting mitochondrial respiration activity in muscle tissue.

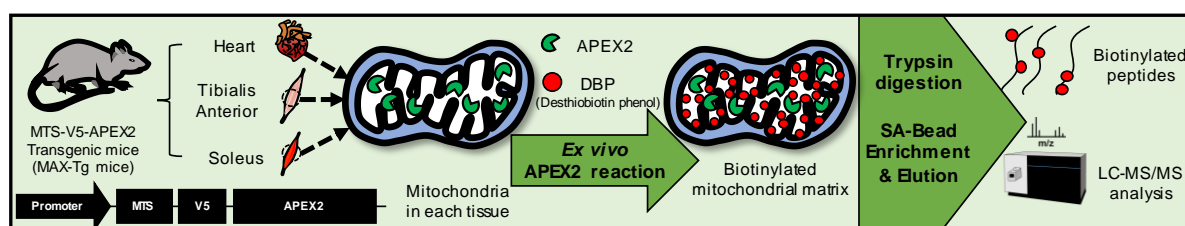


Figure 1. Scheme for tissue-specific mitochondrial matrix proteome mapping using MAX-Tg mice