Transcriptomic and metabolic insights into hyperammonemia:
the complementary therapeutic roles of toll-like receptor 4 inhibitor and ornithine phenylacetate

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Introduction

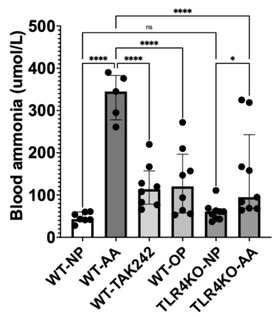
- Hyperammonemia is a critical issue in patients with liver diseases, where elevated ammonia levels predict mortality and a reduction in ammonia levels is linked to improved survival.
- Despite this, no effective therapies are available, highlighting an unmet clinical need.
- Previous studies have identified toll-like receptor 4 (TLR4) as a potential therapeutic target for hyperammonemia by modulating mitochondrial function[1,2].

Aim

- To explore the therapeutic potential of **TLR4 antagonist (TAK-242)** and the **ammonia scavenger Ornithine Phenylacetate (OP)** through transcriptomic analysis to identify pathways for targeted treatment strategies.

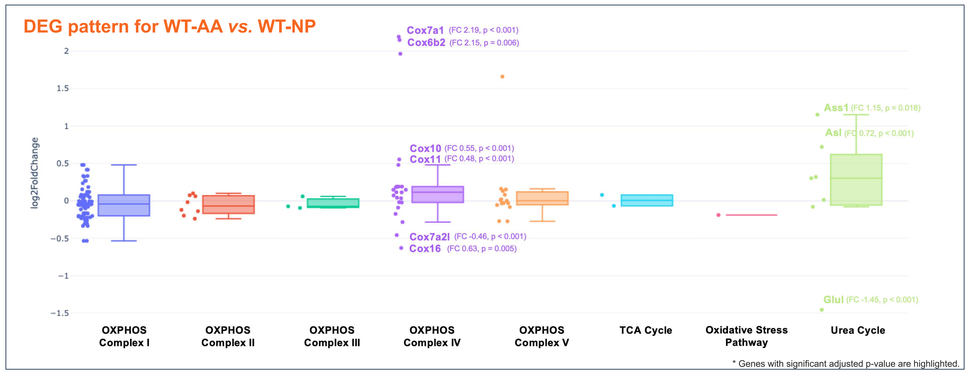
Methods

- A mouse model of chronic hyperammonemia (WT and TLR4KO) was studied[1,2].
- Ammonia levels were significantly elevated in WT-AA mice and both **TAK-242 and OP treatment effectively reduced ammonia levels**.
- Liver transcriptomic analysis was performed using RNA sequencing to investigate key metabolic pathways, including the urea cycle, tricarboxylic acid cycle, oxidative phosphorylation (OXPHOS) complexes, and oxidative stress pathways.

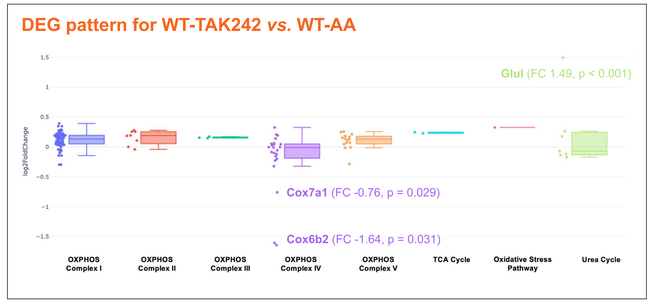


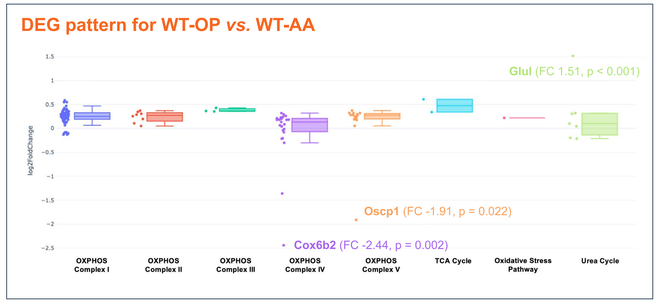
Main findings

1 Hyperammonemia significantly impacted the OXPHOS complex IV and urea cycle.

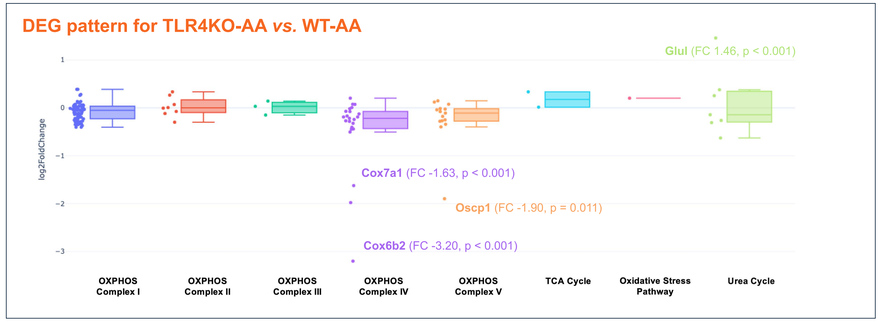


2 Both TAK-242 and OP treatment reverted Cox6b2 and Glul expression. Additionally, Cox7a1 was downregulated in the TAK-242 group, while Oscp1 was downregulated in the OP group indicating distinct mechanisms of action for each treatment.





3 TLR4KO mice exhibited gene expression changes consistent with a combined effect of TAK-242 and OP treatment.



Abbreviations: AA, amino acid; COX, Cytochrome C oxidase; DEG, differentially expressed gene; KO, knock-out; NP, normal protein; OP, Ornithine Phenylacetate; TAK242, toll-like receptor 4 inhibitor; TLR4KO, TLR4 knock-out; WT, wild-type

Conclusions

- TLR4 plays an important role in mediating metabolic and mitochondrial dysfunction induced by hyperammonemia.
- The shared and distinct gene expression changes observed with TAK-242 and OP treatments highlight complementary mechanisms, which could be leveraged for more effective therapeutic strategies.

References

1. Kerbert A et al. *Sci. Adv.* 2025;11(10):eado1648
2. Sriphoosanaphan S et al, EASL Congress 2024

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