IPAP18 Innovations in Pharmacy ADVANCES & PERSPECTIVES

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#IPAP18 Posters

H_2S metabolism in mitochondrial Complex I deficiency. Influence of Coenzyme Q10 supplementation.

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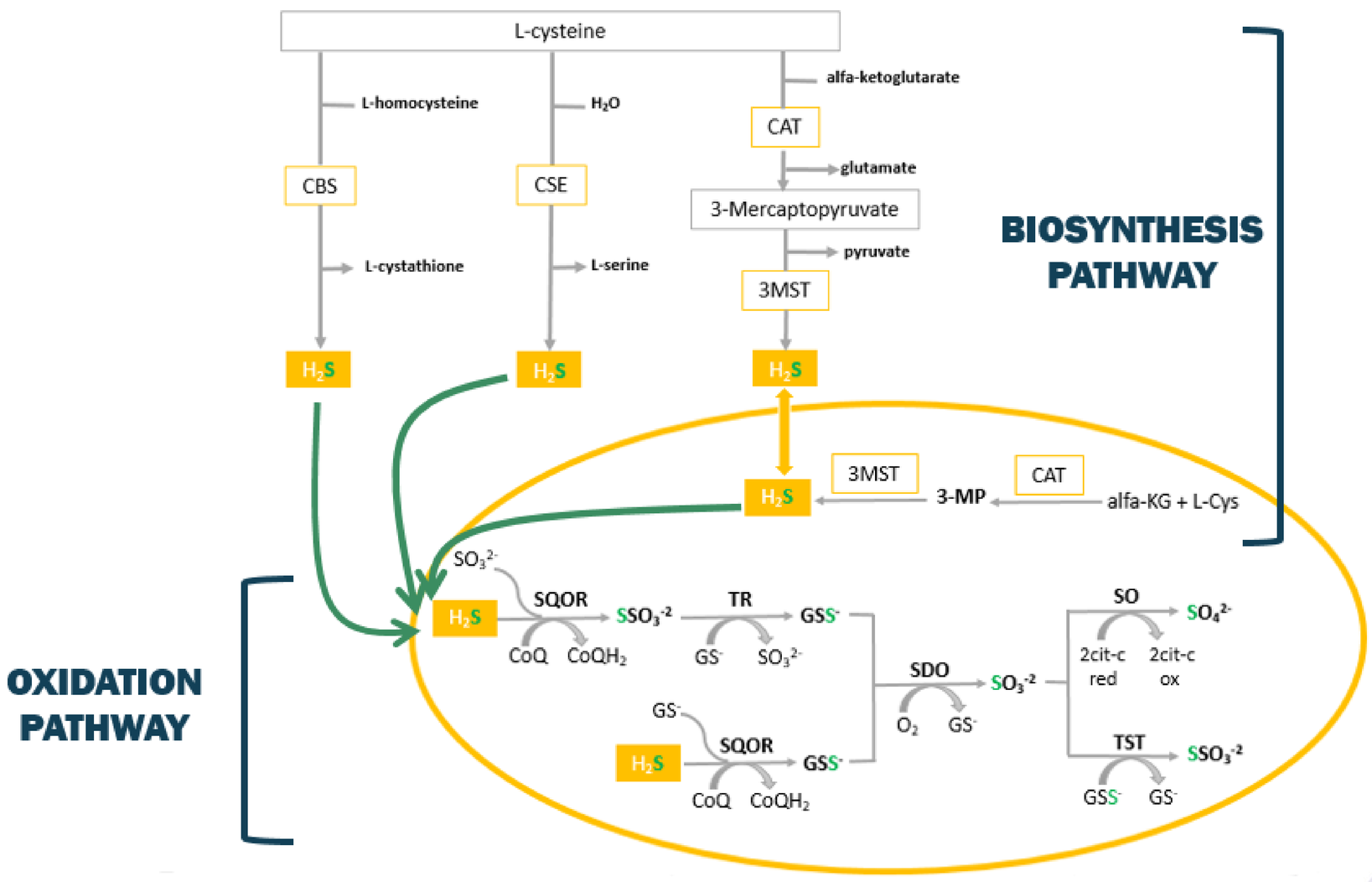
BACKGROUND

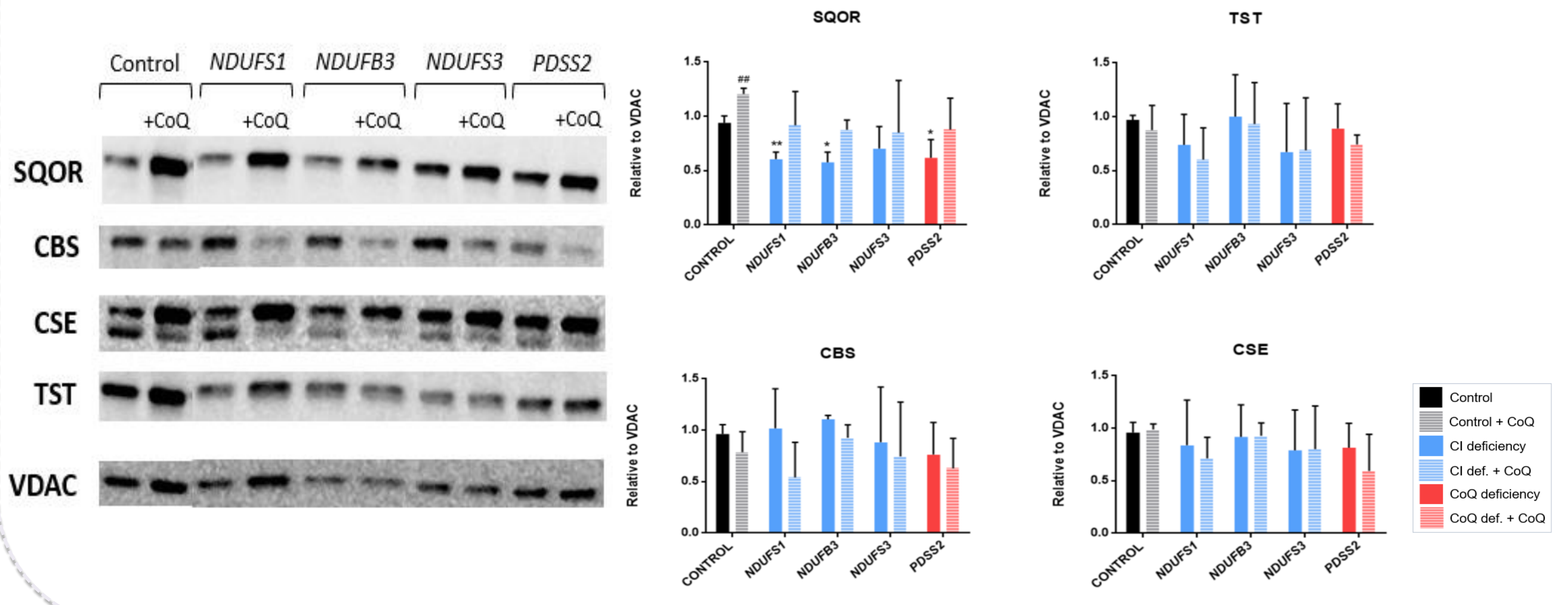
The cellular levels of H_2S are regulated by the **transsulfuration pathway** (biosynthetic) and by the mitochondrial **oxidation pathway** (catabolic), being the latter one involved in the mitochondrial energy production through the activity of **Sulfide:Quinone Oxidoreductase (SQOR).** The SQOR depends on the levels of CoQ, since a deficiency of this molecule causes a drastic reduction of the levels of the enzyme. However, it is unknown how sulfide metabolism responds to supraphysiological levels of CoQ_{10} after exogenous supplementation and if imbalances in sulfide metabolism may be also a common feature in other mitochondrial diseases, such as Complex I deficiency (CI).



AIM

Our purpose is to evaluate the enzymes of the sulfide metabolism pathway in mitochondrial dysfunction like **Complex I and CoQ deficiency** in physiological conditions and after the **supplementation with CoQ_{10}.**

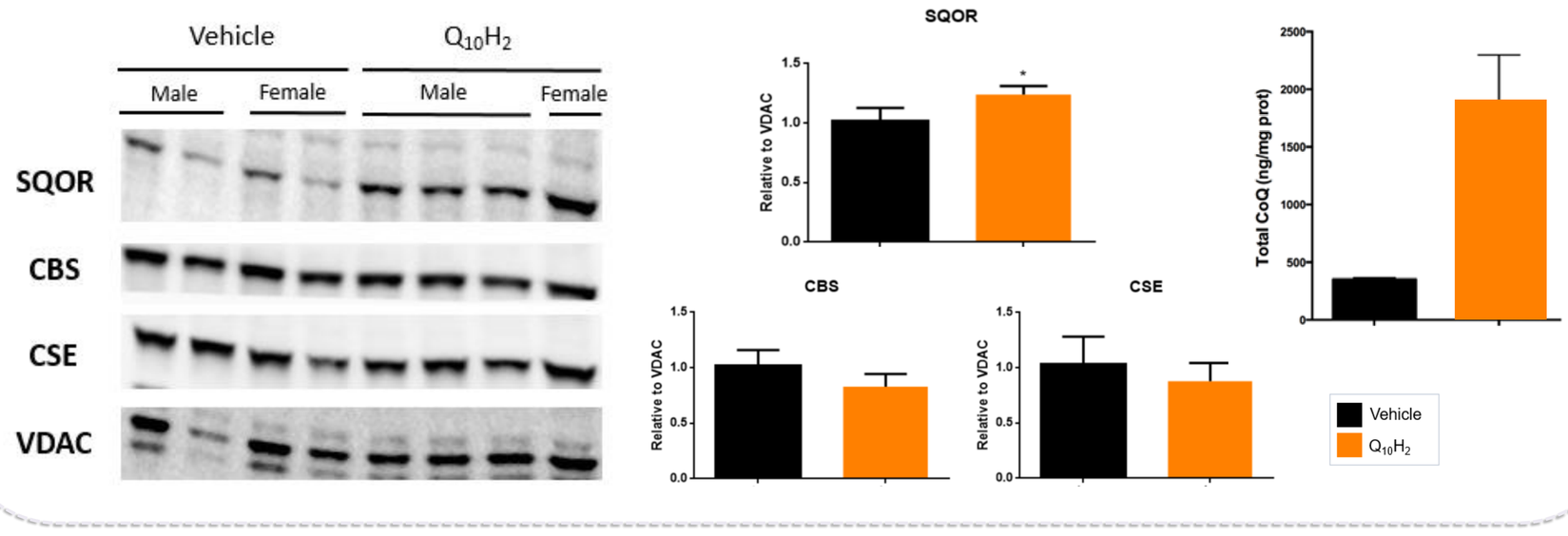
Results in fibroblasts treated with CoQ_{10}



Gene	Regular medium (A)	Regular medium + 100 µM CoQ_{10} (B)	(B/A)
	CoQ_{10} (ng/mg prot)	CoQ_{10} (ng/mg prot)	Increase in CoQ_{10}
CONTROL	83.2 ± 13.3	715335 ± 304041	8597
NDUFB3	88 ± 22.8	3260636 ± 1498894	37074
NDUFS1	75±8.6	265735±144425	3543
NDUFS3	93±9.2	446627 ± 169118	4802
PDSS2	18.8 ± 11.2	2046794 ± 9957	108872

Defect	Gene	Mutation	Residual CI activity
Complex I deficiency	*NDUFB3*	c.64T>C, p.Trp22Arg c.208G>T, p.Gly70X	17%
	NDUFS1	c.683T>C, p.V228A c.755A>G, p.D252G	37%
	NDUFS3	c.595C>T homo; p.R199W	40%
			Residual CoQ_{10} levels
Primary CoQ_{10} deficiency	*PDSS2*	c.[964C>T];[1145C>T]	15%

Results in mouse model treated with $Q_{10}H_2$



Results in kidney of *Ndufs4* KO mice

CONCLUSIONS

- SQOR levels depends on the mitochondrial function:
  - ⬇ in CI and CoQ deficiency fibroblasts
  - ⬆ in *Ndufs4* KO mice tissues
- The enzymes of the biosynthetic pathway were not affected by defects in CI.
- The effect of the exogenous supplementation of CoQ_{10} showed a tendency to increase the SQOR levels.
- The levels of CoQ_{10} and SQOR influences the protein levels of the transsulfuration enzymes.

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