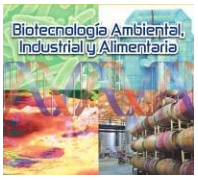
Poster



The mitochondrial phosphatase PPTC7, ¿a biomarker of coenzyme Q10 deficiency or a therapeutic target?

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ABSTRACT

PPTC7 is a PP2C-type cation divalent phosphatase of the mitochondrial matrix that catalyzes the dephosphorylation of phosphoserine and phosphothreonine residues. This enzyme is involved in post-translational modifications to regulate mitochondrial biogenesis and mammalian development through coenzyme Q10 biosynthesis (CoQ10) and the mitochondrial import proteins. Several models have demonstrated the importance of PPTC7 as a regulator of mitochondrial proteins. For instance, Ptc7 is an orthologue of PPTC7 in S. cerevisiae that regulates mitochondrial function by activating citrate synthase, a crucial enzyme in the Krebs cycle. Furthermore, PPTC7 expression can be modulated according to mouse liver metabolic changes, and low PPTC7 expression has been associated with altered oxidative phosphorylation profiles and mitochondrial dysfunction in obese C57BL/6 mice (ob/ob). These studies have proven its role as a regulator of mitochondrial metabolism, in particular, PPTC7 activates the COQ7 hydroxylase encoded by the COQ7 gene, which is one of the 11 genes involved in the CoQ10 biosynthetic pathway. Some COQ proteins facilitate the complex assembly involved in the synthesis process and others act enzymatically in the synthesis, such as COQ7, which is critical in the conversion of the molecule demethoxyubiquinone (DMQ) to 5-hydroxyubiquinone. Mutations in COQ genes cause primary coenzyme Q10 deficiency, a rare disease characterized by ataxia, myalgia and renal dysfunction, among others. Preliminary transcriptomic analysis by this group has revealed low levels of PPTC7 expression in fibroblast samples from patients with primary and secondary coenzyme Q10 deficiency. Its role in coenzyme Q10 synthesis and the relationship between CoQ deficiencies in humans has not been fully elucidated, so this study aims to examine the role of the PPTC7 as a biomarker of coenzyme Q10 deficiency. To identify a cause-effect relationship, we performed PPTC7 gene and protein expression, cellular respiration, and the variation of coenzyme Q10 concentration in two different conditions: a) in control fibroblasts after the inhibition of CoQ10 synthesis generated by para-aminobenzoic acid (pABA), and b) in patients fibroblasts cultured in presence of exogenous CoQ10. Moreover, this study explores the PPTC7 overexpression in HEK293 cells as a potential therapeutic approach for mitochondrial diseases.

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