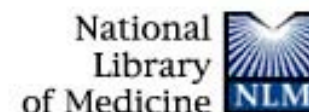


An almost final solution to the Ethylmalonic acid syndrome



*Valeria Tiranti
ERNDIM Meeting
October 22-23, 2009
Basel*





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1: Lancet. 1991 Dec 14;338(8781):1522-3.

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New clinical phenotype of branched-chain acyl-CoA oxidation defect.

Burlina A, Zacchello F, Dionisi-Vici C, Bertini E, Sabetta G, Bennet MJ, Hale DE, Schmidt-Sommerfeld E, Rinaldo P.

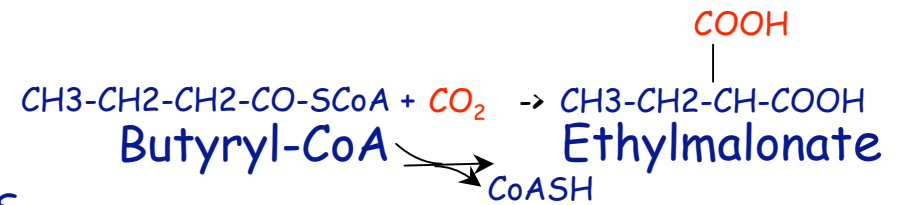
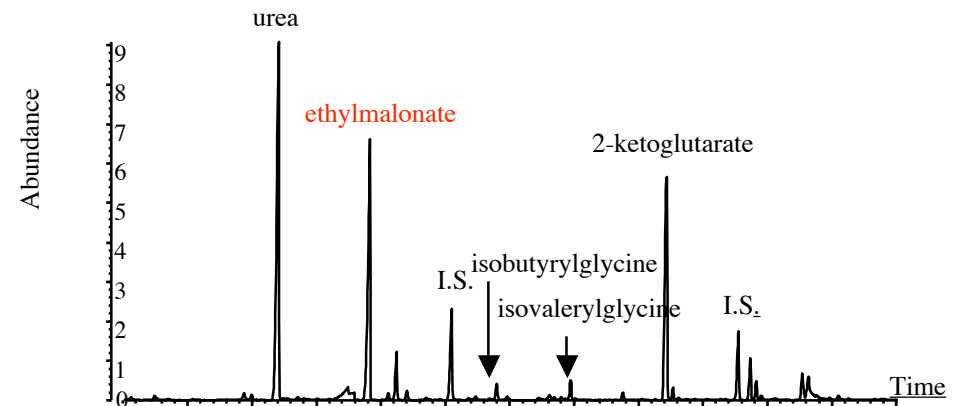
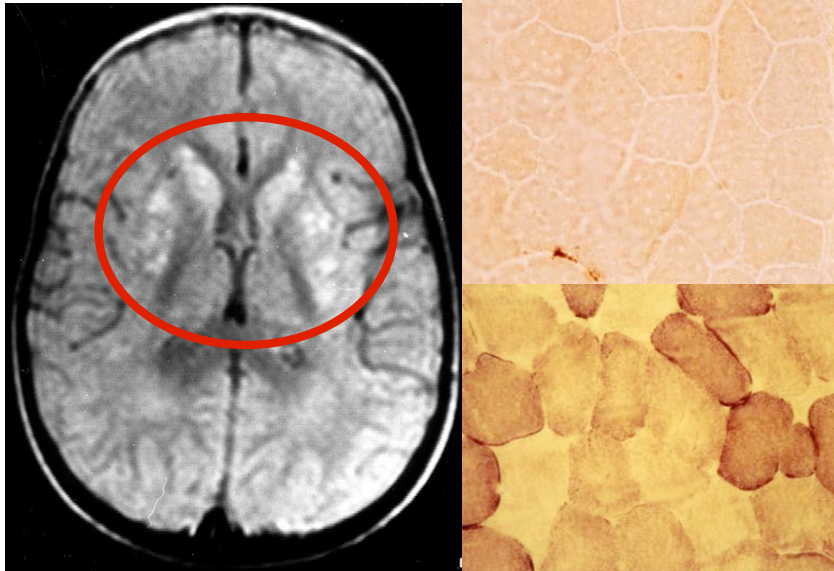
Publication Types:

- Letter

PMID: 1683940 [PubMed - indexed for MEDLINE]

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Ethylmalonic Encephalopathy (EE)



CNS

- early-onset hypotonia, developmental delay
- later spasticity, then global failure

Vascular system

- acrocyanosis
- petechiae, microematuria, internal bleedings

Gastrointestinal system

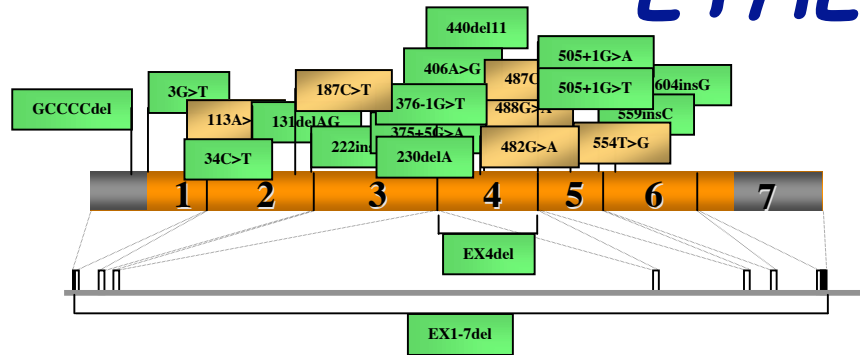
- chronic diarrhoea

Biochemistry

- COX deficiency (only in muscle)
- lactic acidosis
- ethylmalonic aciduria
- elevated C4-C5 acylcarnitine



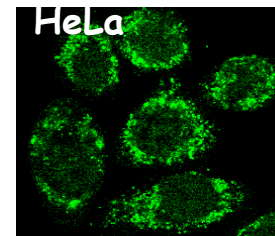
ETHE1: the gene



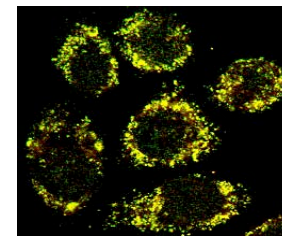
✓ 50 EE patients
✓ 28 non-EE EMA patients

Ethe1: the protein

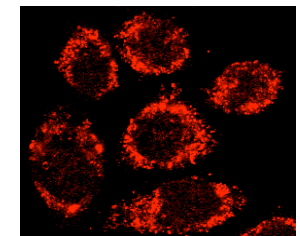
✓ It is a mitochondrial matrix protein



ETHE1



merge

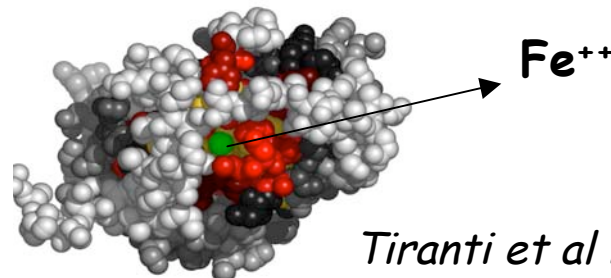


Mitotracker

✓ It works as an homodimer

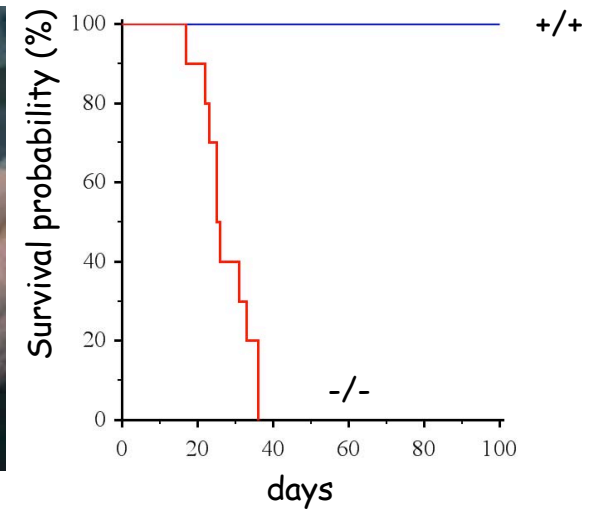
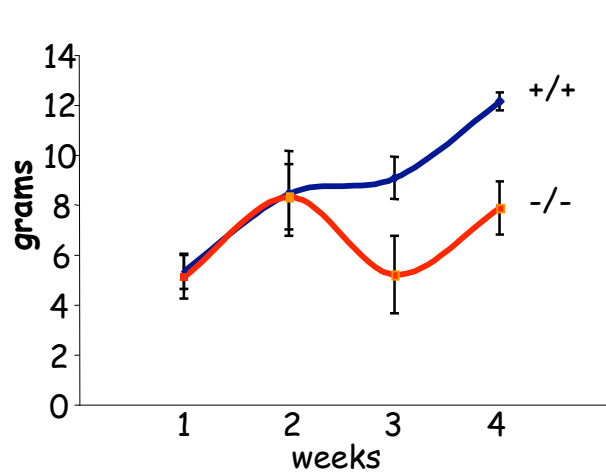


✓ It binds iron



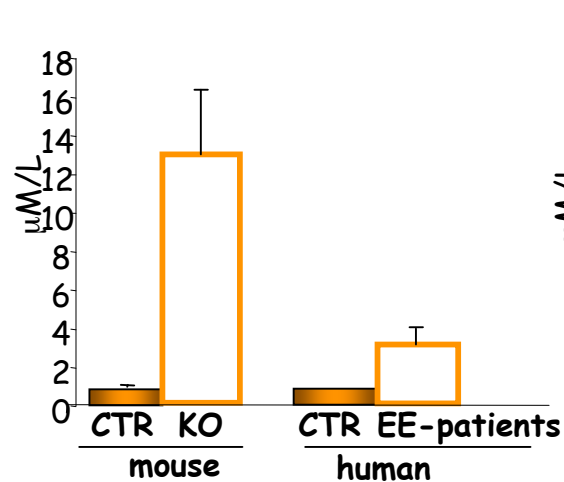
Tiranti et al 2004-2006, Mineri et al 2008

ETHE1^{-/-} mouse phenotype

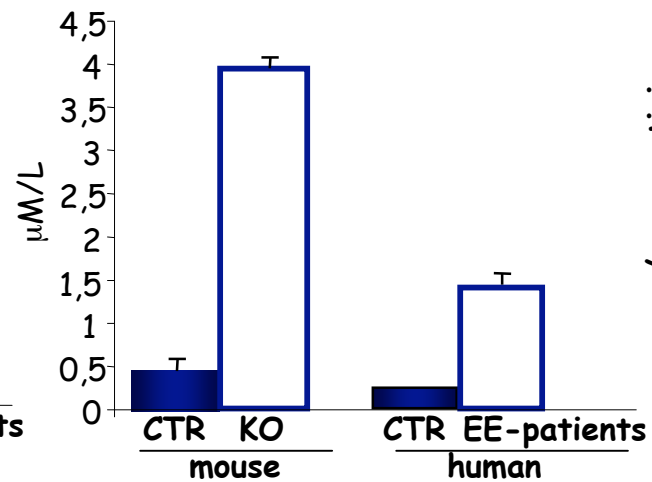


Metabolites in body fluids

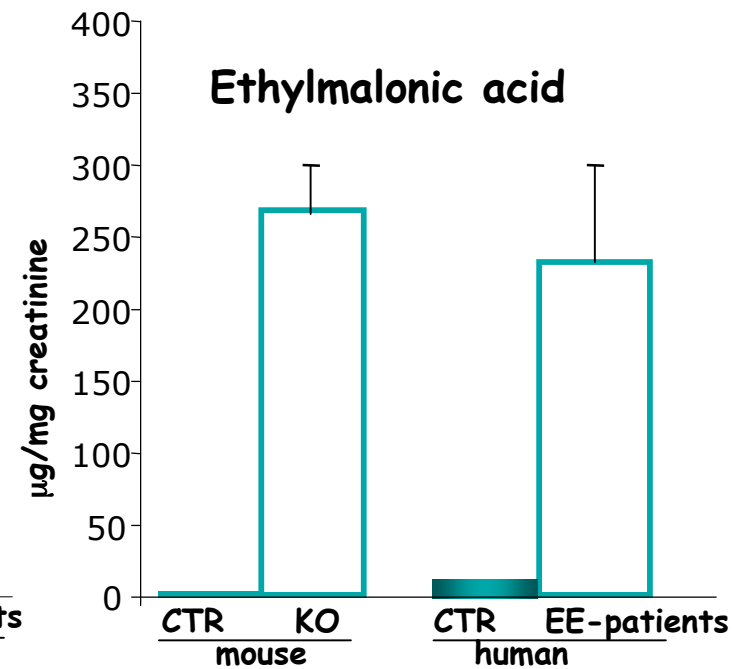
C4 acylcarnitine



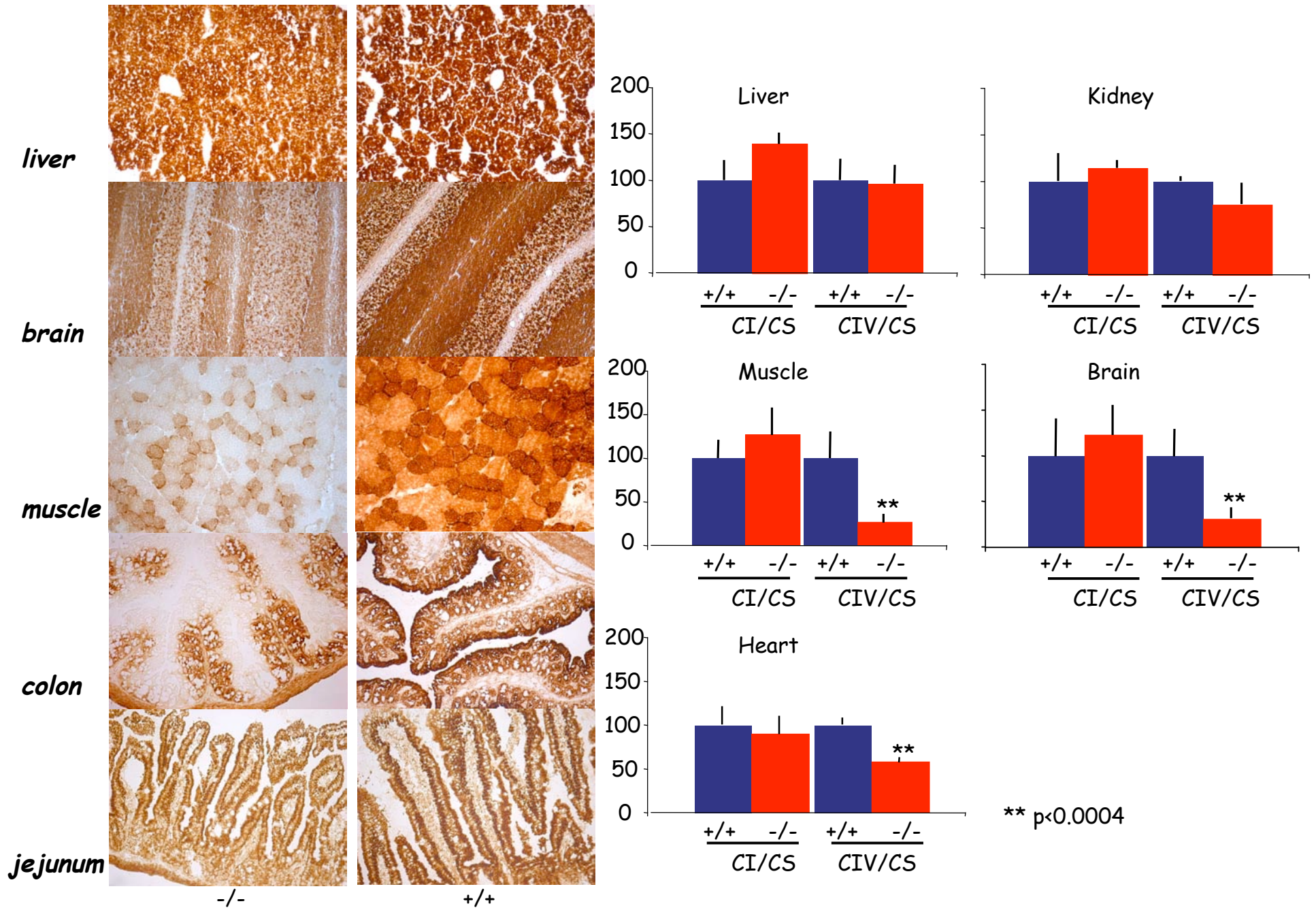
C5 acylcarnitine



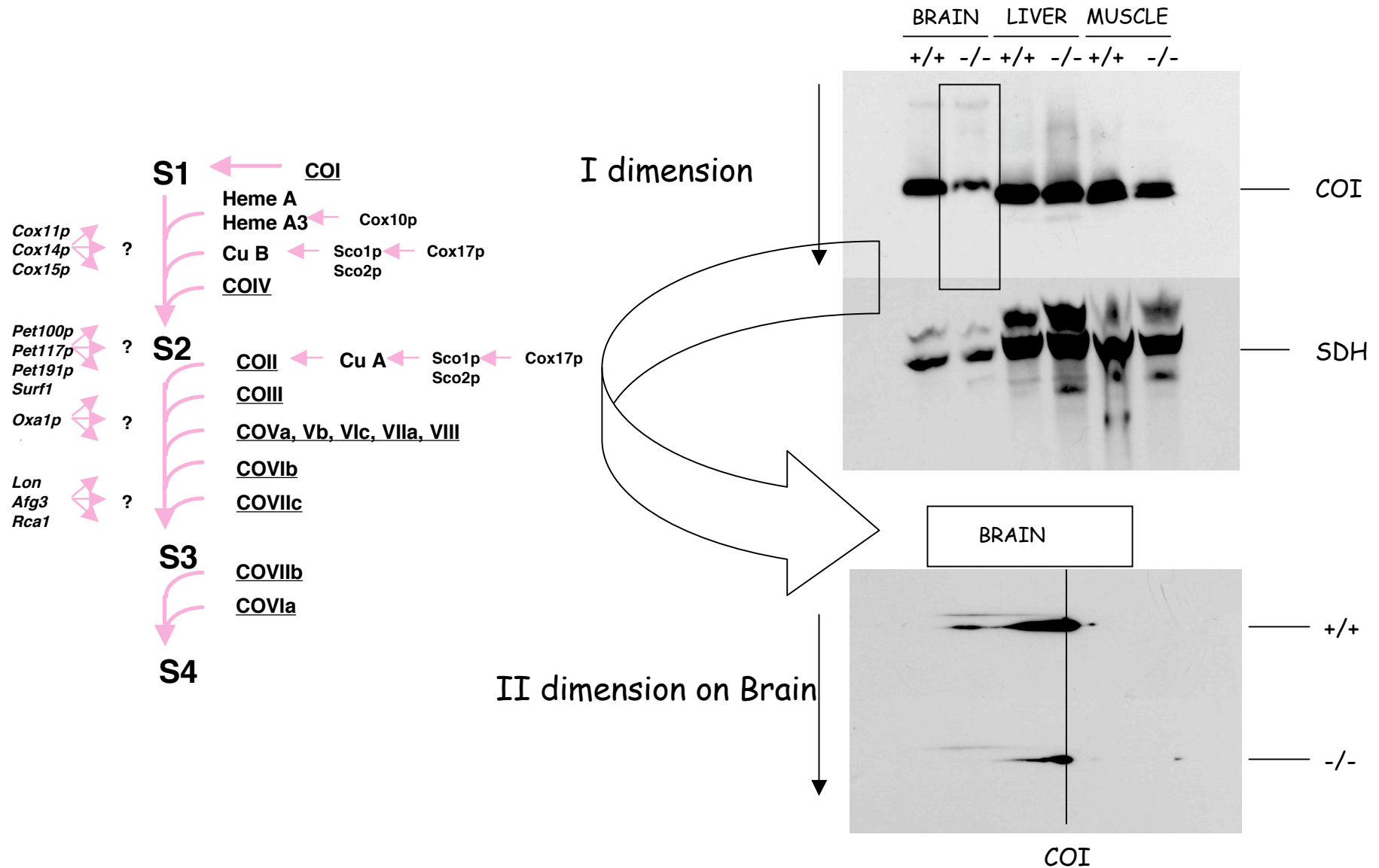
Ethylmalonic acid



Respiratory chain complex activities in mouse tissues



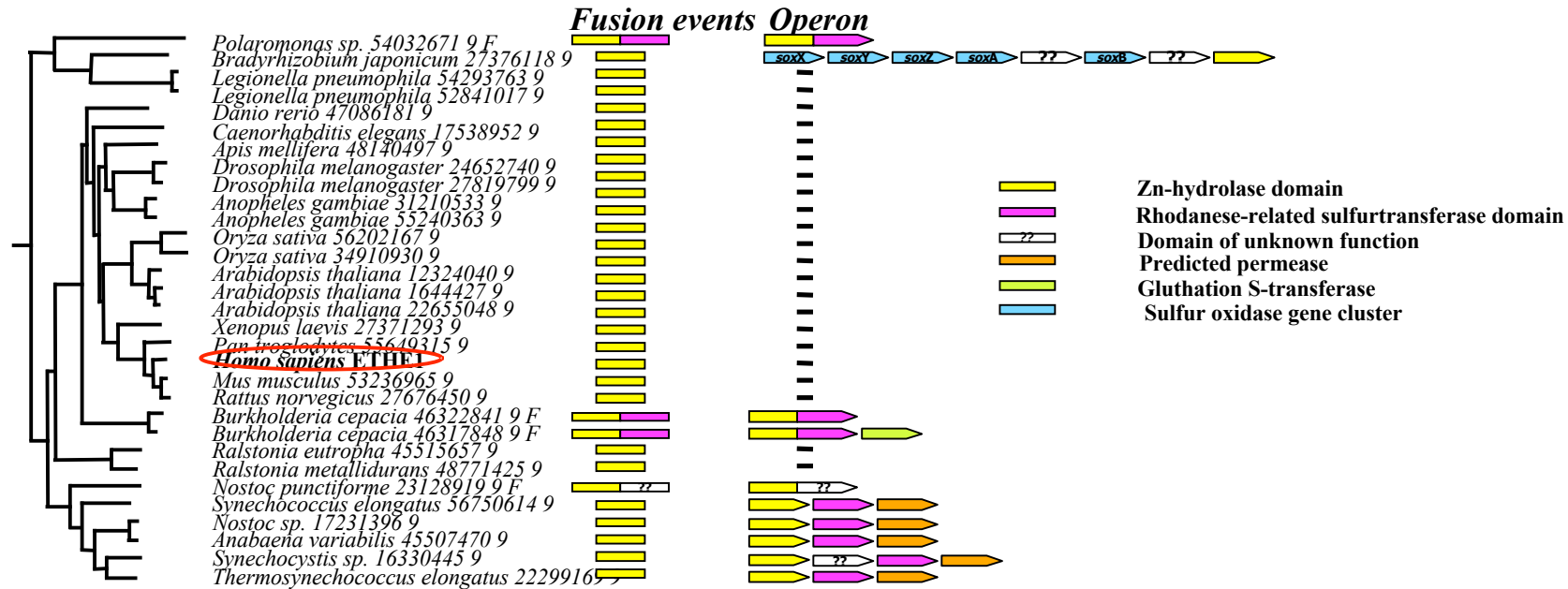
Western-blot analysis of COX assembly in ETHE1 KO mice



Bioinformatic search

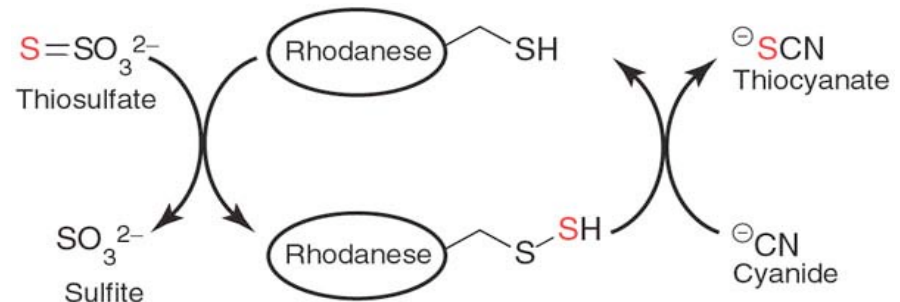


ETHE1-like proteins are present in operons containing Rhodanese-like proteins or as Chimeric proteins ETHE1/Rhodanese

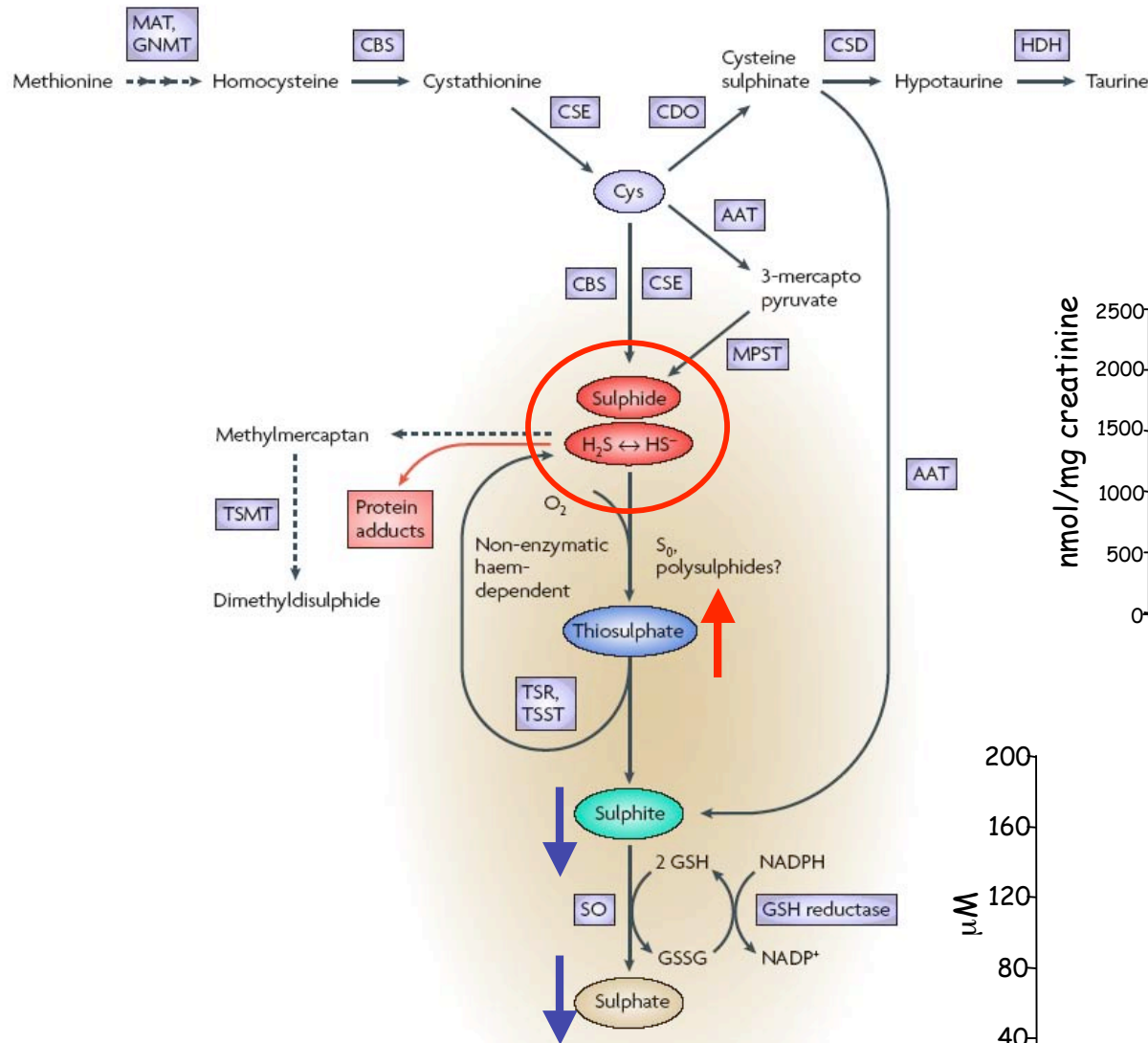


RHODANESE (TST, Thiosulphate Sulfurtransferase)

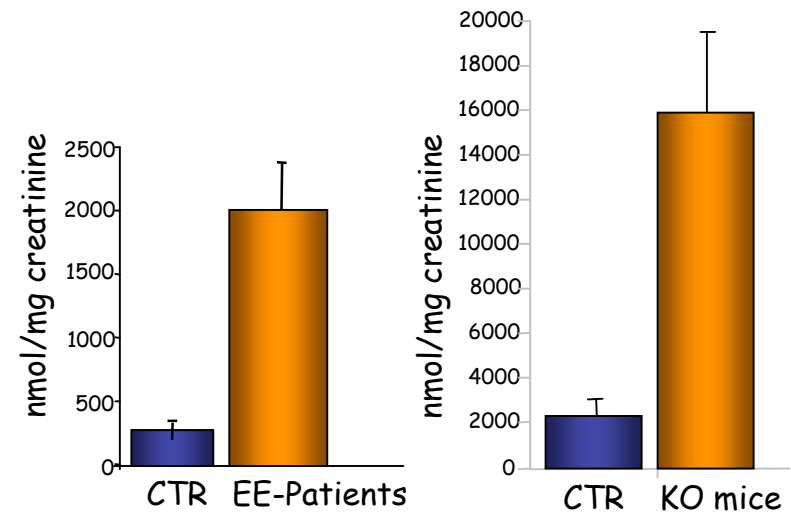
- ✓ Mitochondrial matrix protein
- ✓ Unknown biological function (Cyanide detoxification, Iron-sulfur cluster formation, energetic metabolism)
- ✓ It is involved in sulfur metabolism



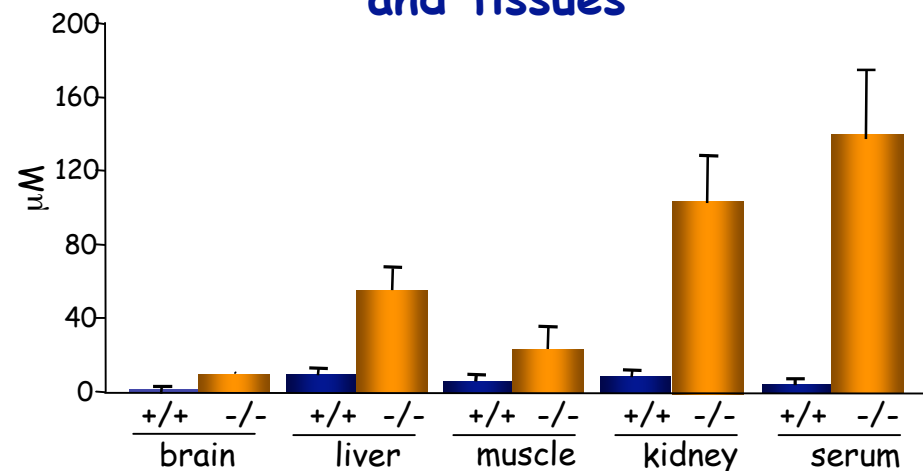
Sulfur metabolism



Thiosulphate in urines

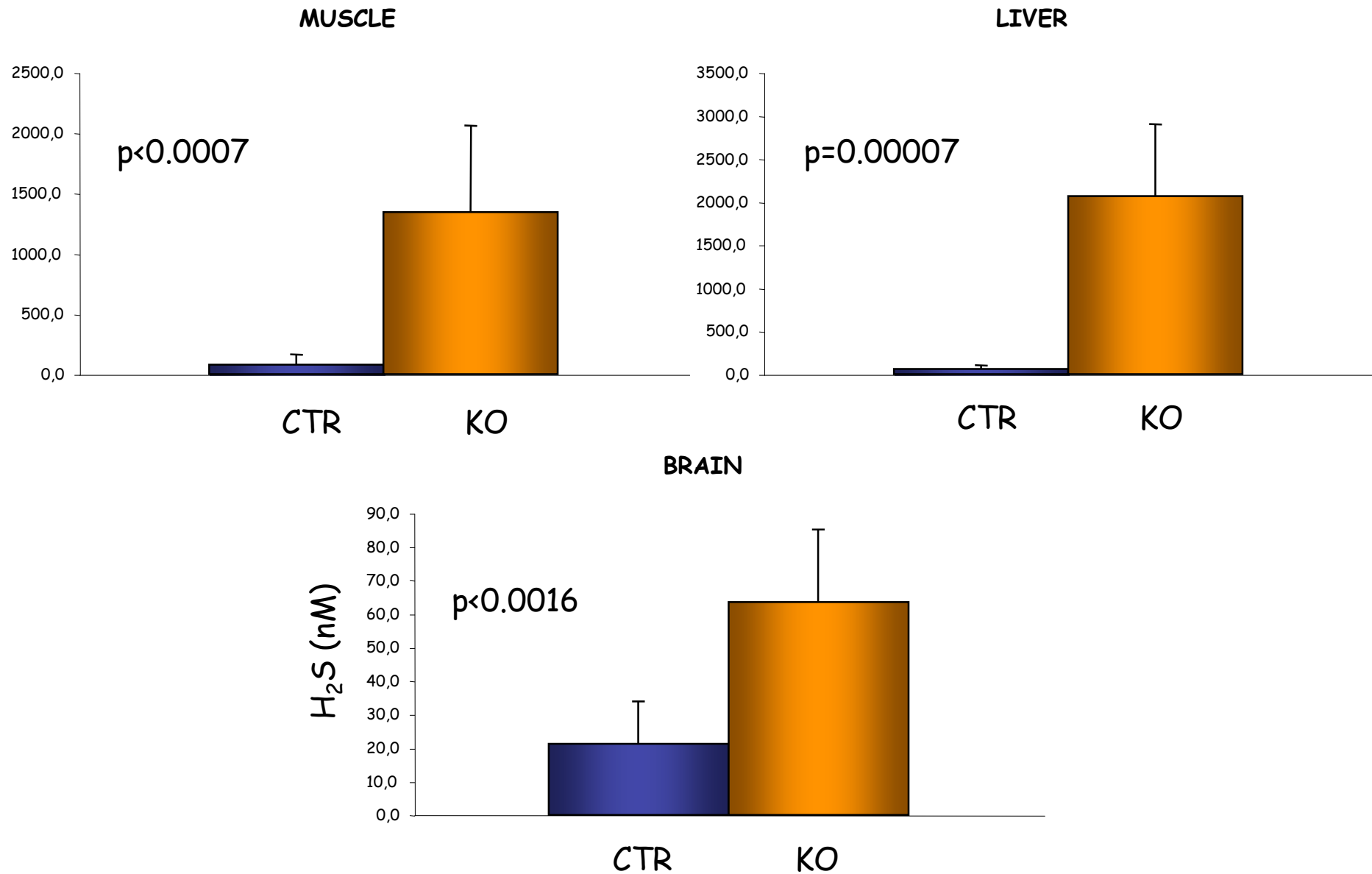


and tissues

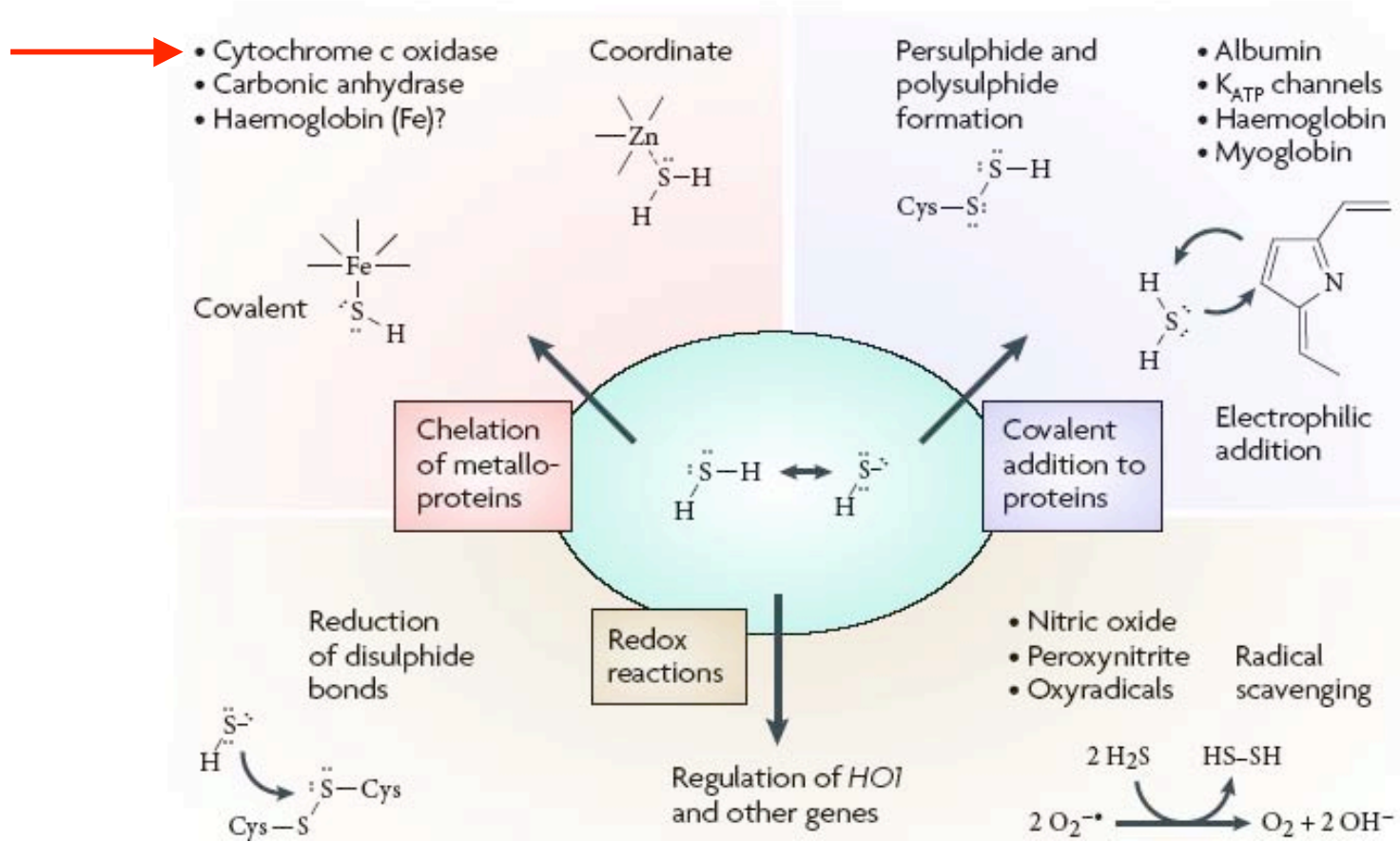


Szabo, Nat Rev Drug Discov 2007

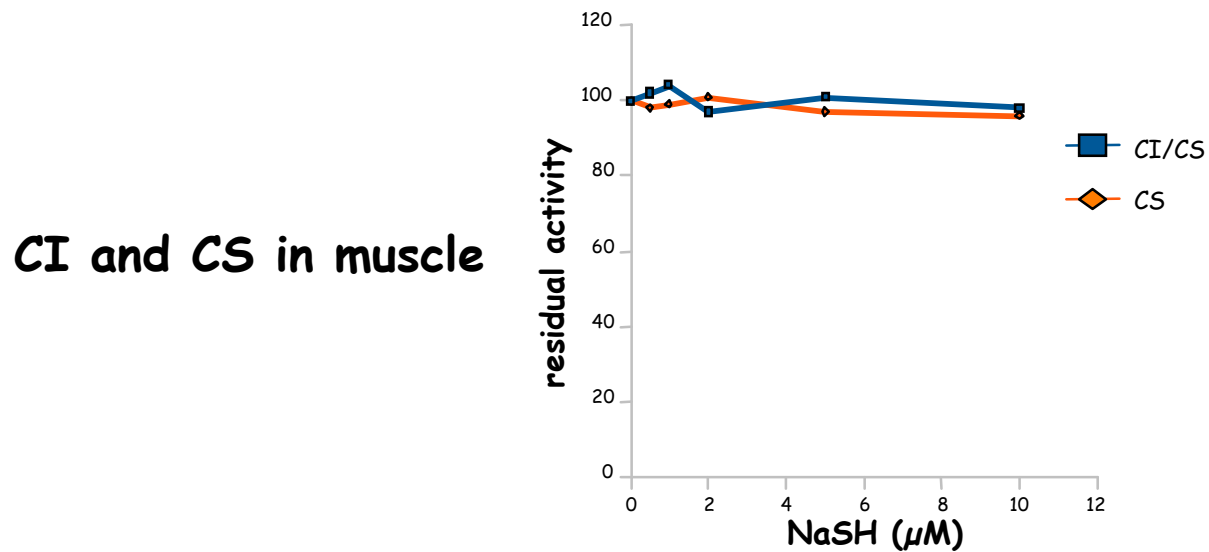
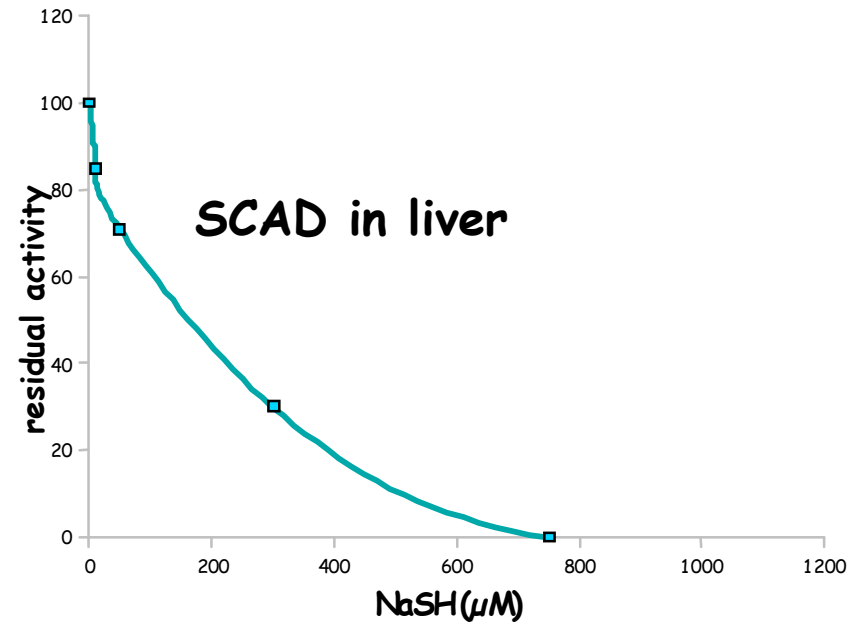
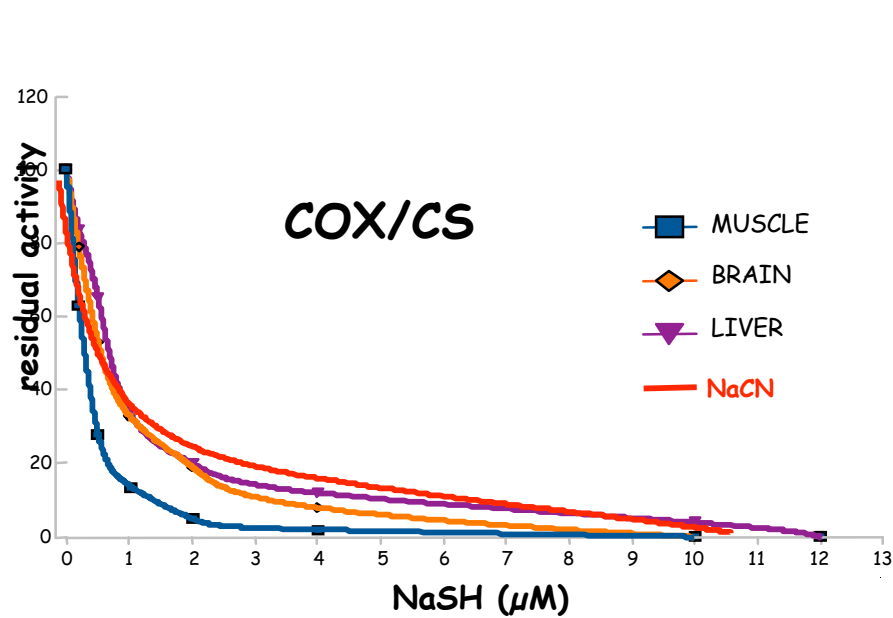
H₂S concentration in tissues of *ETHE1* knockout mice



H₂S inhibits cytochrome c oxidase (COX)



H₂S inhibits enzymatic activities



Conclusions 1

- The pathogenetic mechanism of Ethylmalonic Encephalopathy (EE) relies on high levels of H_2S , that are toxic for both COX and SCAD
- H_2S can act as a vasodilator thus explaining the acrocyanosis and can be toxic for the microvessels thus explaining the petechiae

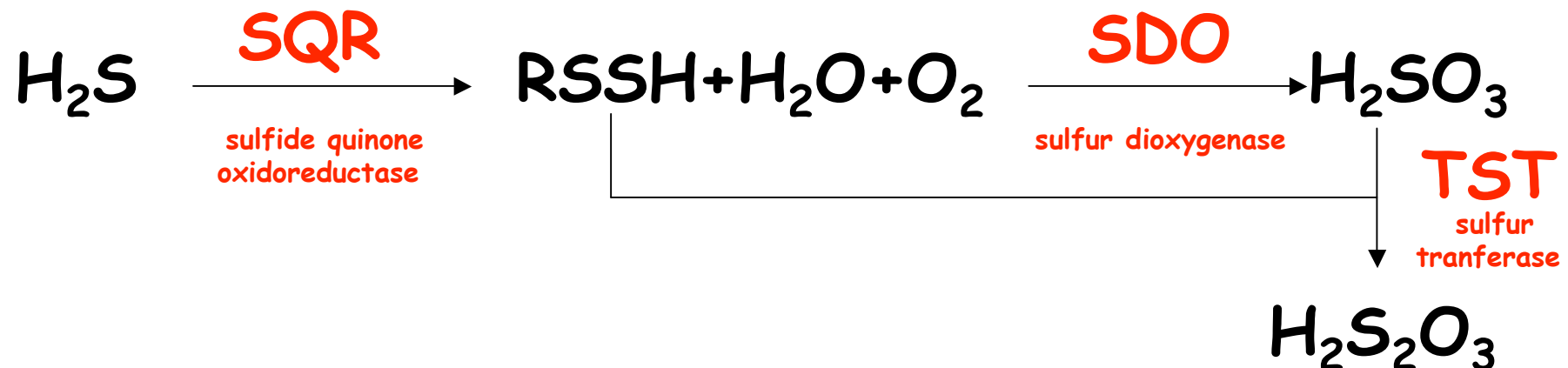
Which is the role of ETHE1????

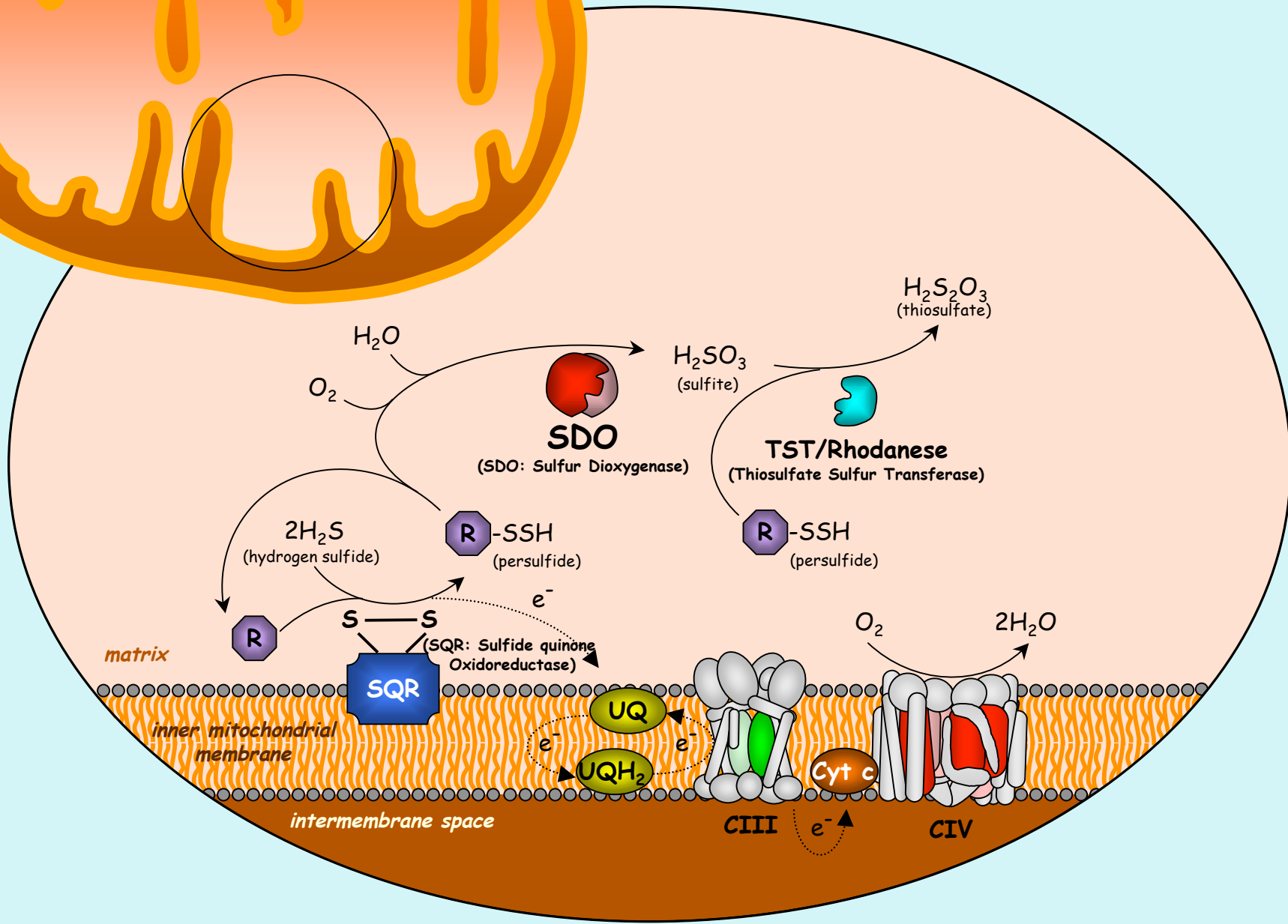
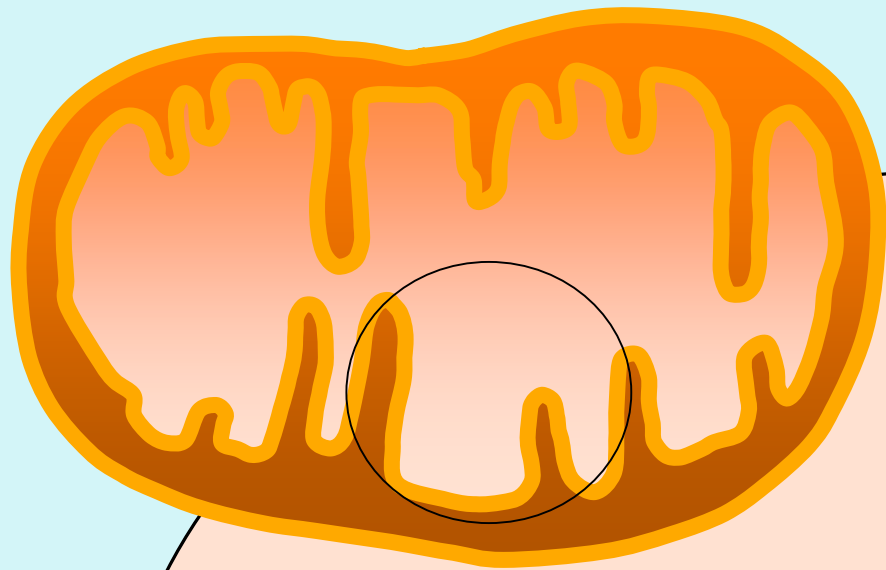
Three enzymatic activities catalyze the oxidation of sulfide to thiosulfate in mammalian and invertebrate mitochondria

Tatjana M. Hildebrandt and Manfred K. Grieshaber

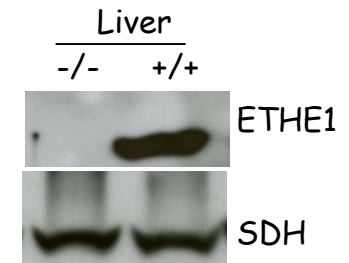
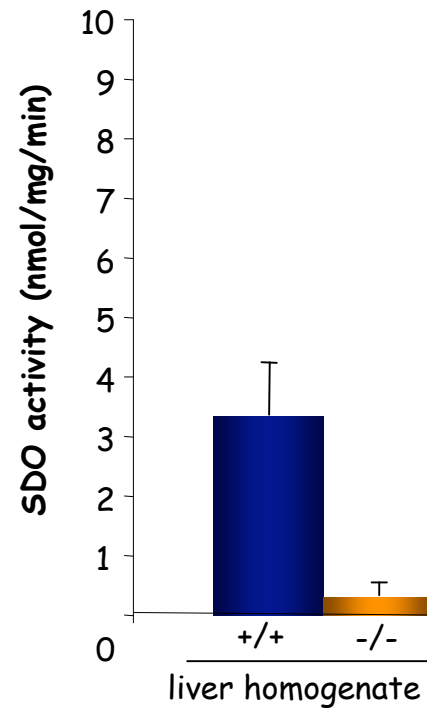
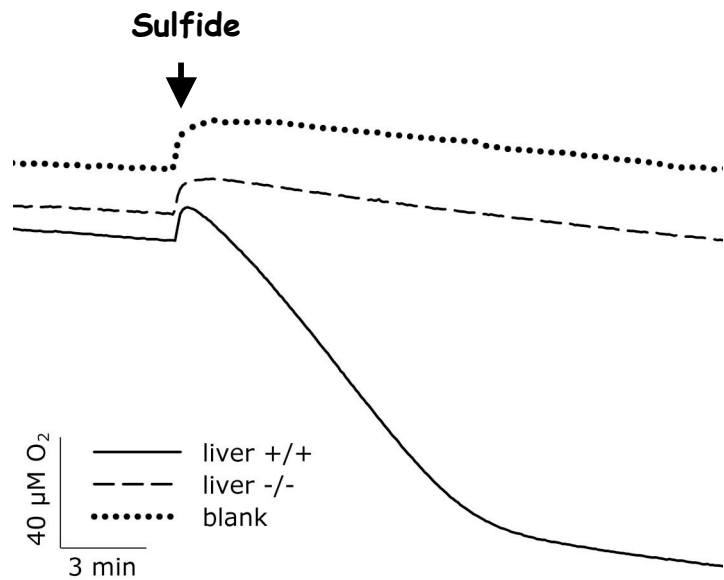
Institut für Zoophysiologie, Heinrich-Heine-Universität Düsseldorf, Germany

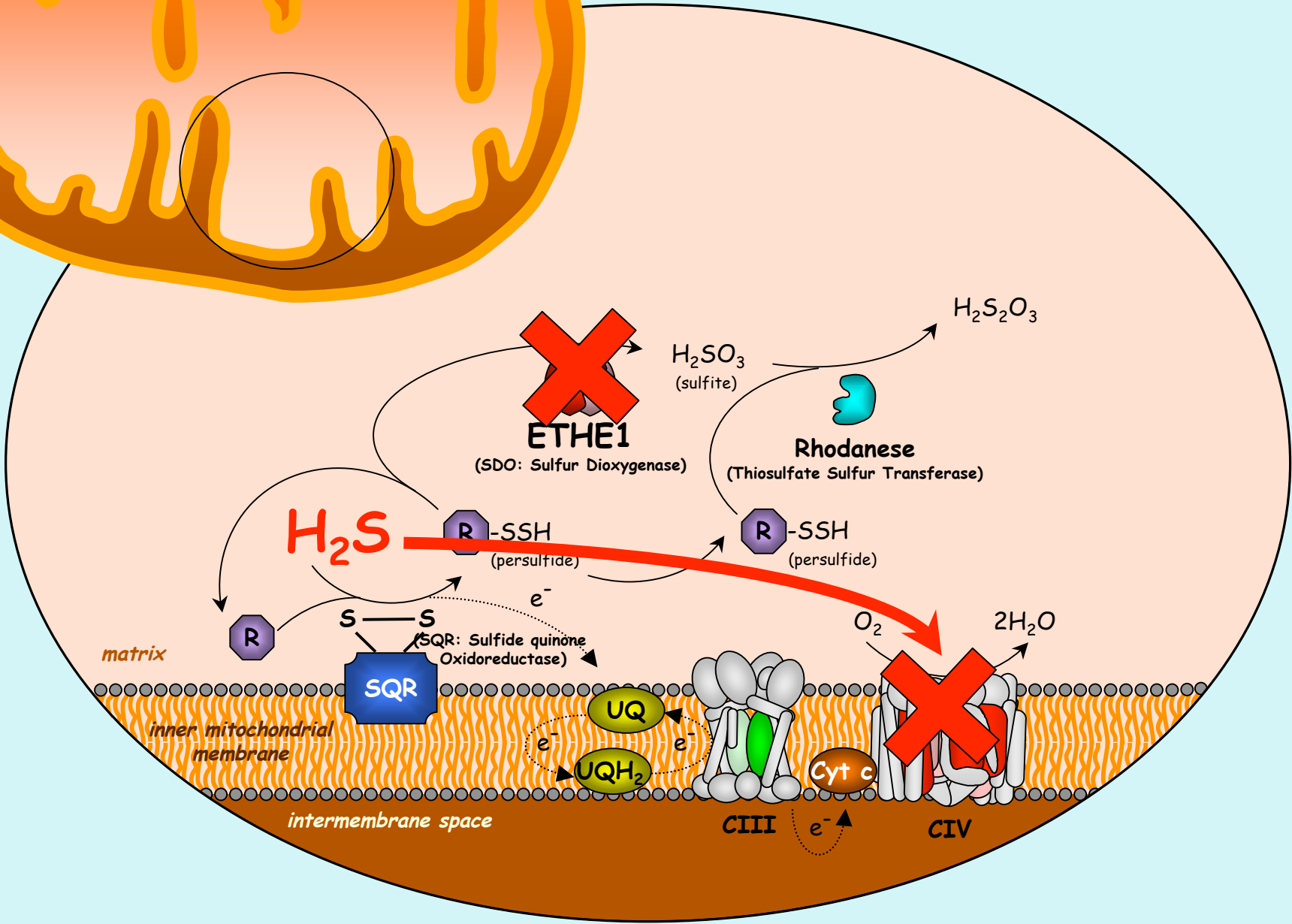
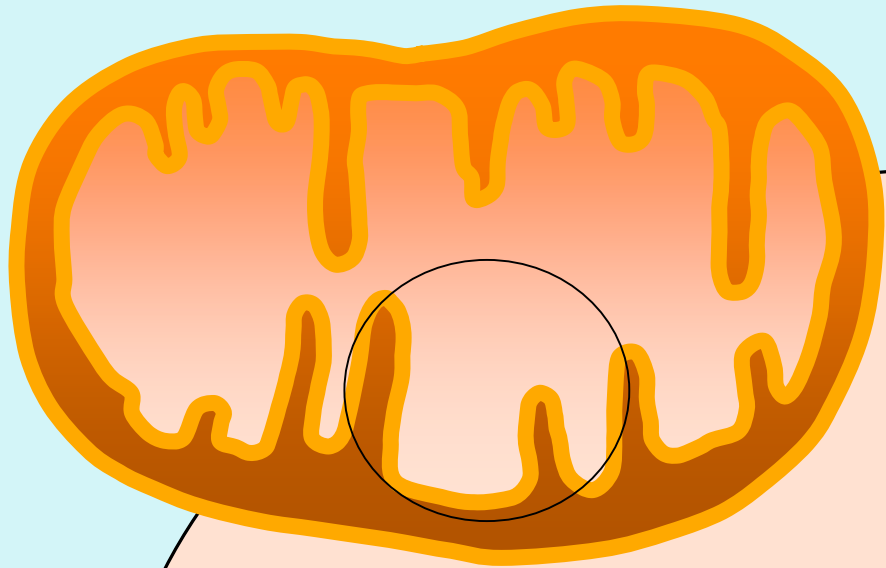
H_2S (sulfide) is the first inorganic substrate for mitochondrial respiratory chain in mammals





SDO activity in liver of *ETHE1* $-/-$ homogenates

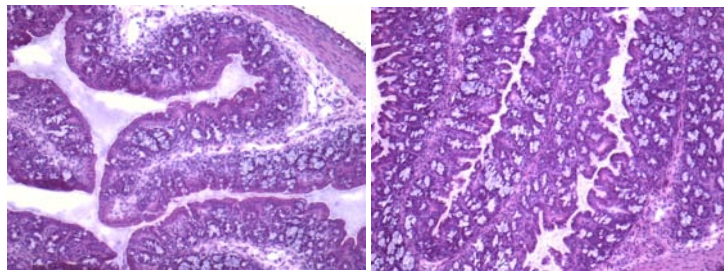
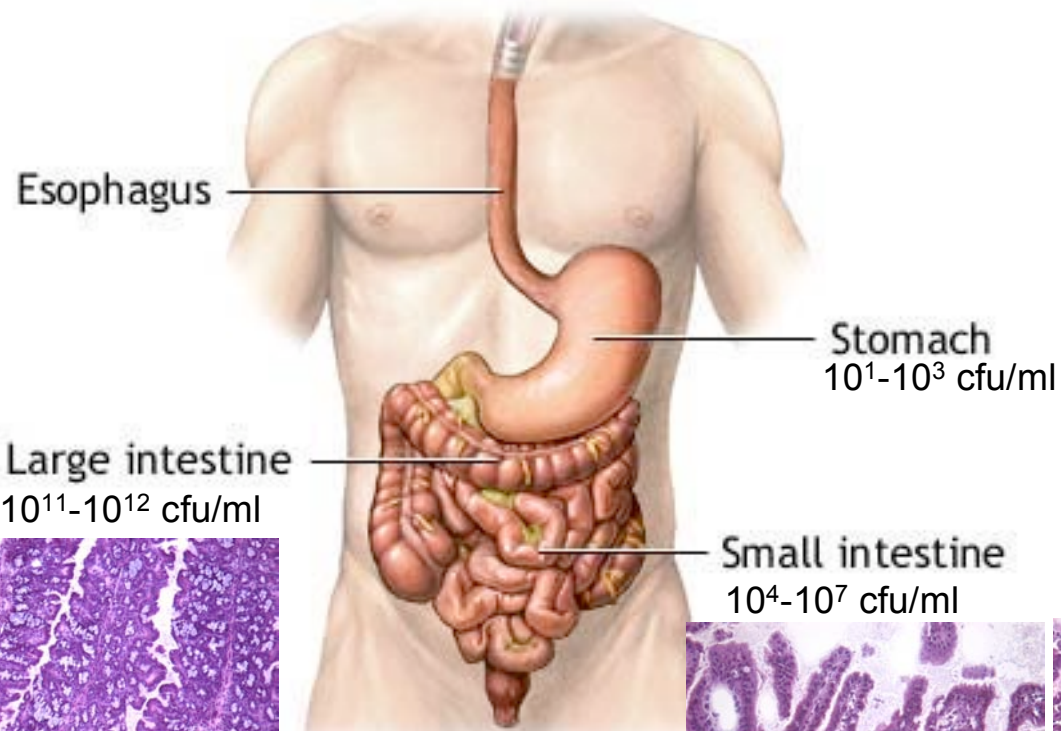




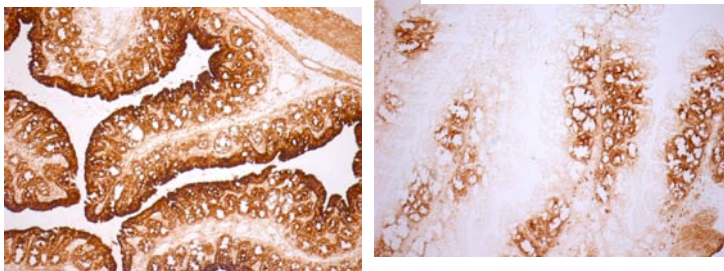
Conclusions 2

- *ETHE1*, encodes a mitochondrial sulfur dioxygenase that takes part in aerobic energetic exploitation of, and detoxification from, H_2S
- EE is the first example of a mitochondrial disorder caused by genetically determined poisoning of the respiratory chain
- The creation of organ-specific conditional *KO* animals, can be useful to identify the main source of H_2S generation in EE, e.g. exogenous absorption from the gut flora vs. endogenous production

H₂S-producing gut flora and mucosal COX



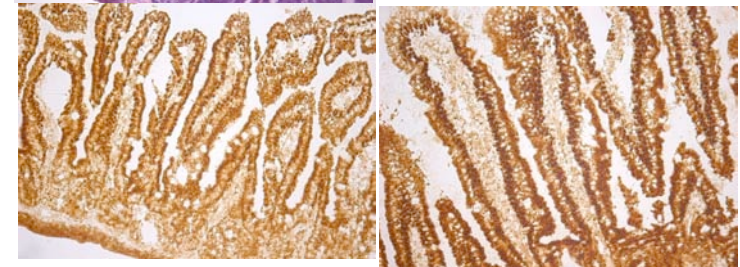
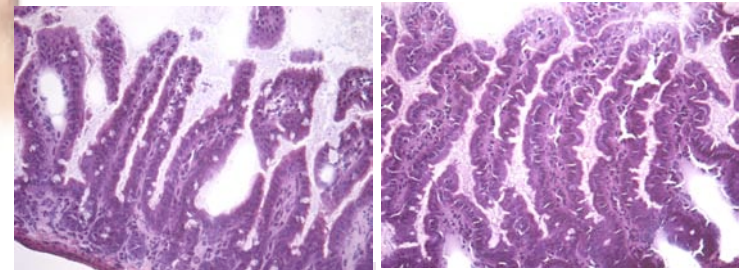
← H&E →



WT

KO

← COX →



KO

WT

- The toxic mechanism underpinning Ethylmalonic Encephalopathy makes effective therapy a realistic goal: for instance antibiotic control of H₂S-producing bacterial flora vs. H₂S neutralization using GSH as a sulfide acceptor

Final considerations and future perspectives

A specific treatment against the proliferation of H_2S -producing anaerobic bacterial flora in the large intestine leads to substantial improvement of the clinical conditions in experimental murine EE

- (1) the diffusion of H_2S through the colonic mucosa could be a major, but not the only cause of disease in *Ethe1*^{-/-} mice and patients
- (2) the restriction of bacterial production of H_2S and its neutralization by NAC, may be therapeutically beneficial in the mouse, and possibly human, disease condition.



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CENTRO PER LO STUDIO DELLE MALATTIE MITOCONDRIALI PEDIATRICHE

Fondazione Pierfranco e Luisa Mariani

THANK YOU!!

Unit of Molecular Neurogenetics



Massimo Zeviani



Barbara Garavaglia



Eleonora Lamantea



Carlo Viscomi



Ivano DiMeo



Rossana Mineri



Egill Briem

Collaborations

Tatjana Hildebrandt

Mike Levitt

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Gigliola Fagiolari

Cecilia Tiveron

All the clinicians world-wide
who referred the patients to
our Centre