National Heart Centre Singapore
SingHealth

SingHealth DUKE-NUS ACADEMIC MEDICAL CENTRE
CARDIOVASCULAR SCIENCES

Mitofusin 2 as a novel therapeutic target to prevent adverse post-myocardial infarction remodelling

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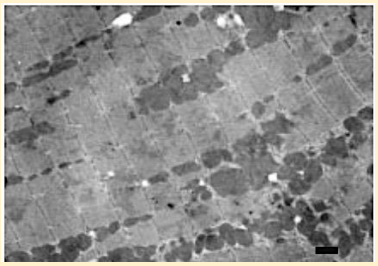
JCR Conference 2018, Busan, South Korea

Disturbances in the mitochondria

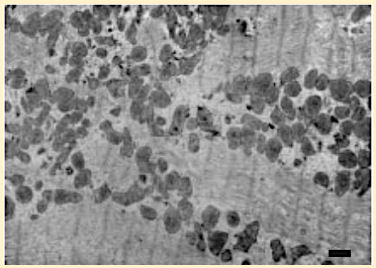
Disturbances in autophagy

Normal mitochondria

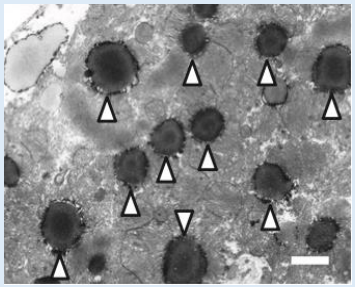


Oxidative stress
Ca^{2+} overload
IR

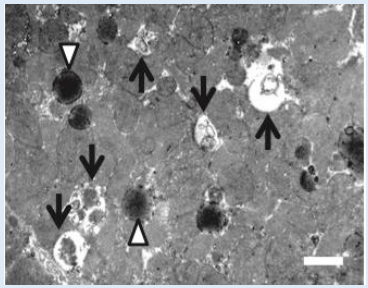
Mitochondrial fragmentation



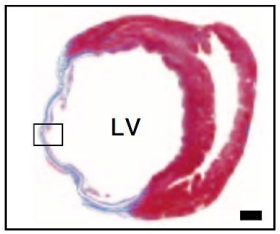
24 h post-MI



↑Lysosomes



↑*Autophagosomes*



Post-MI remodelling

Mitofusin 2 (Mfn2)

757 aa

Chandhok G. et al. (2018)

OMM
Endoplasmic reticulum

Leboucher, G. P. et al. (2012)
de Brito, O.M. et al. (2008)

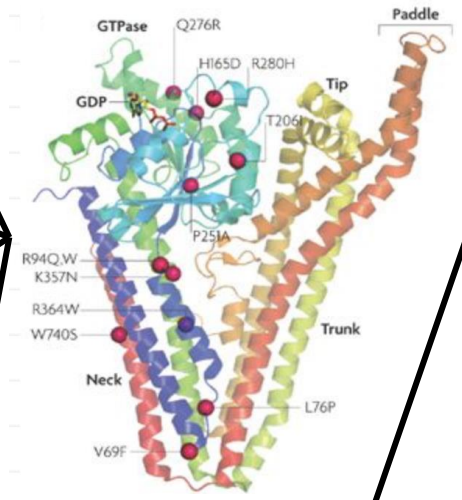
Morphology of Mitochondria (fusion)

Chen, Y. and Dorn, G.W. (2013)

Mitochondrial metabolism

Chen, Y. and Dorn (2013)

Mfn2



Transmembrane GTPase

Chandhok G. et al. (2018)

Tethering

de Brito, O.M. et al (2008)

Receptor

Chen Y. et al. (2013)

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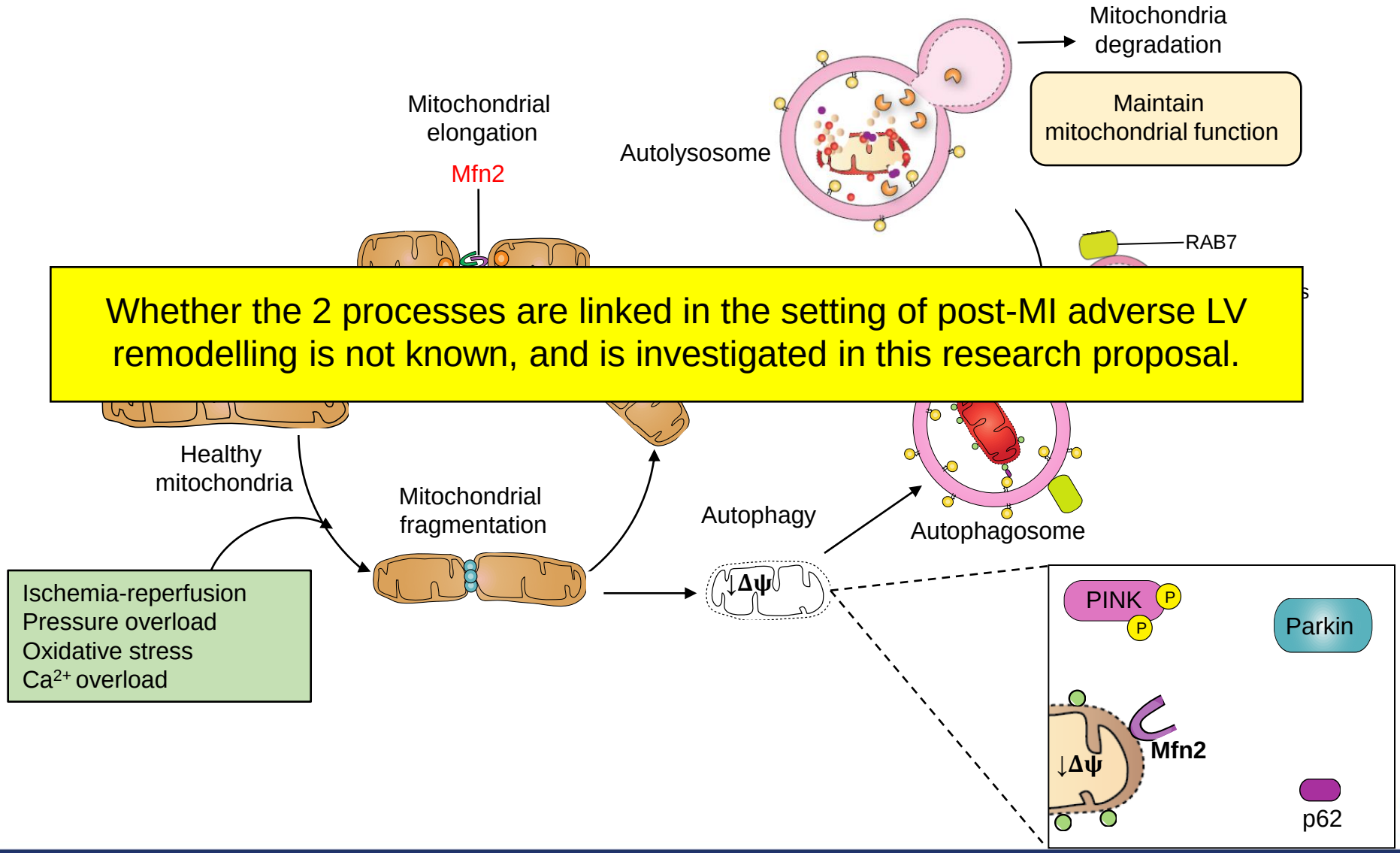
Mfn2 and autophagy in heart



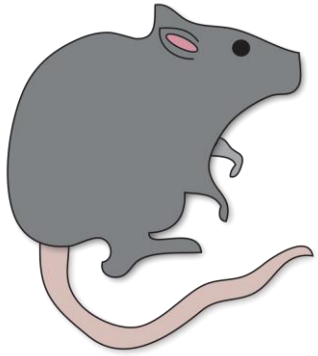
Scientific Rational

In this project, we investigate the role of Mfn2 as a novel therapeutic target for preventing adverse post-MI LV remodeling and heart failure.

- **Hypothesis:** A reduction in myocardial Mitofusin 2 levels following acute myocardial infarction results in an adverse left ventricular remodelling by inhibit autophagy flux.
- **Aim 1:** To investigate the role of Mfn2-ablation and autophagy in the heart.
- **Aim 2:** To investigate whether myocardial Mfn2 levels are reduced, and autophagy flux are inhibited during post-AMI adverse.

Materials and Methods

Myh6-nuclear-directed "turbo"Cre Mfn2 mice



Postnatal heart-specific ablation of Mfn2 using Myh6-directed nuclear-localized Cre

Genotype analyses

Control

Mfn2KO

Echocardiography

3
7
12
16
18
28
34
weeks-old

Histology

Immunoblot analyses

Control *Myh6-nuclear-directed "turbo" Cre^{-} Mfn2 $^{fl/fl}$*

Mfn2KO *Myh6-nuclear-directed "turbo" Cre^{+} Mfn2 $^{fl/fl}$*

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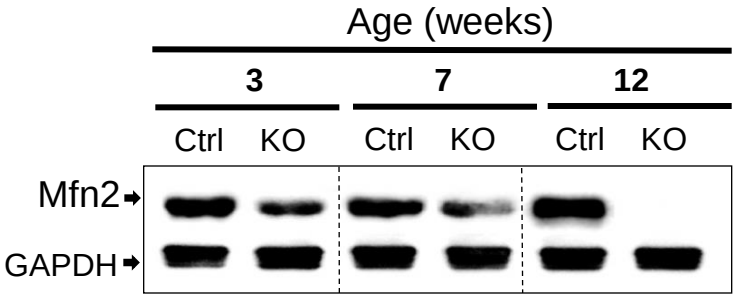
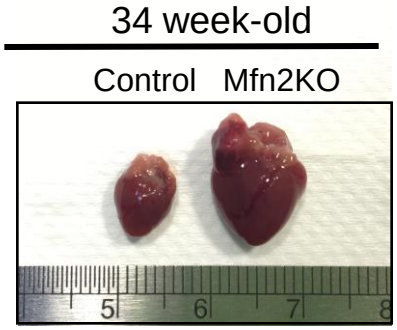
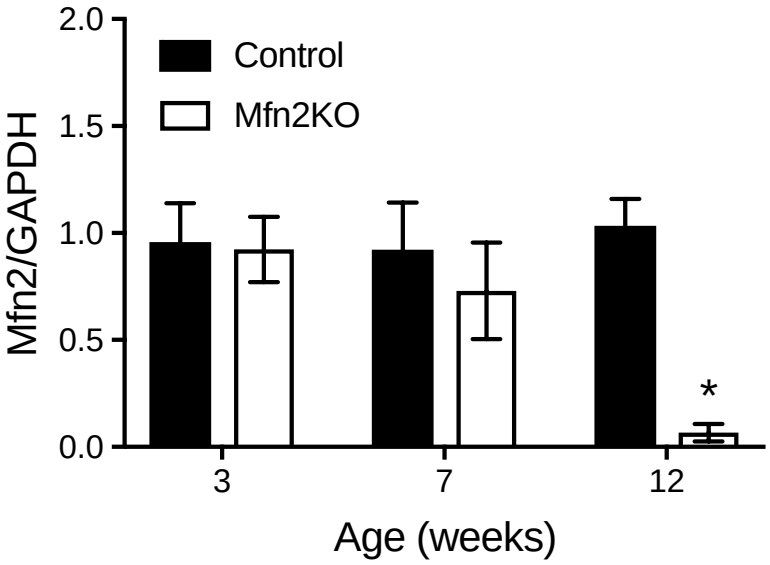
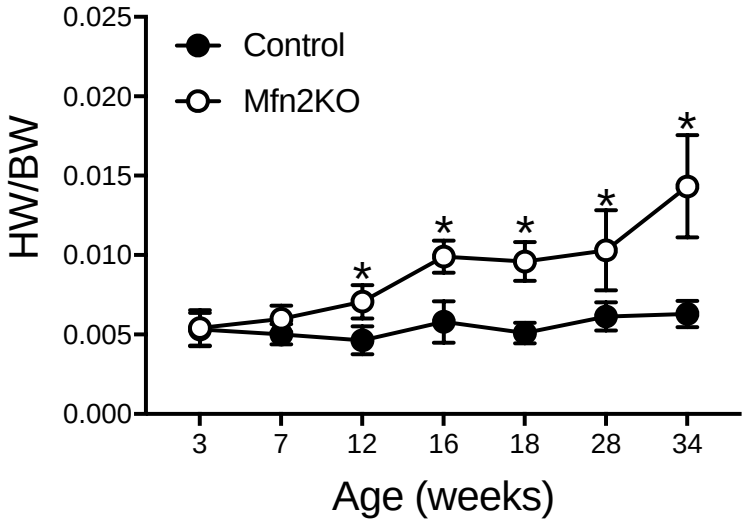
Deletion of Mfn2 in cardiac myocytes display significant gross abnormalities

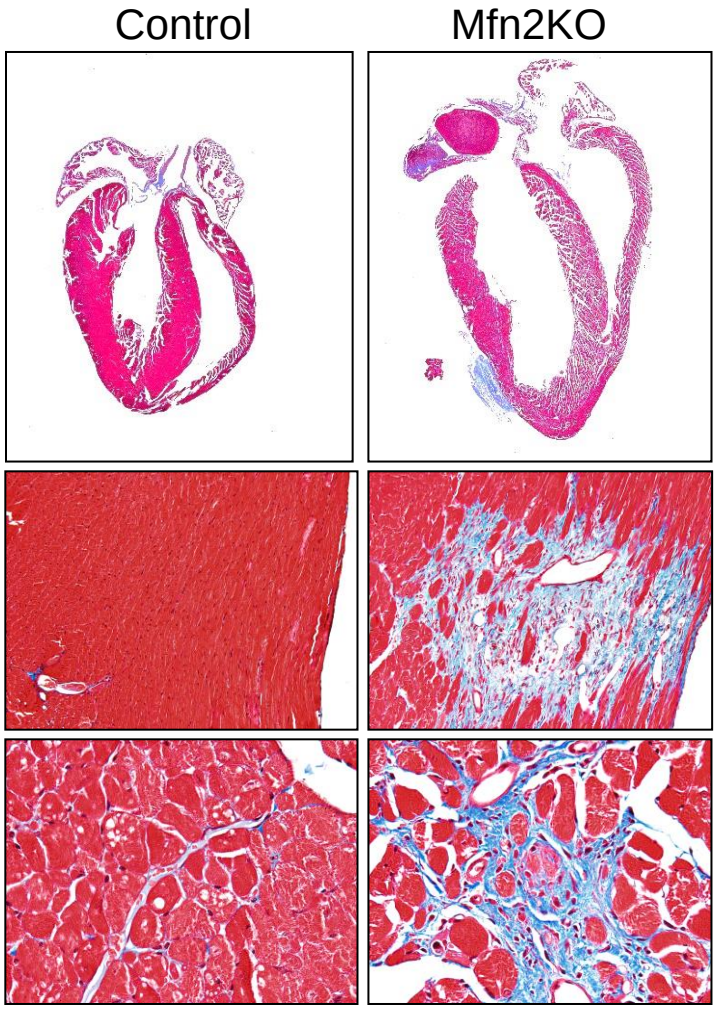


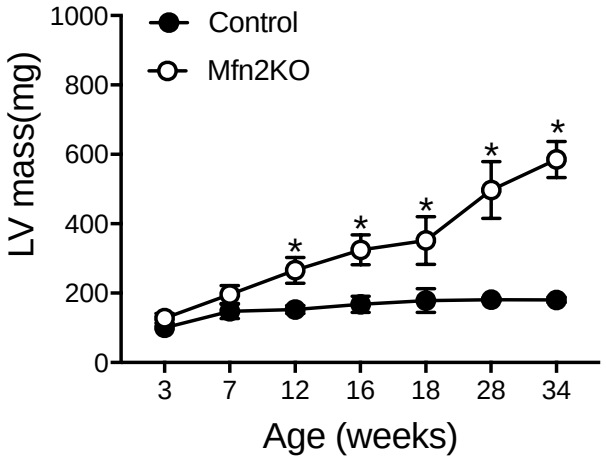


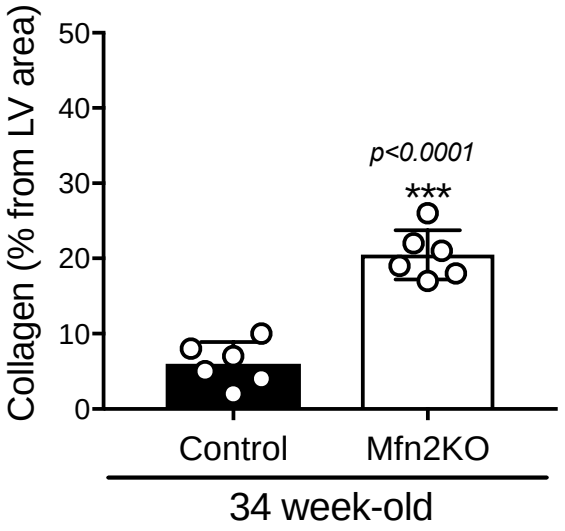




Deletion of Mfn2 in cardiomyocytes increases left ventricle mass and collagen deposition

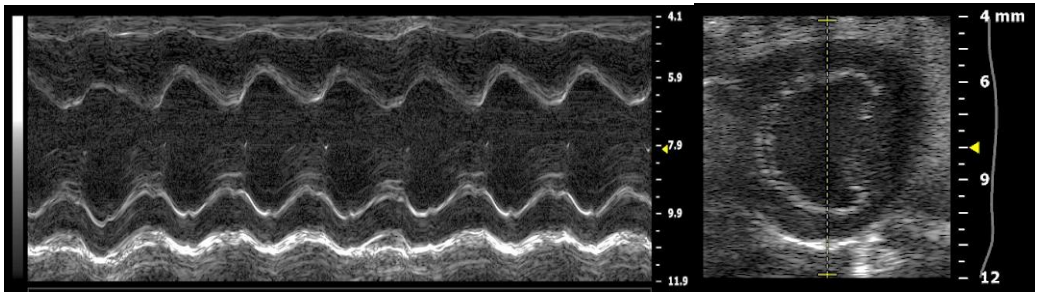




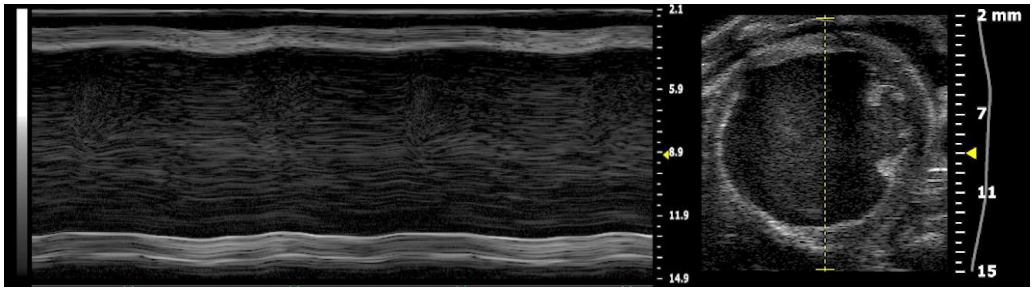


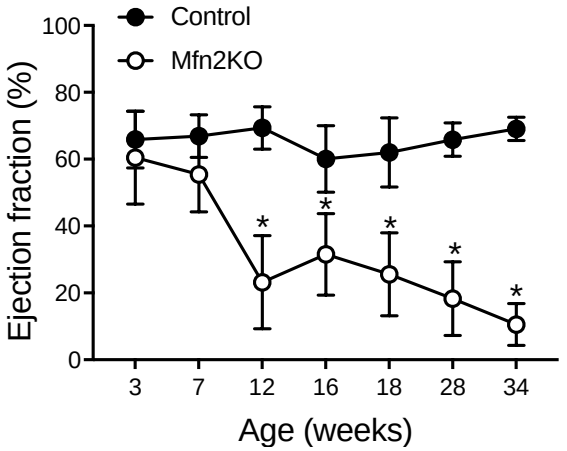
Mfn2 deficiency in cardiomyocytes induces a progressive dilated cardiomyopathy

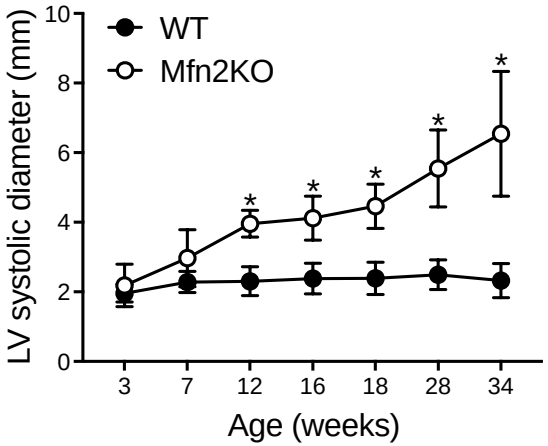
Control (34 week-old)



Mfn2KO (34 week-old)







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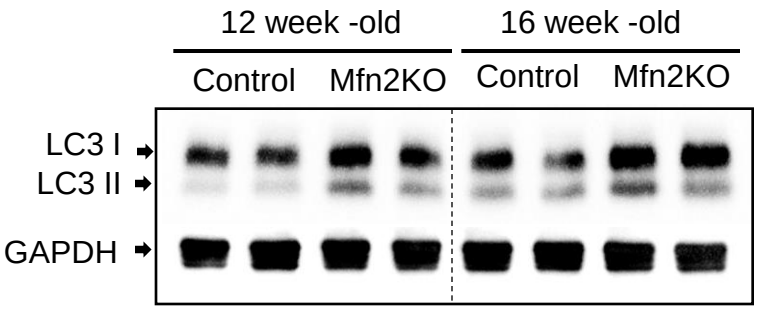
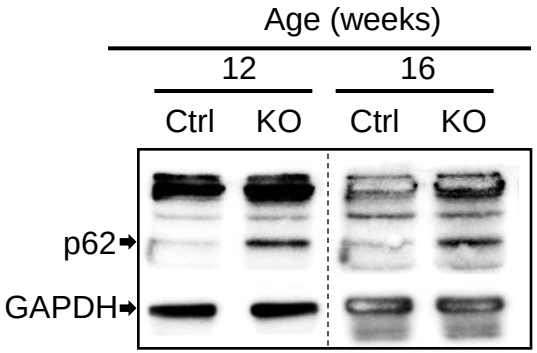
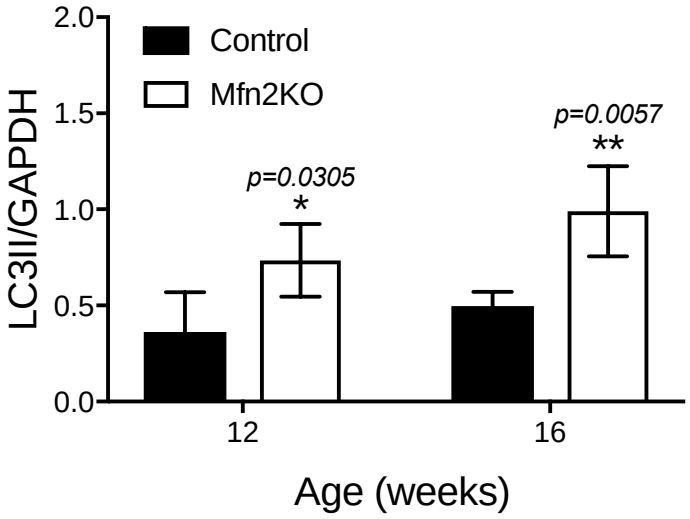
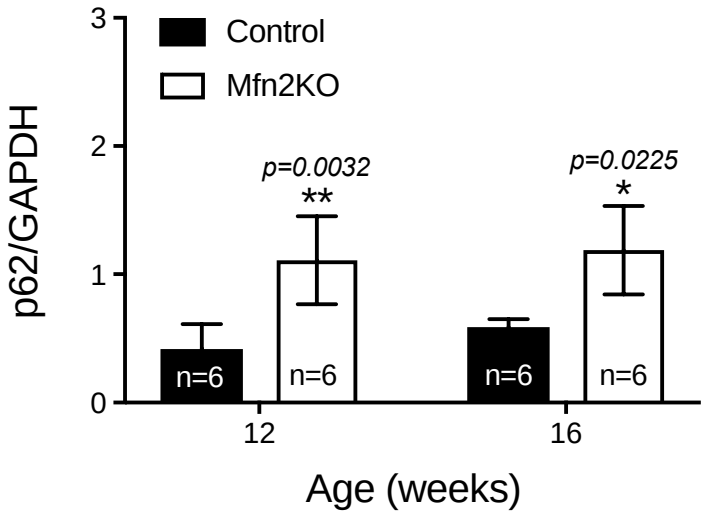
Mfn2 ablation in cardiomyocytes inhibit autophagy flux









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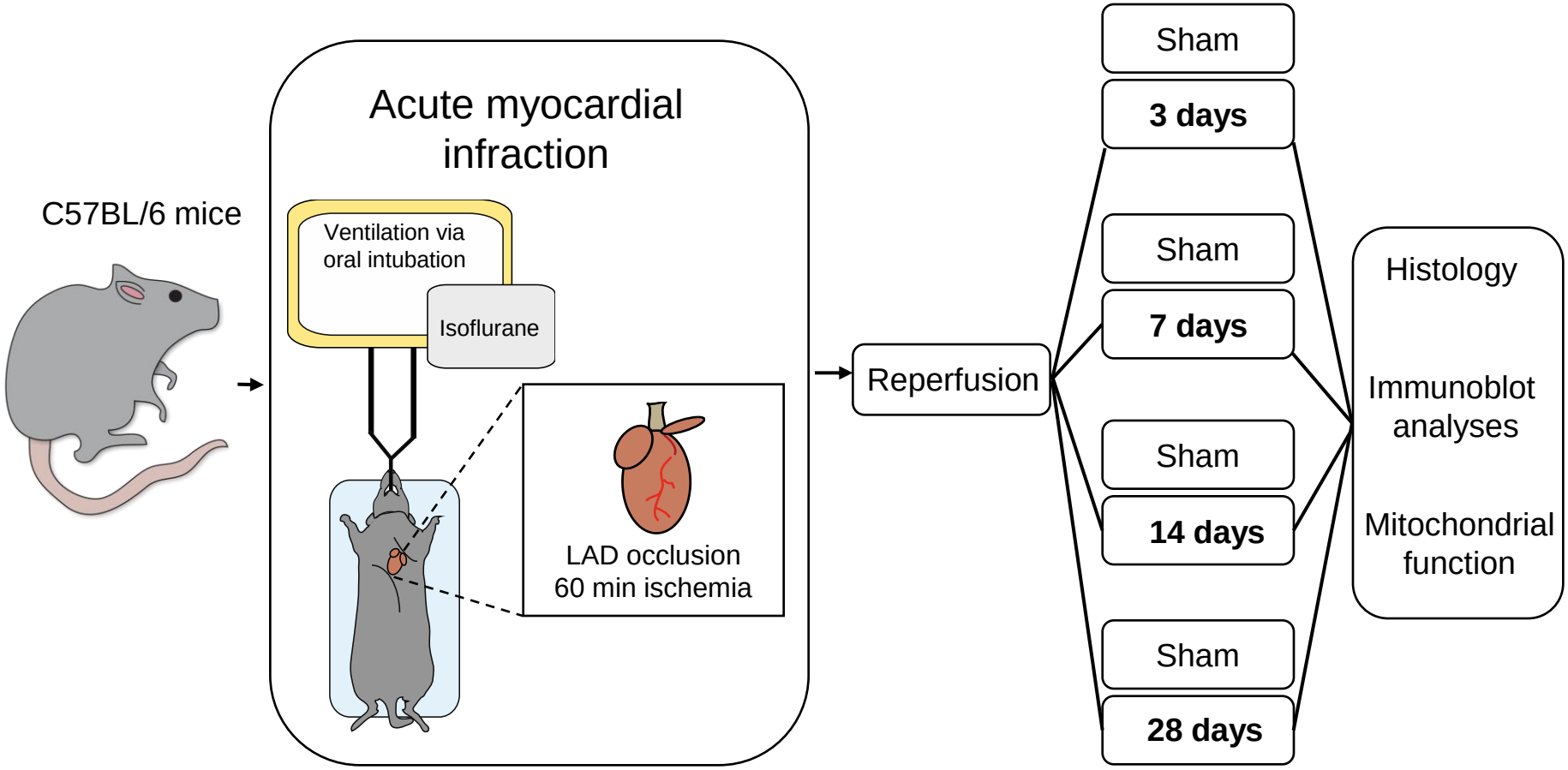
Aim 2

To investigate myocardial Mfn2 levels and autophagy flux during chronic post-MI adverse LV remodelling.

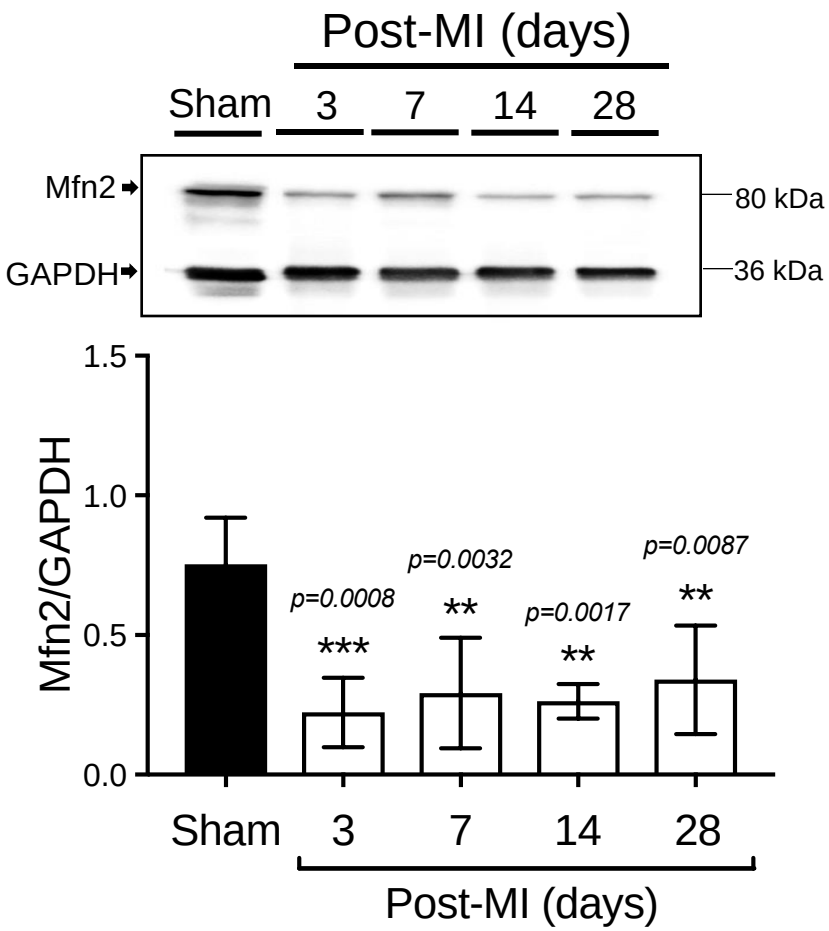
1. To investigate whether myocardial levels of Mfn2 decrease following MI.

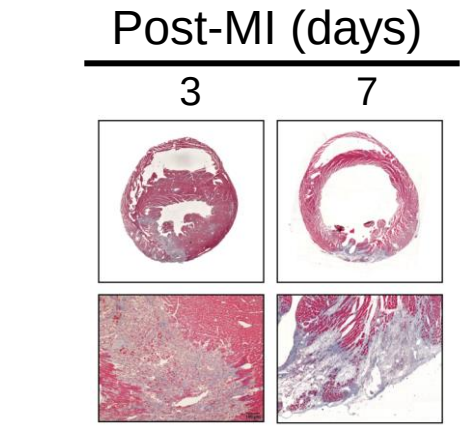
2. To investigate autophagy activity following MI.

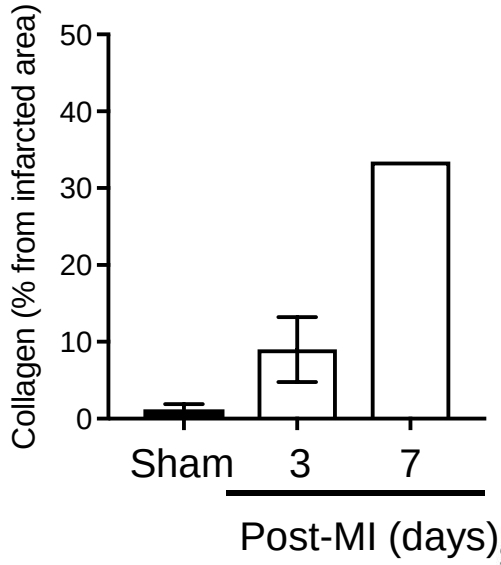
Materials and Methods



Post-infarction remodelling reduces levels of Mfn2







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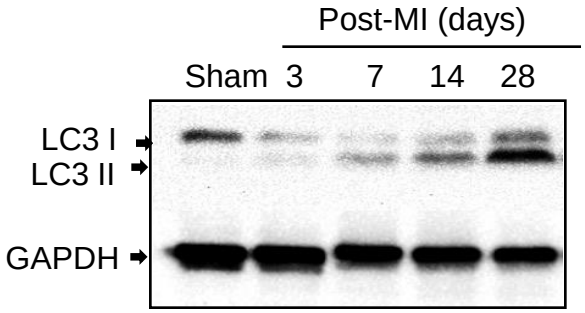
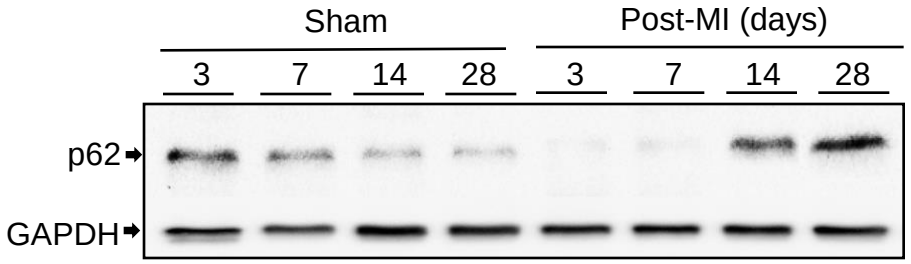
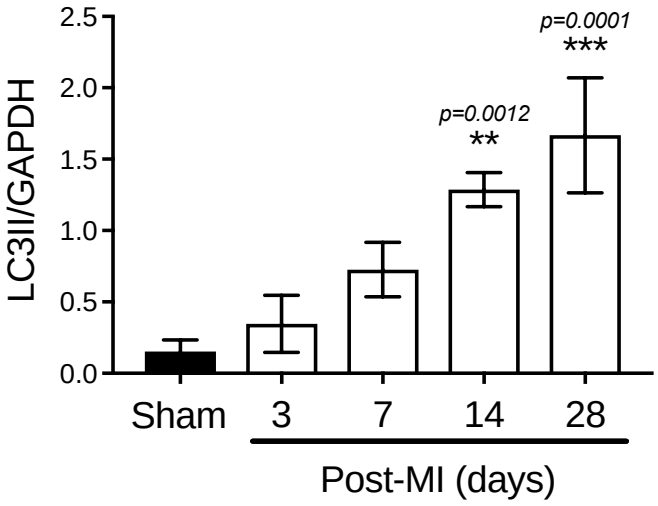
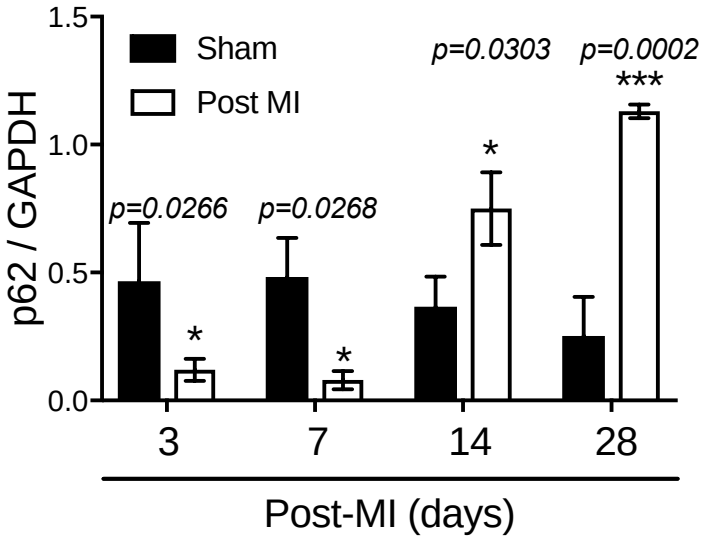
Autophagic activity increases during late healing stage of MI









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Summary

- Ablation of Mfn2 induces a progressive dilated cardiomyopathy and inhibit autophagy flux.
- Post-infarction remodelling decreases levels of Mfn2 protein.
- Autophagy activity increases during the late healing stage of MI.
- Post-MI remodelling inhibits autophagy flux.

Acknowledgements

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