ROLE OF CYCLOOXYGENASE 2 (COX-2) IN LIVER MITOCHONDRIAL FUNCTION AFTER ISCHEMIA-REPERFUSION INJURY

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INTRODUCTION

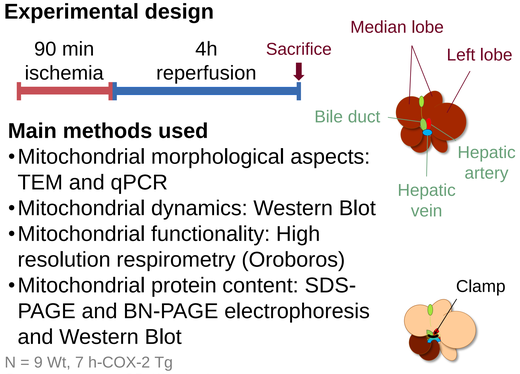
Cyclooxygenase 2 (COX-2) is a key enzyme in the synthesis of prostaglandins, however is only expressed in those situations in which dedifferentiation or proliferation occur. Using genetically modified mice to selectively express human COX-2 (hCOX-2 Tg) in hepatocyte, we demonstrated an increased tolerance to ischemia-reperfusion injury (IRI) with an increased functional recovery, a diminished cellular necrosis and less inflammation (1). It is known that mitochondria have a major role in IRI damage by increasing oxidative stress, decoupling metabolic state and inducing apoptosis.

AIM

In this work, we analyzed different aspects in order to characterize the impact of COX-2 in mitochondrial function after IRI.

MATERIALS AND METHODS

Experimental design



Main methods used

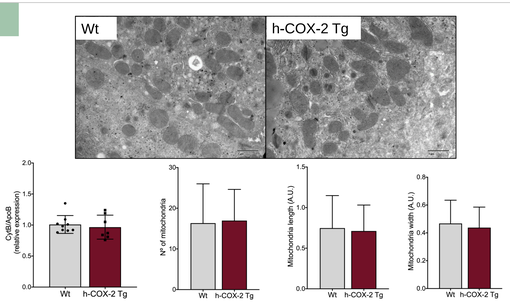
- Mitochondrial morphological aspects: TEM and qPCR
- Mitochondrial dynamics: Western Blot
- Mitochondrial functionality: High resolution respirometry (Oroboros)
- Mitochondrial protein content: SDS-PAGE and BN-PAGE electrophoresis and Western Blot

N = 9 Wt, 7 h-COX-2 Tg
Statistics: mean±SD (Student's t-test or One-way ANOVA, * p<0,05, ** p<0,001)

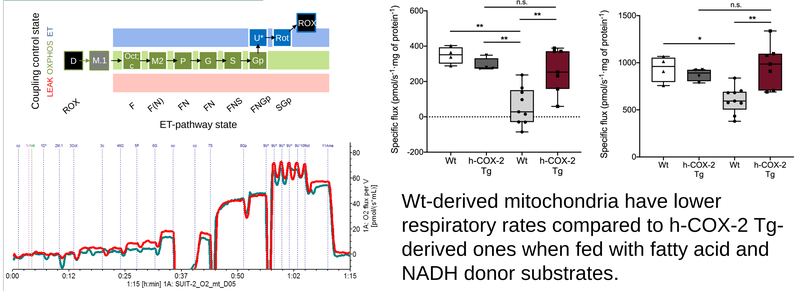
RESULTS

Mitochondrial morphology

No major differences where observed in mitochondrial number, morphology and distribution across the tissue, when compared Wt and h-COX-2 Tg liver sections.

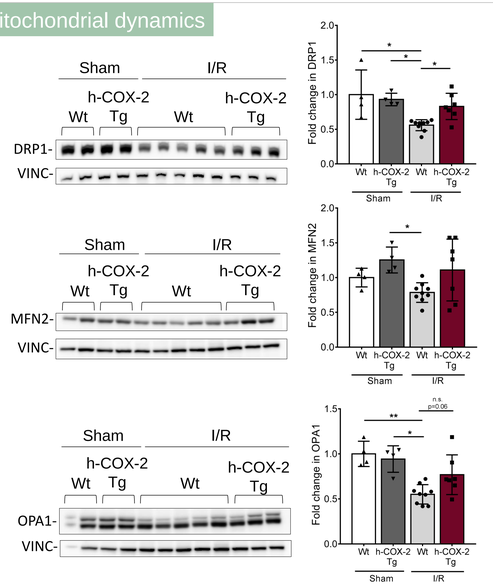


Mitochondrial functionality



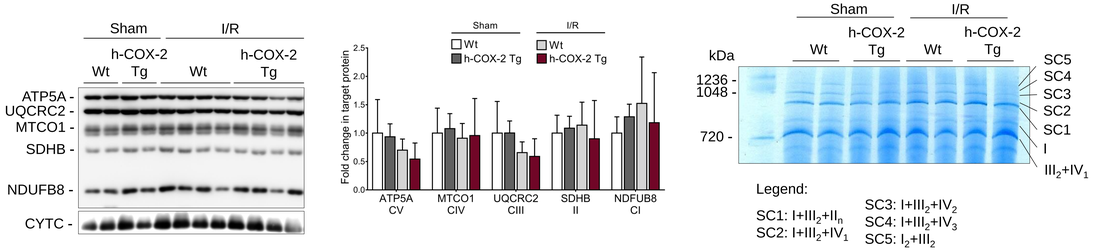
Wt-derived mitochondria have lower respiratory rates compared to h-COX-2 Tg-derived ones when fed with fatty acid and NADH donor substrates.

Mitochondrial dynamics



Principal fusion and fission mitochondrial proteins where under-expressed in Wt compared to h-COX-2 after IR.

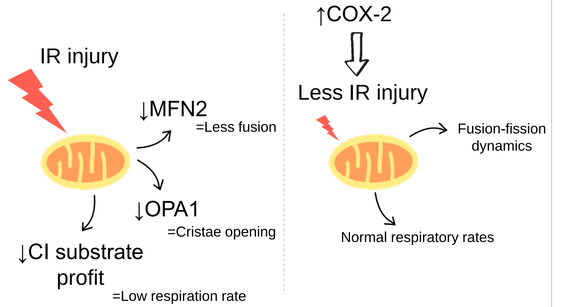
Mitochondrial protein content



The Individual expression of ETC complexes is no different between conditions and/or genotypes. No difference is observed in the assembly of ETC complexes into super-complexes.

CONCLUSIONS

These data suggest a new link between COX-2 and mitochondria, which might contribute to the protective effects of COX-2 against IRI.



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(1) Motiño O et al. Protective Role of Hepatocyte Cyclooxygenase-2 Expression Against Liver Ischemia-Reperfusion Injury in Mice. Hepatology. 2019 Aug;70(2):650-665. doi: 10.1002/hep.30241.

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