ATP Synthase Assembly Factor 2 is Essential for Maintaining Heart Function

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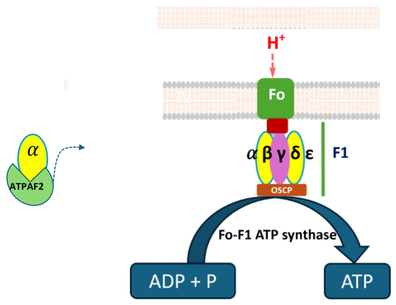
Introduction

- The heart is an energy-demanding organ, even more so in heart failure, leading to an ATP deficit
- ATP is made by ATP synthase, a rotary enzyme in the mitochondria made up of the F0-F1 complex assembly.
- F1 complex gets assembled from smaller subunits of 3 α, 3 β, 1 **ε**, 1 **Δ**, and 1 γ with the help of ATP synthase assembly factors.
- Yeast studies documented that the F1 complex is assembled by ATPase assembly factor 1 (ATPAF1) and ATAF2. However, the roles of ATPAFs in mammals remain largely unknown.
- We previously studied ATPAF1 KO mice and indicated that ATPAF1 plays an essential role in cardiac structure/function.
- Because ATPAF2 KO causes embryonic lethality in mice, we employed the conditional gene targeting strategy to investigate the role of ATPAF2 in the adult heart.

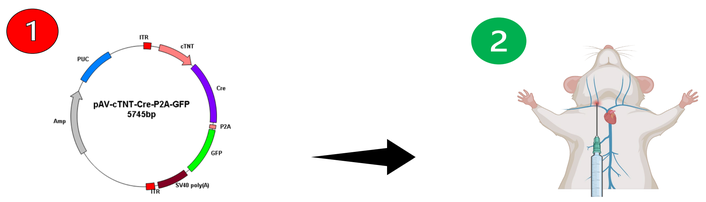


ATP synthase F0-F1 complex in the electron transport chain

Objective

To test the hypothesis that ATPAF2 is essential in maintaining bioenergetics and thus cardiac performance in adult mice

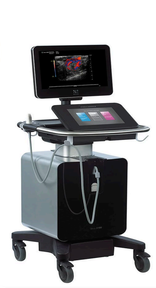
Methods



Adeno-associated vector serotype 9 with cardiac troponin promoter containing Cre (control), with no Cre (experimental)

ATPAF2$^{fl/fl}$ mice were injected with AAV9-cTnT with Cre (experimental) and without Cre (Control) through Jugular vein injection at 10^12 GC/kg dose

Methods



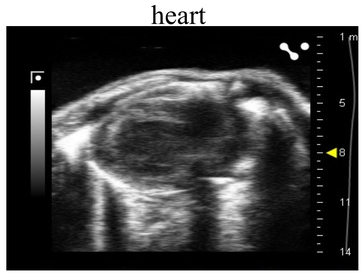
Left ventricle echocardiographic assessment and strain analysis through speckle tracking

Mitochondrial oxygen consumption was assessed using High-Resolution Respirometry using Oxygraph-2k OROBOROS

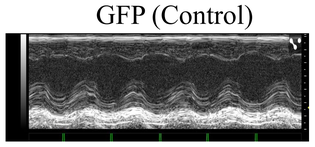
Results

1. ATPAF2 deletion impaired cardiac function

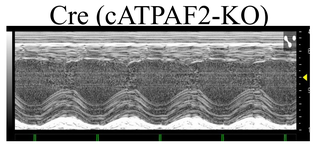
Representative B-mode image of the Left ventricle of a mouse heart

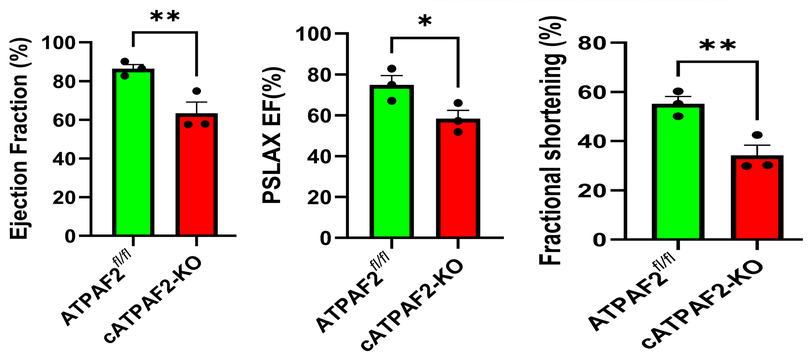


M-mode of a mouse with AAV9-cTnT-GFP (Control)



M-mode of a mouse with AAV9-cTnT-Cre (cATPAF2-KO)





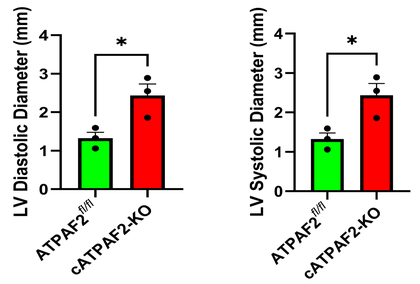
Echocardiographic assessment revealed that cATPAF2-KO mice exhibit a significant reduction in LV ejection fraction and fractional shortening compared to control mice.

Conclusions

- The mice show a significant increase in systolic and diastolic function when cATPAF2 factor is removed
- These findings suggest that cATPAF2 is a necessary and essential factor in maintaining cardiac function, potentially improving ATP synthase bio-assembly.

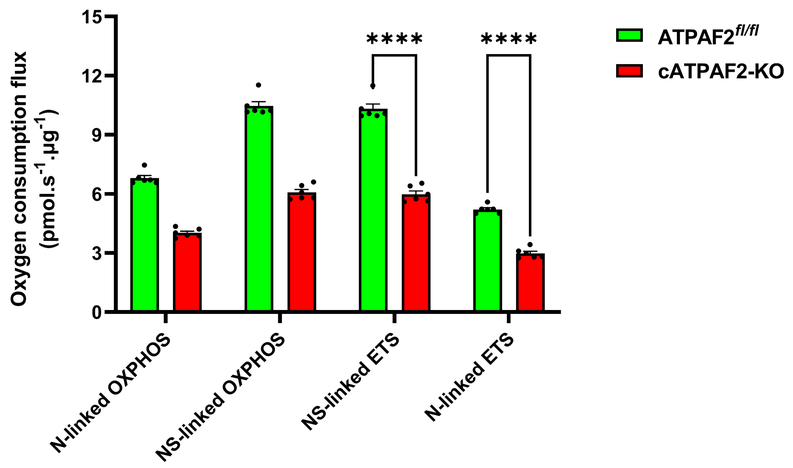
Results

2. ATPAF2 deletion altered LV systolic and diastolic dimensions



- cATPAF2-KO mice have a significant increase in left ventricular systolic and diastolic dimensions compared to control mice.
- Compared to Control mice, cATPAF2-KO mice exhibited an increase in left ventricular systolic and diastolic volume

3. Cardiac mitochondrial function was impaired in adult mice with cardiac-specific ATPAF2 KO



Mitochondrial function was assessed using the high resolution respirometry (Oroboros O2k) on mitochondrial isolated from the heart of ATPAF2-KO and control mice. Mitochondria from cATAF2-KO hearts exhibit a significant reduction in mitochondrial oxygen consumption driven by Complex I and Complex I+II during oxidative phosphorylation and the electron transfer system.

Future Directions

Further studies are required to fully understand the bioenergetic dysregulation from ATPAF2 deficiency and its role in pathological states such as heart failure

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