The role of macrophage migration inhibitory factor (MIF) in induced cardiac hypertrophy

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Hypertrophy

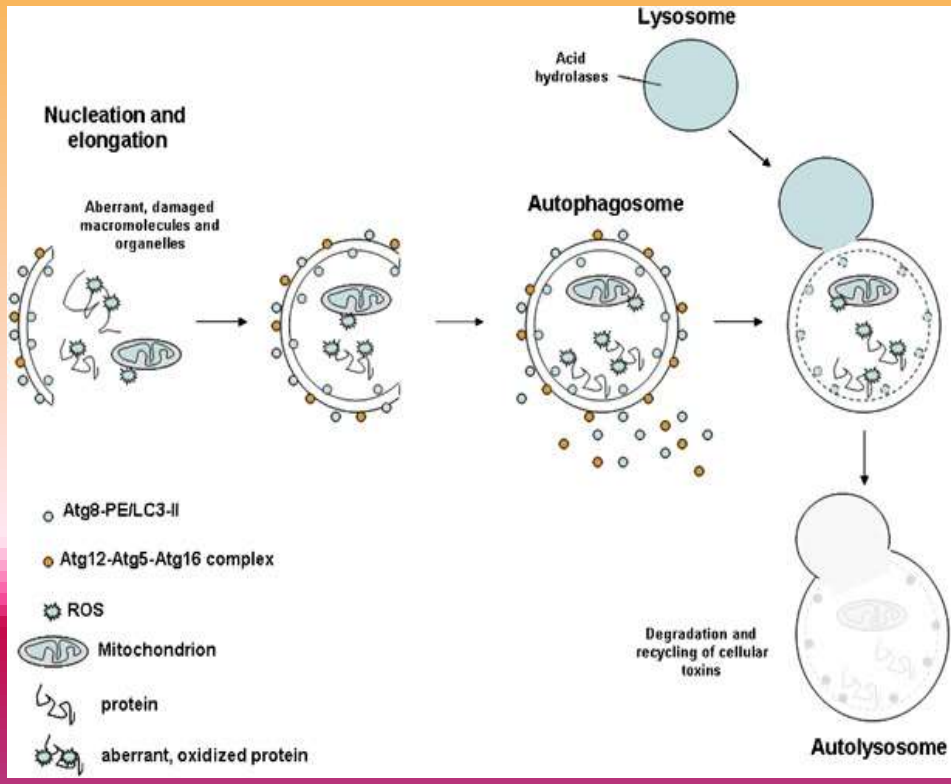
- Remodeling process to cope with the increased ventricular work load.
- Includes:

  Increase in protein synthesis

  Enlargement of cardiomyocyte
- Pathological hypertrophy results in irreversible heart dysfunction.

Autophagy

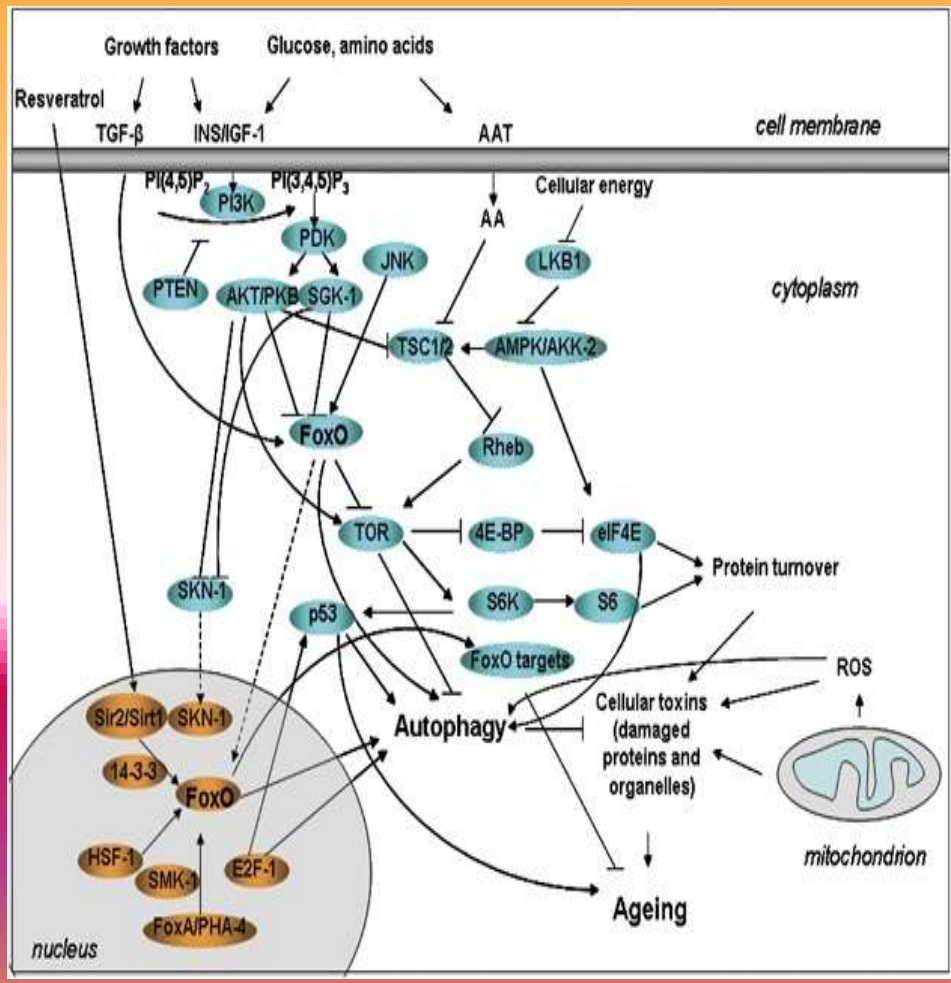
- Function is essential
- Under physiological conditions, autophagy is cytoprotective.
- However, pathological autophagy can be detrimental to the cell.
- Characterized by a double membrane structure.



Vellai, T. "Autophagy Genes and Aging." *Cell Death and Differentiation (2009) 16, 94–102.*

AMP-Activated Protein Kinase (AMPKα) Pathway

- AMPK is an upstream mediator of the autophagic flux.
- Macrophage migration inhibitory factor (MIF) can potentiate AMPK phosphorylation
- Recent research has indicated that AMPK protects the heart against hypertrophy



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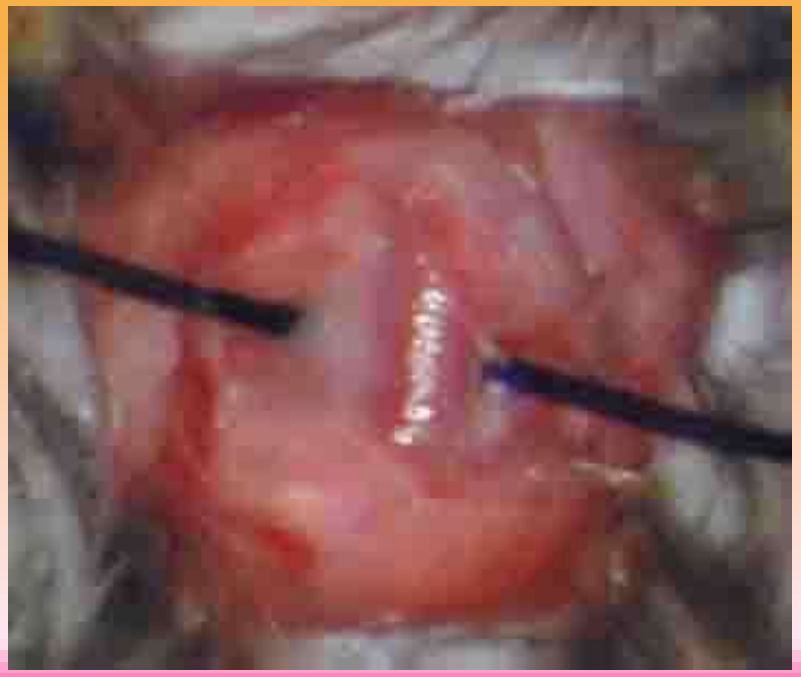
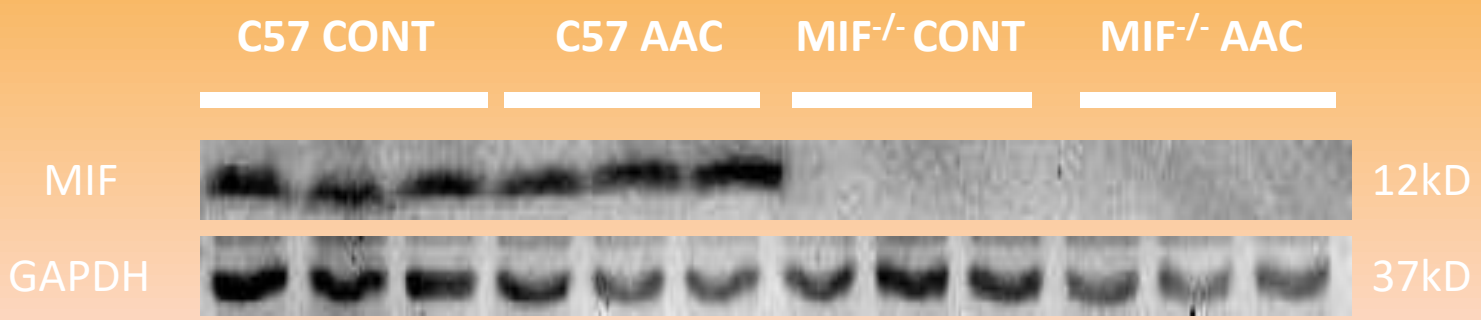
Abdominal Aortic Constriction (AAC)



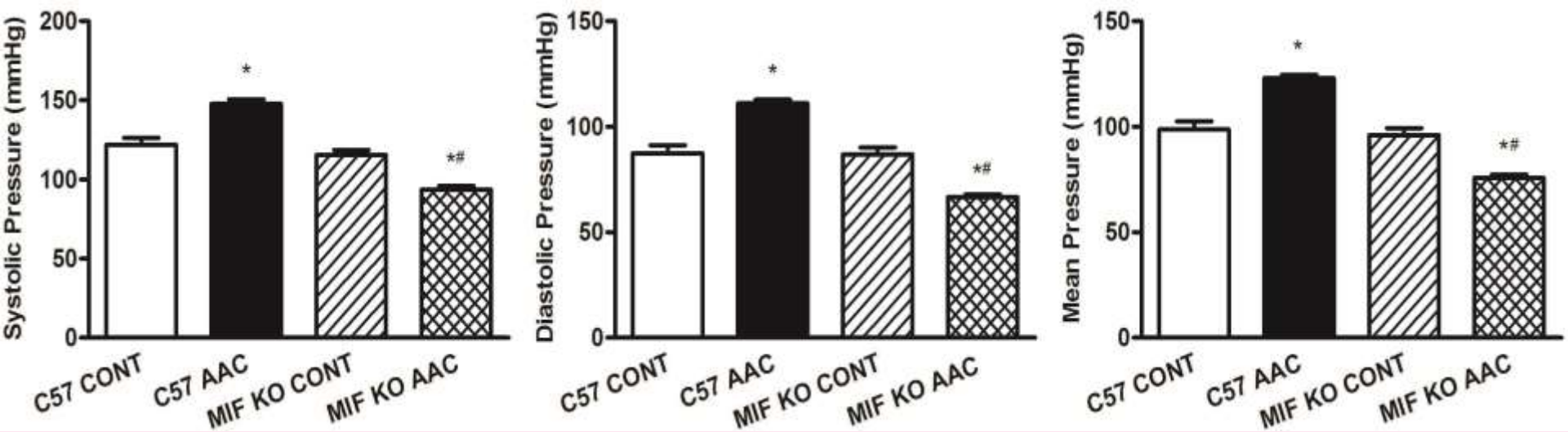
Wild type and MIF Knockout (KO) mice were subjected to the AAC surgery at three months old, and sacrificed one month later.

Results

AAC significantly induces MIF expression in C57 mice.

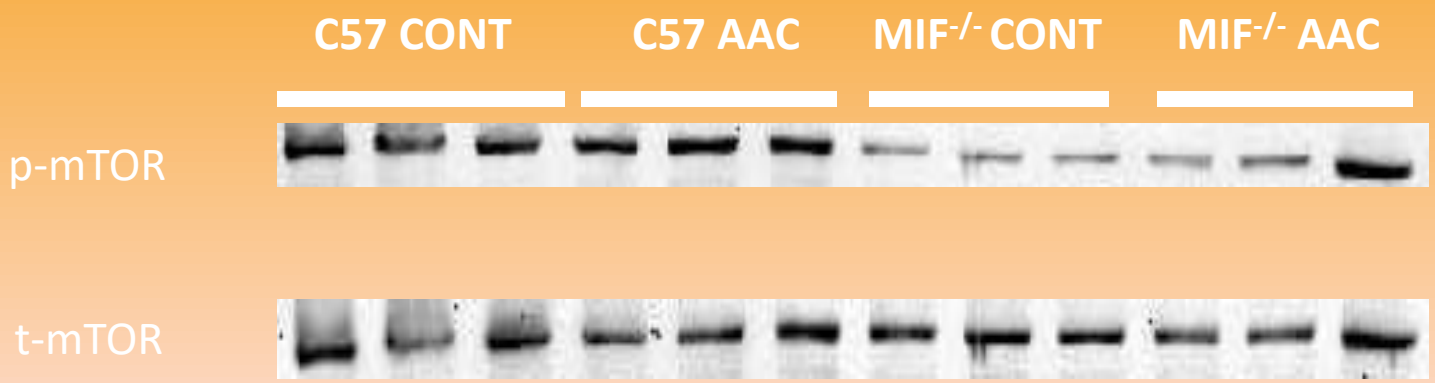


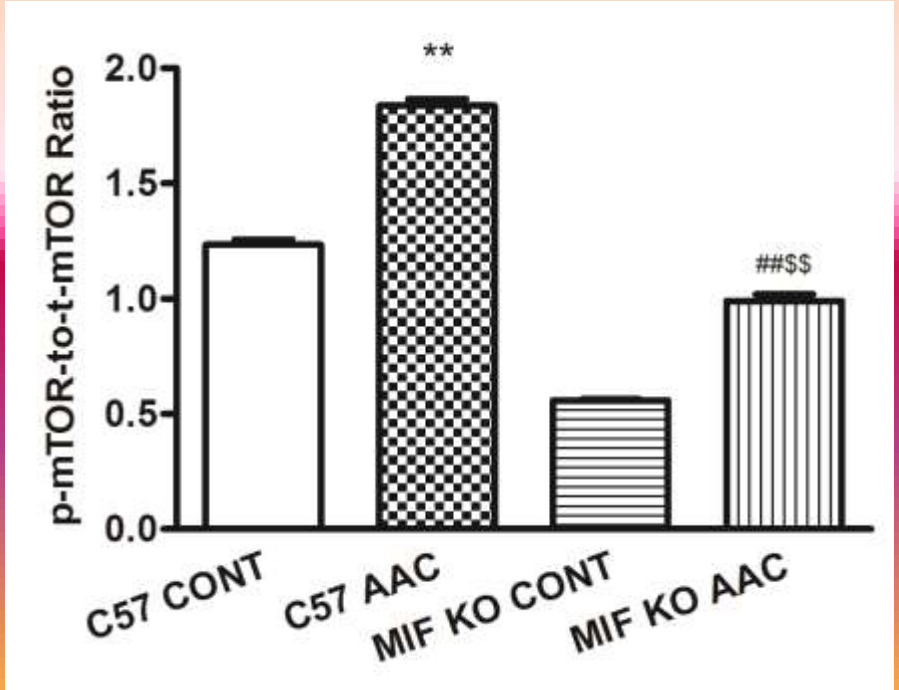
Blood Pressure



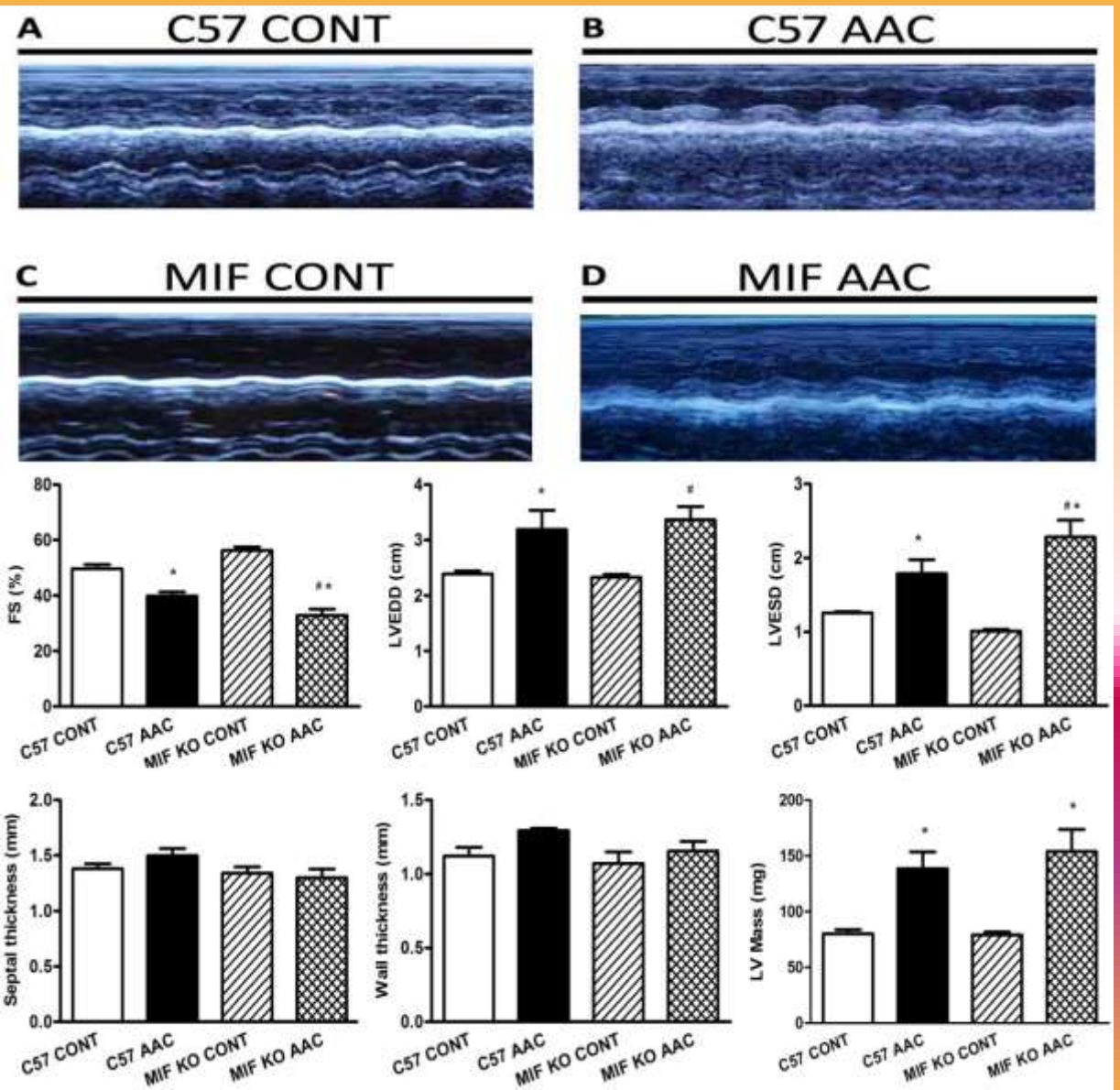
The AAC surgery significantly increased the blood pressure of the C57 mice, but not the MIF $^{-/-}$.

AAC significantly induces mTOR phosphorylation in C57 mice and MIF$^{-/-}$ mice.



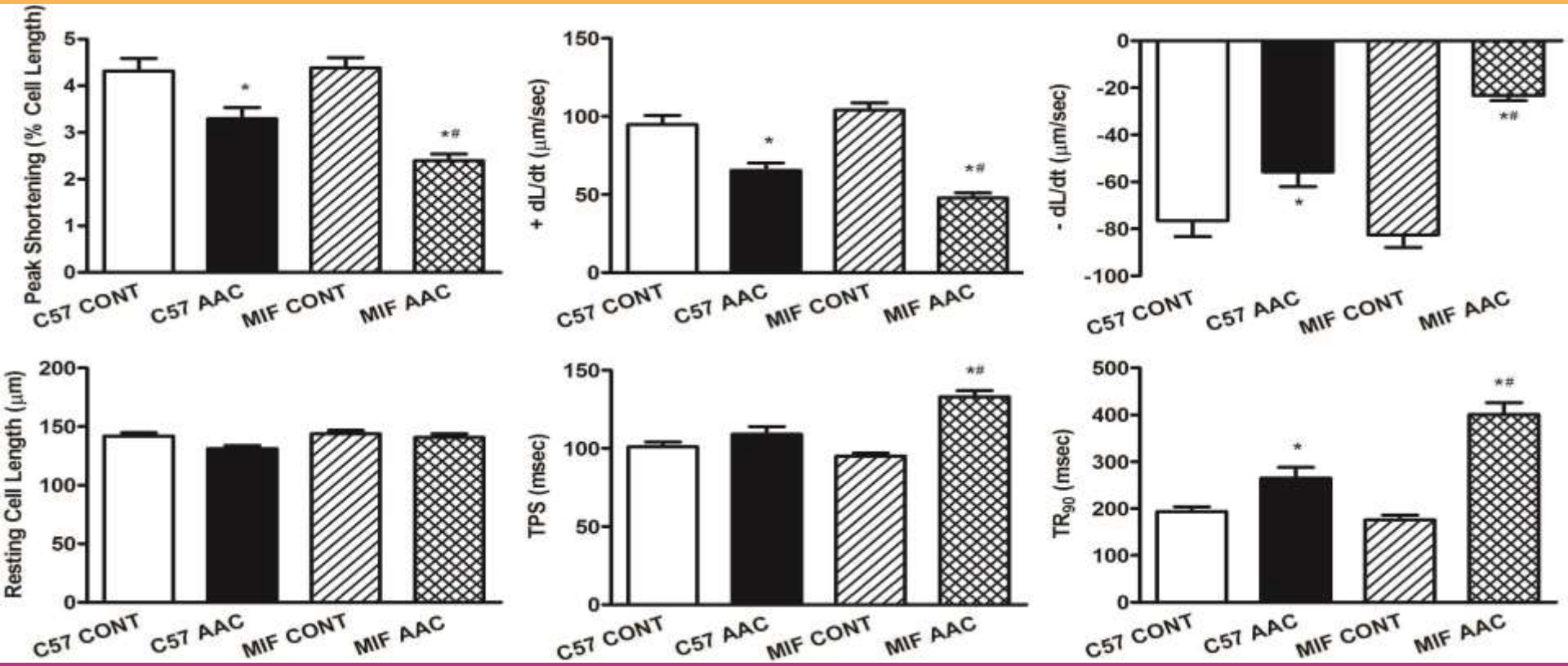


ECHO (Echocardiography)



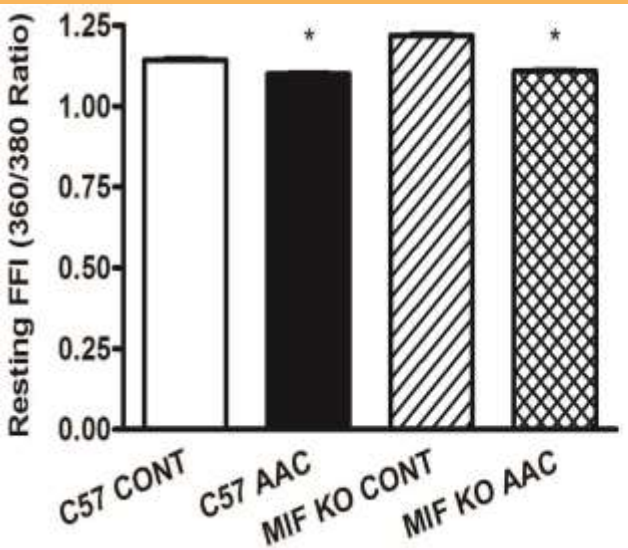
- The AAC surgery induced cellular changes in the cardiomyocytes, which was heightened by MIF$^{-/-}$.

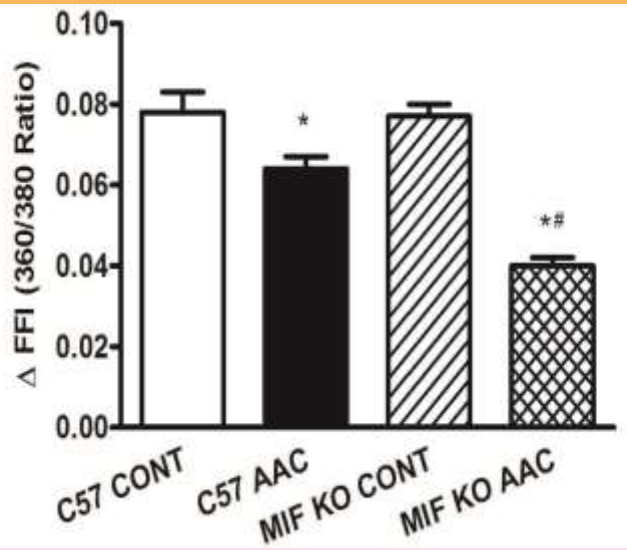
Isolated Cardiomyocyte contractile properties

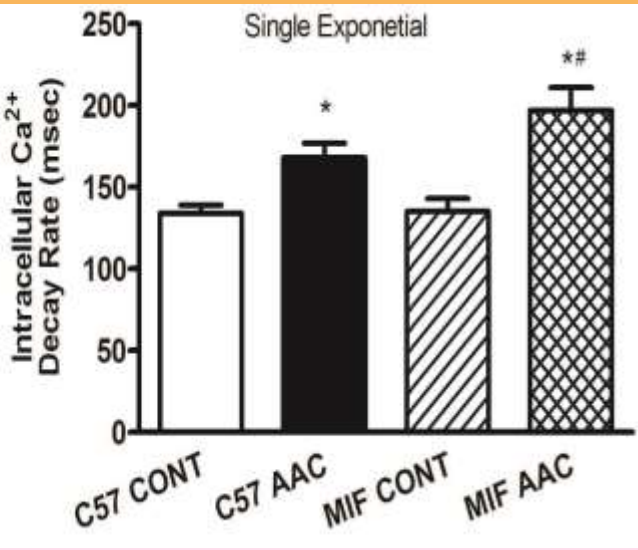


The contractile properties were compromised, and worsened by MIF$^{-/-}$, as a result of the AAC surgery.

Intracellular Calcium Handling

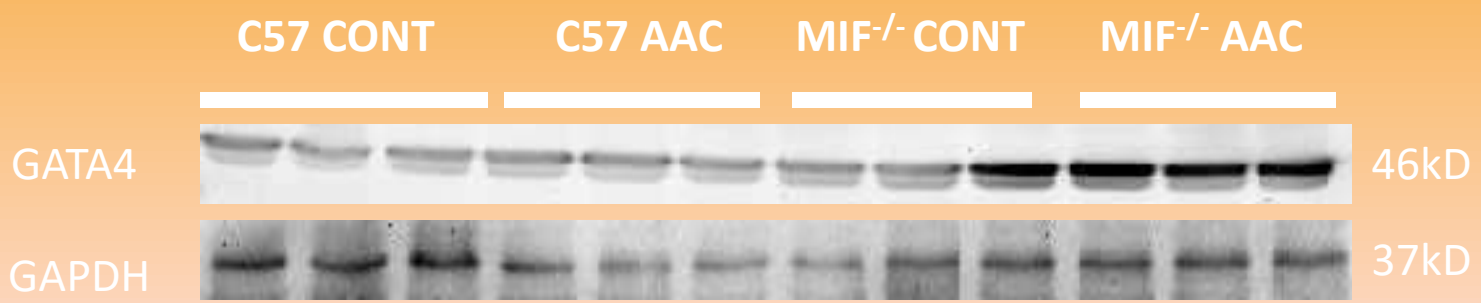




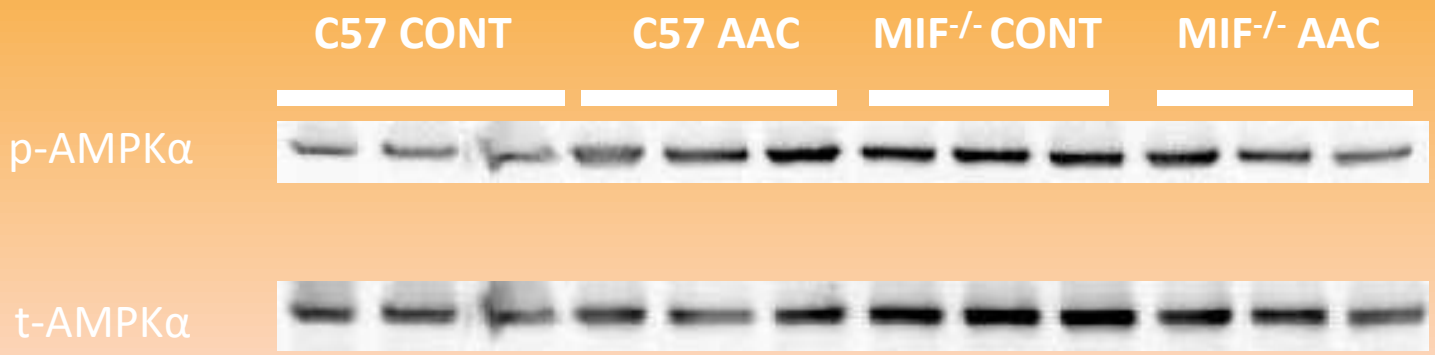


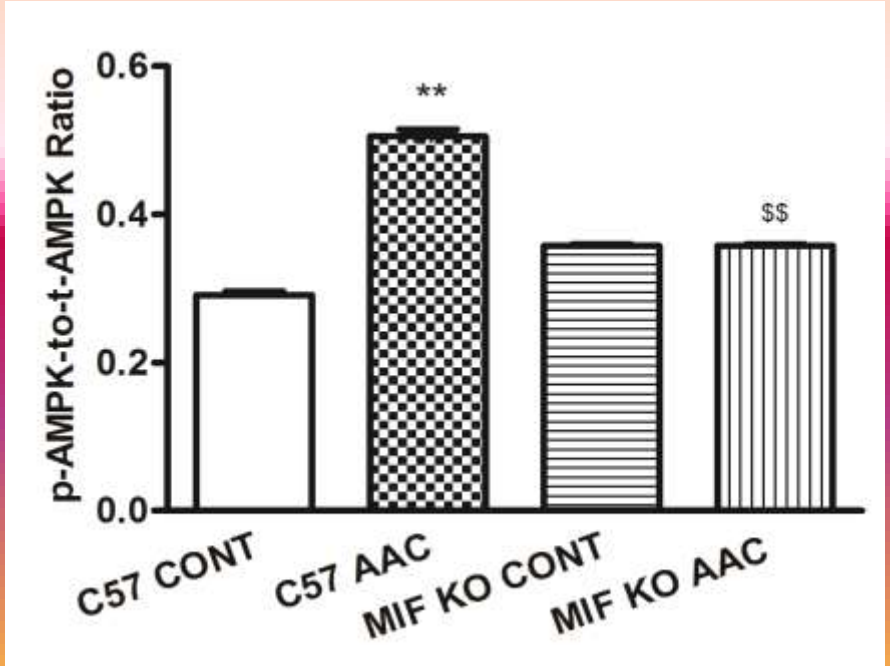
Both MIF $^{-/-}$ and C57 mice experienced irregular calcium regulation due to AAC.

AAC significantly induces GATA4 protein (hypertrophy marker) expression, which is worsened by MIF knockout.

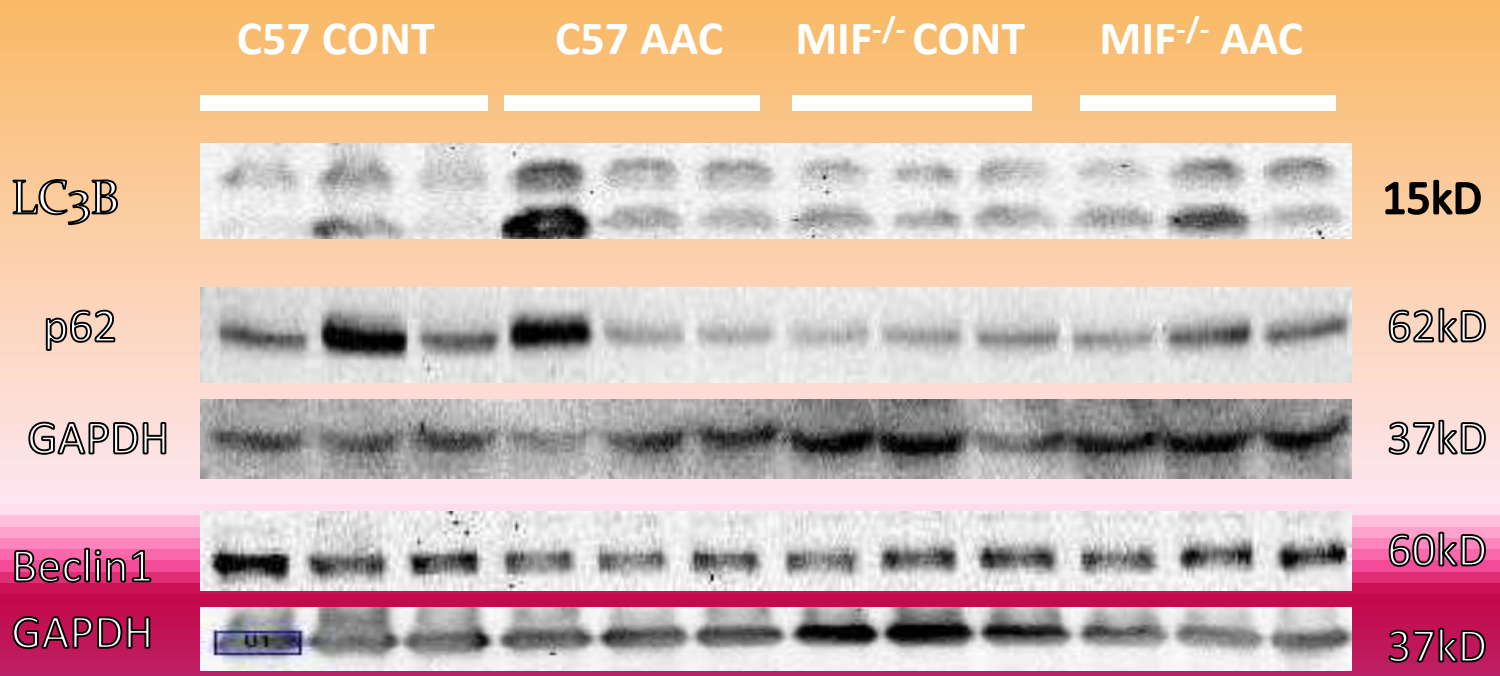


AAC significantly induces AMPK phosphorylation in C57 mice, but not in MIF$^{-/-}$ mice.





Autophagic flux is activated by AAC in C57 mice, but not in MIF$^{-/-}$ mice.



Summary and Conclusion

- MIF proved to be beneficial for the C57 mice.
- MIF KO mice demonstrated amplified signs of hypertrophy.

  C57 mice experienced the autophagic flux, while the MIF KO mice did not.
- The induction of autophagy was favorable for the hypertrophic C57 mice, but, the lack of, may have eventually proved fatal for MIF KO mice.

Thank you!

- Dr. Jun Ren
- Xihui (Alex) Xu
- C-CRAM researchers