Universität Rostock Traditio et Innovatio

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Effects of 24-*nor*-ursodeoxycholic and ursodeoxycholic acid on mitochondrial dynamics in the liver of *Schistosoma mansoni* infected mice

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Introduction

Hepatic fibrosis and granuloma formation, as a consequence of tissue entrapped eggs, characterize the pathology of *Schistosoma mansoni* (*S.m.*) infection. We have previously shown that **24-*nor*-ursodeoxycholic acid** (*nor*UDCA) has pronounced **anti-inflammatory** and **anti-fibrotic** effects in *S.m.* induced liver injury. The mechanism behind this effect is not yet fully understood. *S.m.* infection affects mitochondrial membrane potential, gene expression of mitochondrial biogenesis, dynamics (fusion/fission), and extrinsic and intrinsic apoptosis pathways. Beside regulation of cellular homeostasis, energy production, and oxidative stress, mitochondria are crucial players in regulation of innate and adaptive immune responses.

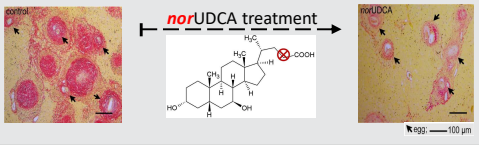
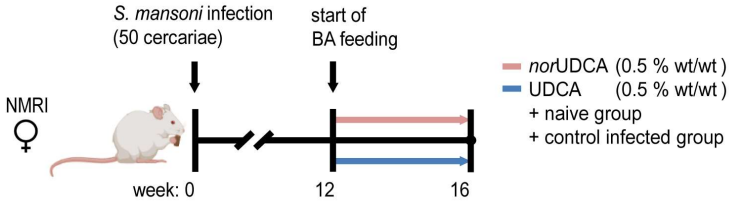


Fig. 1: ***Nor*UDCA ameliorates liver histology of chronically *S.m.* infected NMRI mice** (female, 16 weeks after infection with 50 cercariae; receiving control, ursodeoxycholic acid (UDCA), or *nor*UDCA enriched diet for 4 weeks (SR staining)).

Experimental design



Isolation of mitochondria → protein concentration measurement → High Resolution Respirometry (Oroboros Oxygraph) → **SUIT protocol**: substrate, uncoupler, inhibitor titration

Isolation of RNA from the liver tissue → Reverse Transcription → **qPCR analysis**: expression of mitochondrial fusion and fission genes

Target question: Are the *nor*UDCA-exerted beneficial effects on hepatic fibrosis in murine schistosomiasis based on balancing mitochondrial dysfunction?

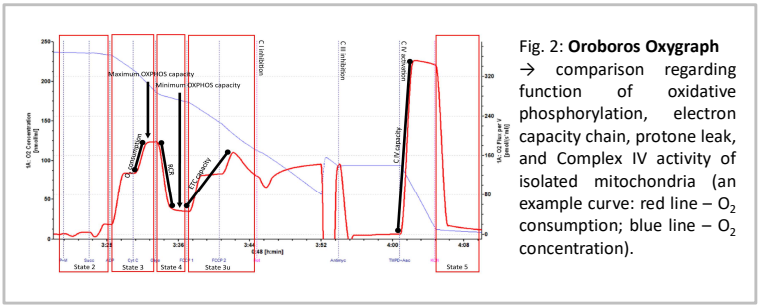


Fig. 2: **Oroboros Oxygraph** → comparison regarding function of oxidative phosphorylation, electron capacity chain, protone leak, and Complex IV activity of isolated mitochondria (an example curve: red line – O_2 consumption; blue line – O_2 concentration).

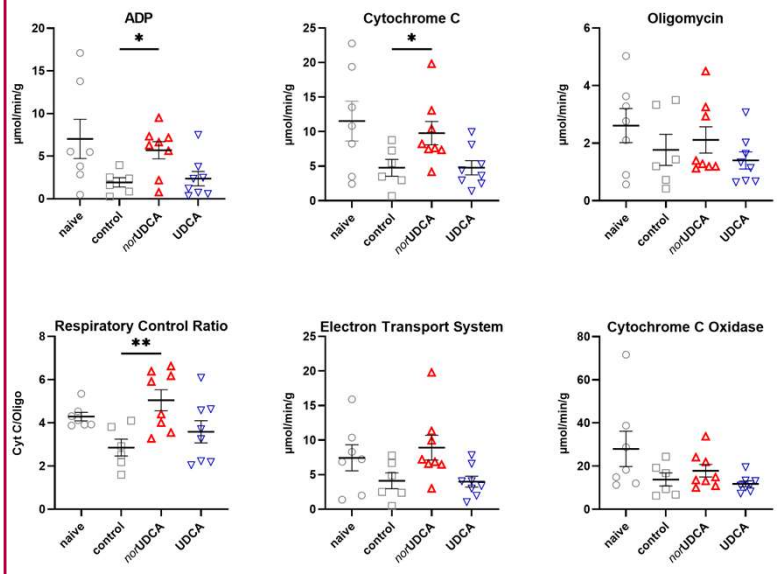


Fig. 3: **Mitochondrial respiration** → Decreased respiratory function in mitochondria isolated from livers of *S.m.* infected groups has been detected by high-resolution respirometry analysis. Concurrently, the benefical effect of *nor*UDCA was find in all measured stages of OXPHOS and ETS, when in the ADP, Cytochrome C, and RCR stages was O_2 consumption increased significantly. For the statistical analysis of treated groups in comparison to infected group was used unpaired t test or Mann-Whitney test if necessary (*p < 0.05; **p < 0.01). Data are shown as mean ± SEM.

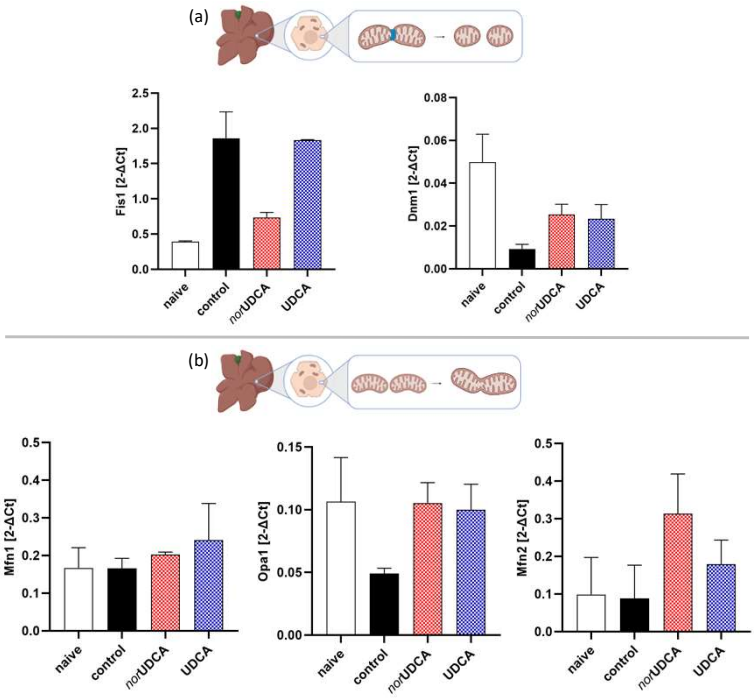
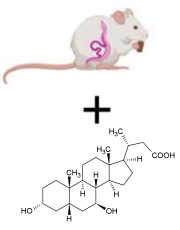


Fig. 4: **Mitochondrial dynamics** → Mitochondrial fusion and fission gene expression analysis of the liver tissue from *S.m.* infected and treated animals shows: trends of (a) decreased fragmentation and (b) improved fusion of hepatocyte mitochondria in *S.m.* infected liver after bile acids treatment; measured Ct values are normalised to GAPDH as a housekeeping gene. Data are shown as mean ± SEM.

Conclusion



- *S.m.* infected animals display decreased O_2 consumption and unbalanced mitochondrial dynamics → indicates **mitochondrial dysfunction**
- Treatment by *nor*UDCA has **beneficial effect on respiration** of isolated mitochondria after infection by *S.m.*
- Mainly *nor*UDCA **improves dynamics** of hepatic mitochondria after disbalanced function caused by *S.m.* infection