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Regulation of myocardial growth and death by the Hippo pathway

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Please Join Us at Keystone Symposia (Mitochondria, Metabolism, and Heart) in Santa Fe, May 8-12, 2017

DISCLOSURE INFORMATION
No relevant financial relationship exists
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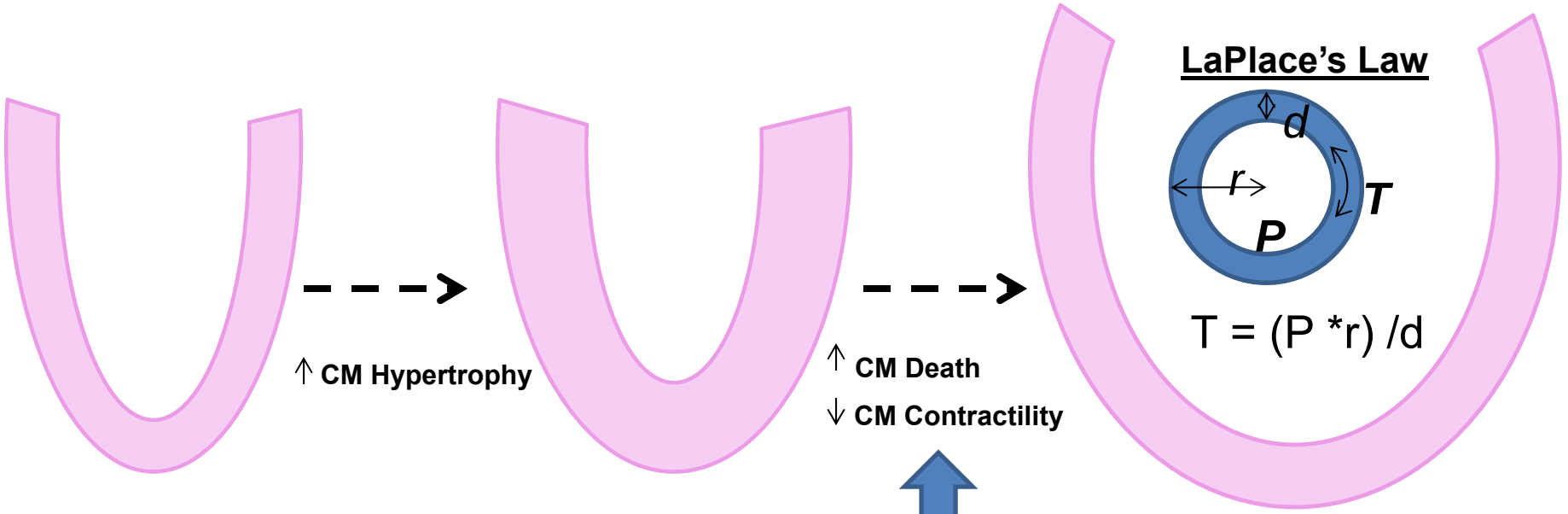
http://www.leducq-autophagy.org/

Two forms of hypertrphy: Compensated and Decompensated



Normal LV Mass

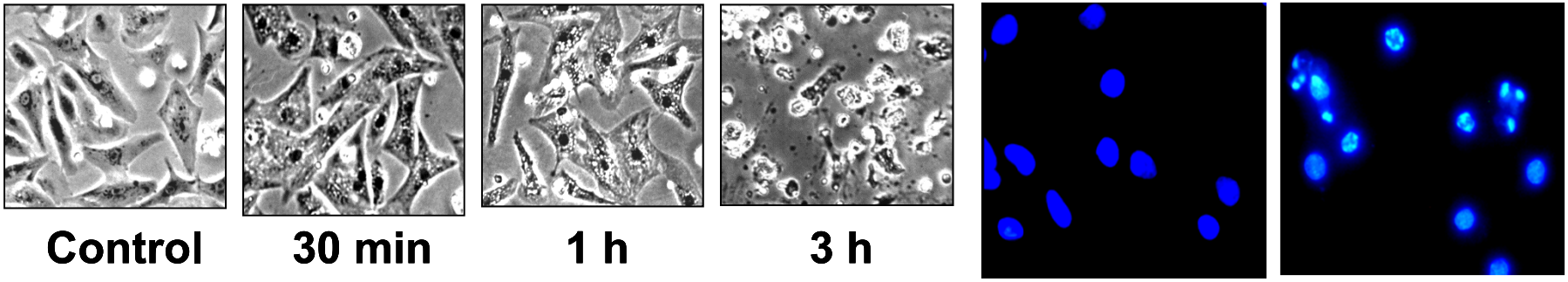
Compensated LV Hypertrophy

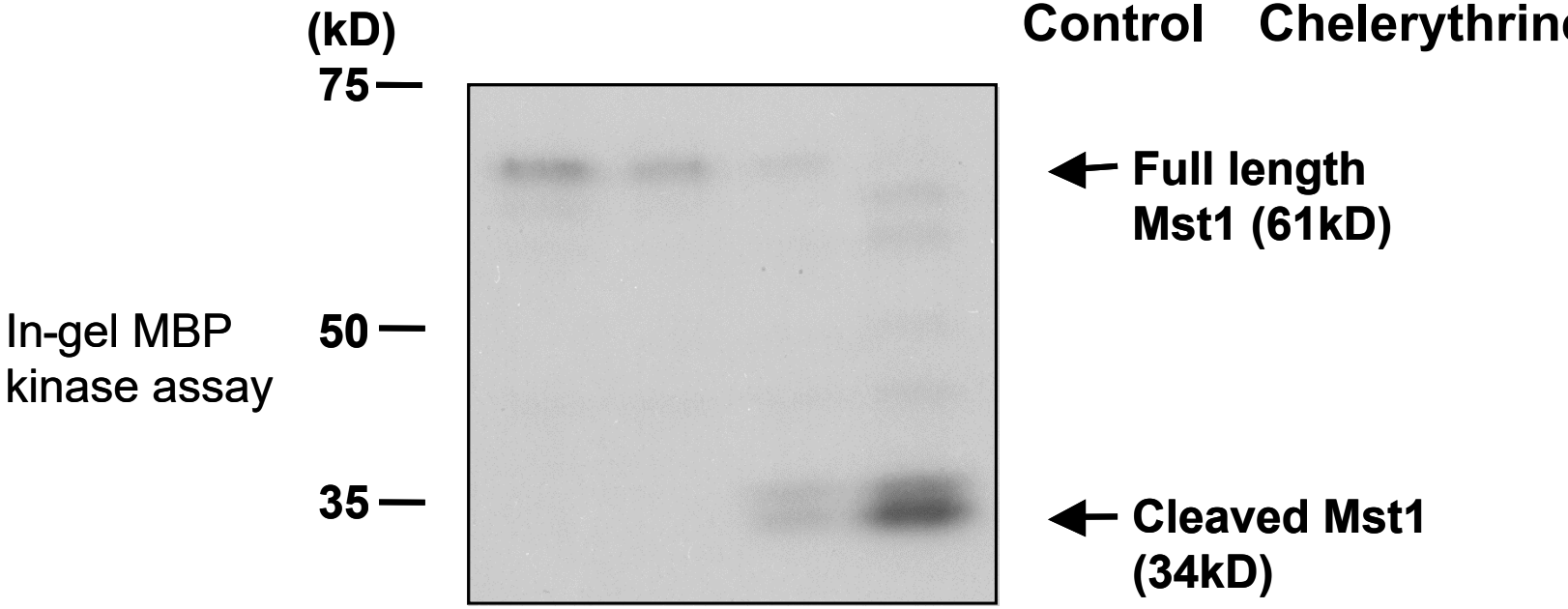
↓ Wall Sress
Preservation of cardiac function

Decompensated LV Hypertrophy LV Dysfunction Heart Failure

Hippo pathway?

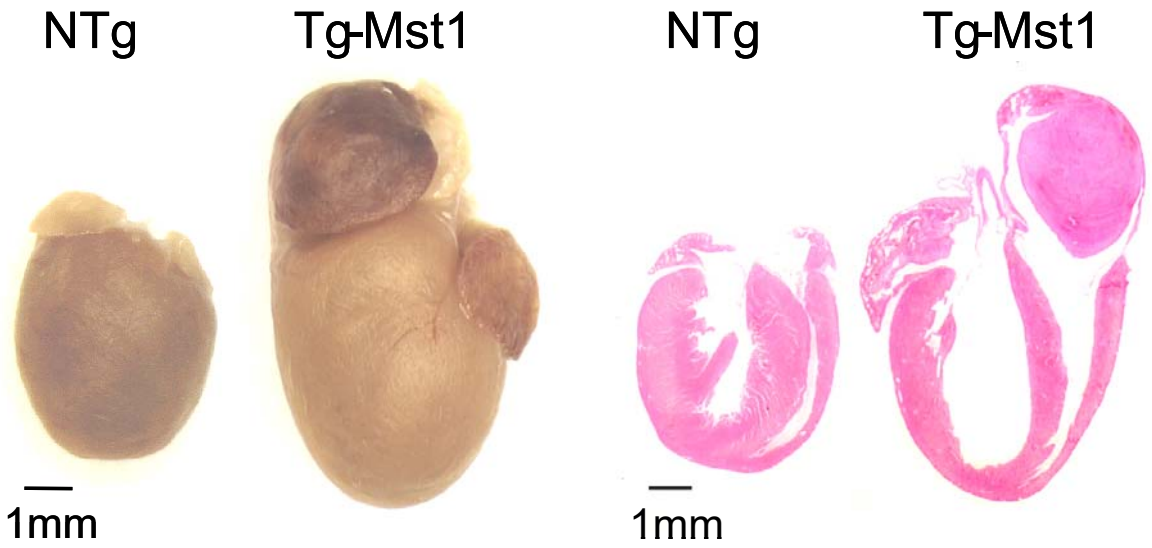
Mst1 is cleaved and activated during apoptosis in cardiac myocytes

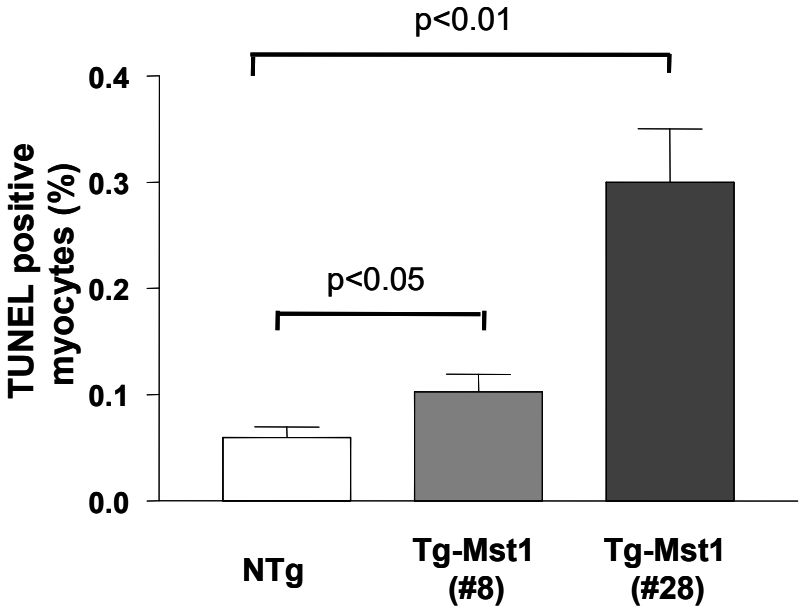


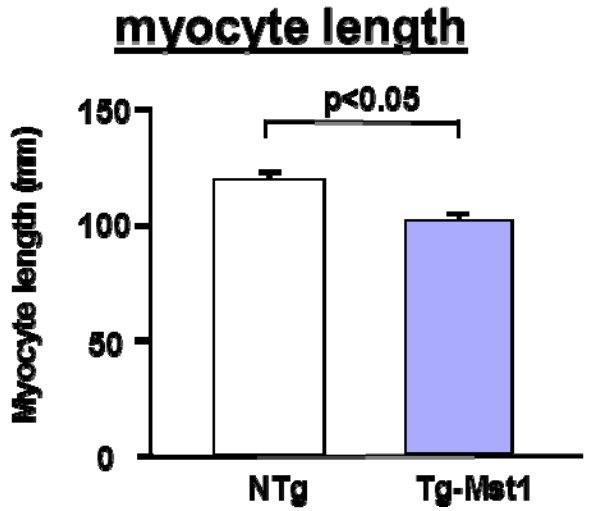


Overexpression of Mst1 induces apoptosis but suppress hypertrophy of cardiomyocytes

Cardiac dilation without compensatory hypertrophy exacerbates LV dysfunction



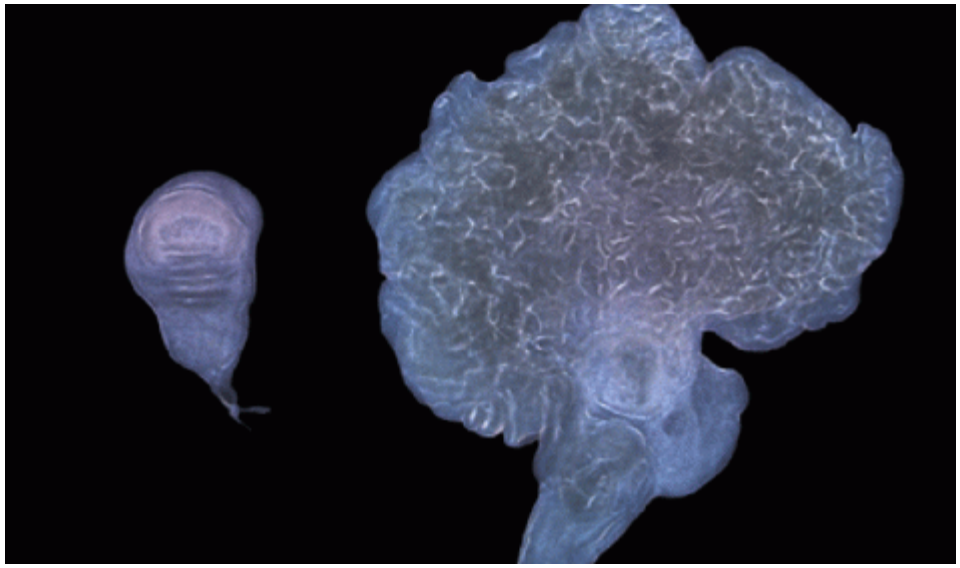




(Yamamoto et al JCI 2003)

Hippo pathway controls organ size

Drosophila
Wing imaginal discs



WT **Mut**

Mouse
Livers

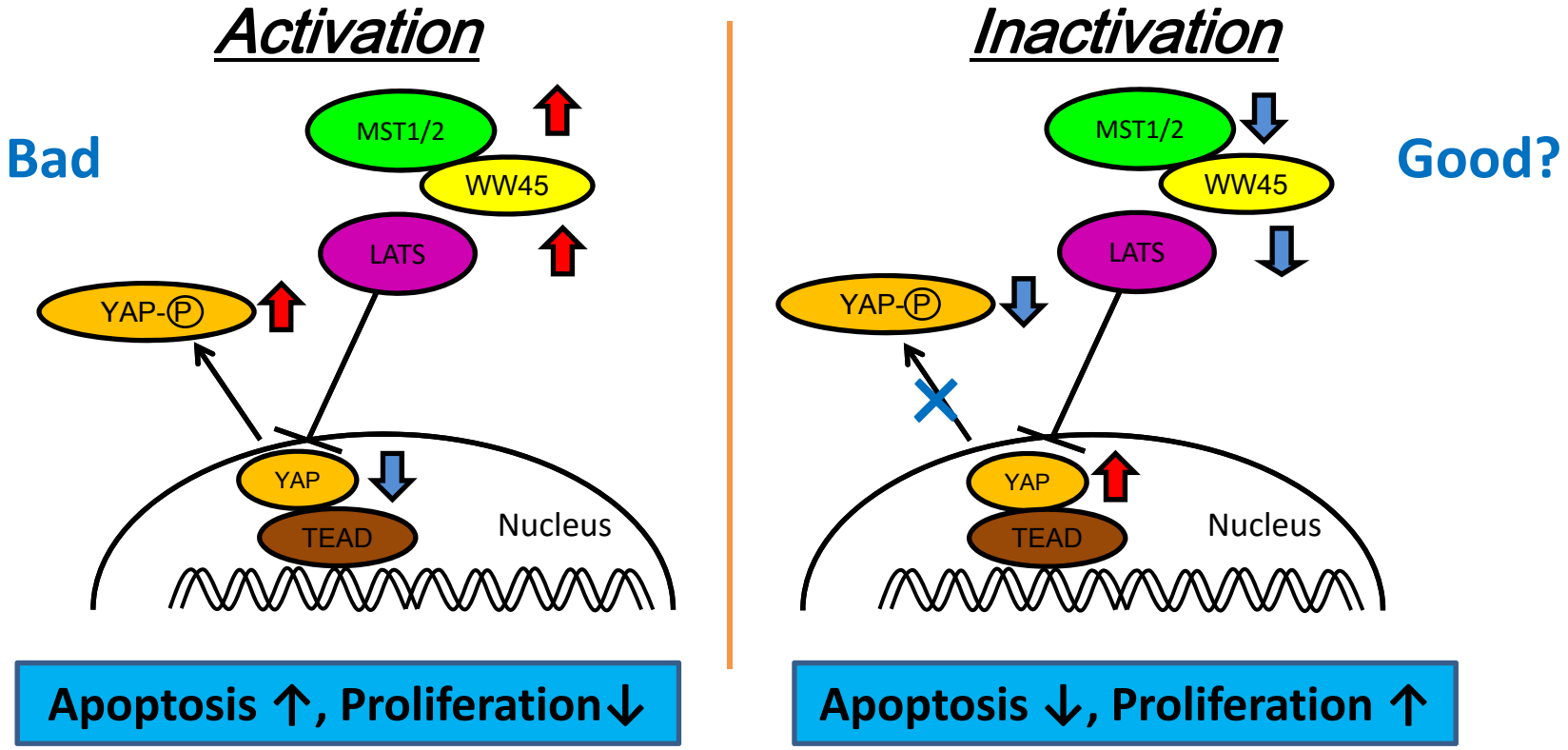
WT **Mut**

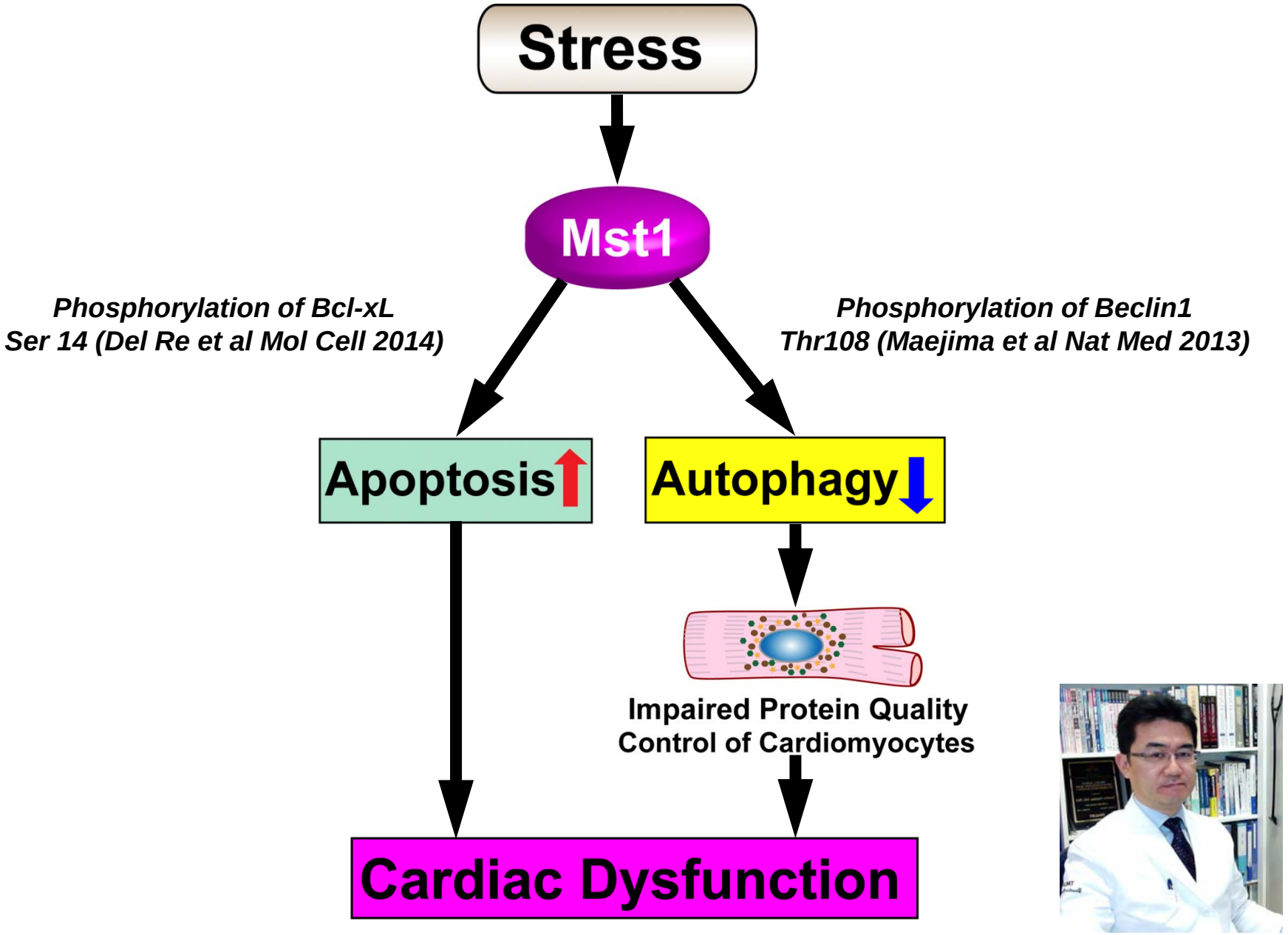
(DJ Pan)

The organ enlargement phenotype in Drosophila is reminiscent of Hippo

Hippo Pathway

- Hippo Pathway is an important regulator of organ growth through modulation of cell proliferation and apoptosis.
- A major target of the Hippo Pathway is YAP, a transcription factor cofactor, that is inactivated by the Hippo pathway.



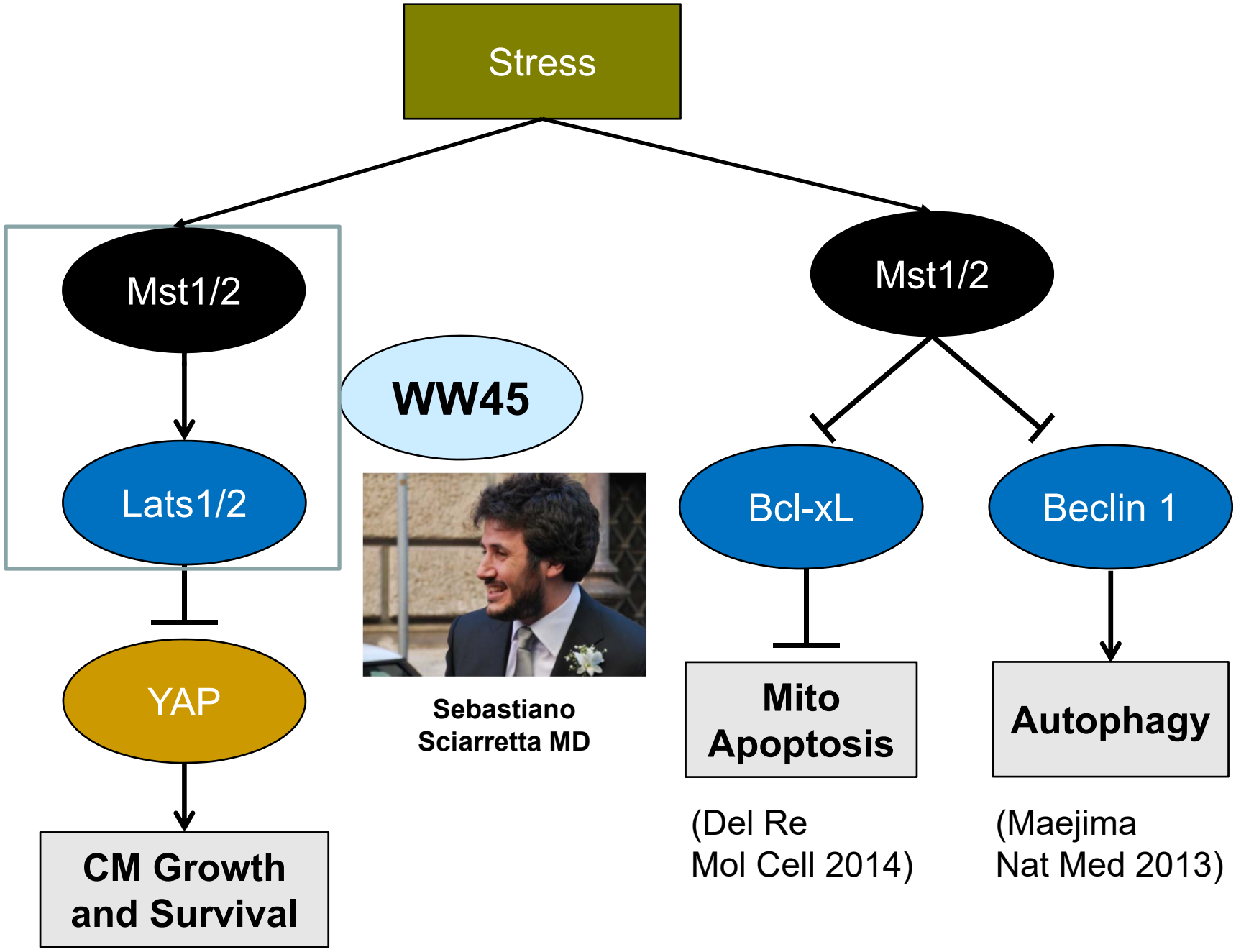


(Maejima et al 2013, Nat Med)

Contents

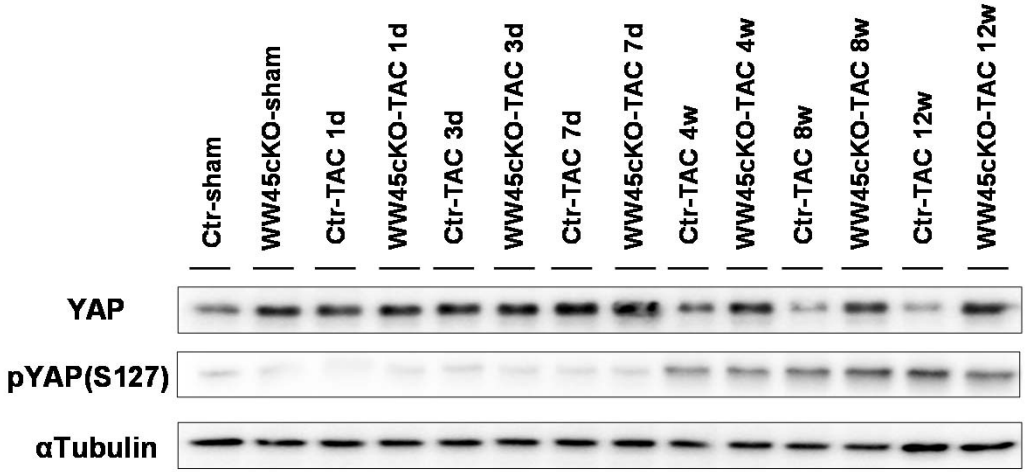
- **Why does the adult heart have the Hippo pathway, an apparently *harmful* signaling mechanism for cardiomyocytes, despite that its capacity for regeneration is limited?**

WW45 (Sav) regulates canonical Hippo pathway

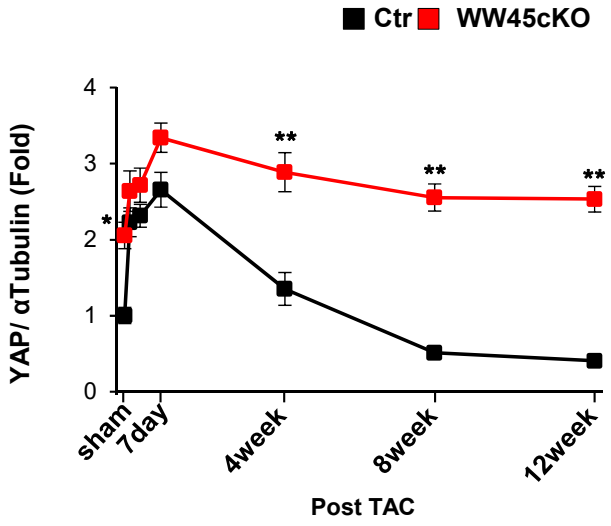


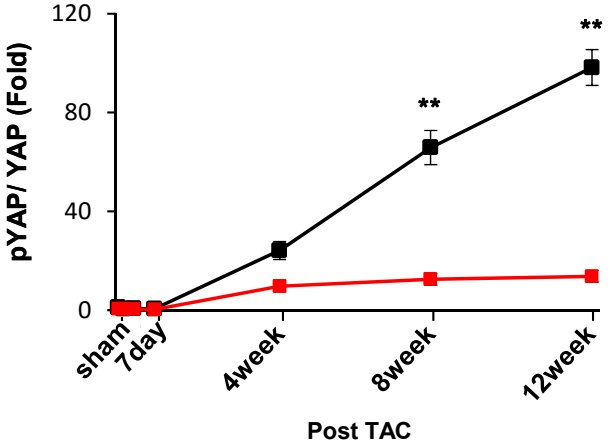
YAP is persistently activated in hWW45 KO mice during pressure overload

hWW45 acts as a scaffold of the Hippo pathway in the heart

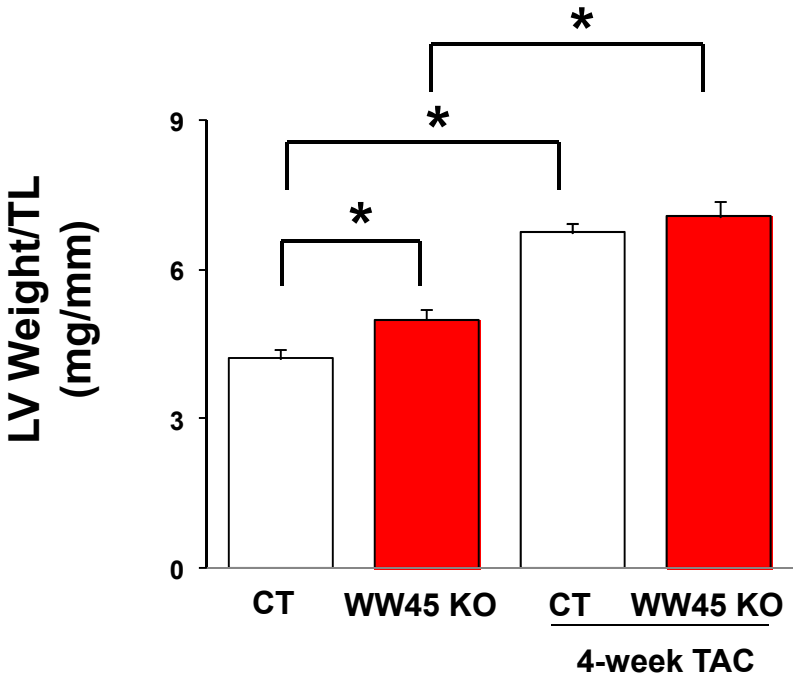


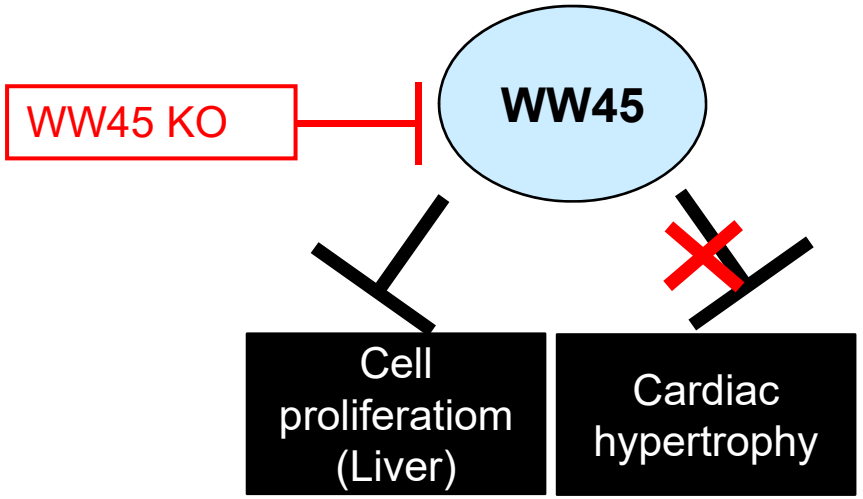
(Dr. Shohei Ikeda)

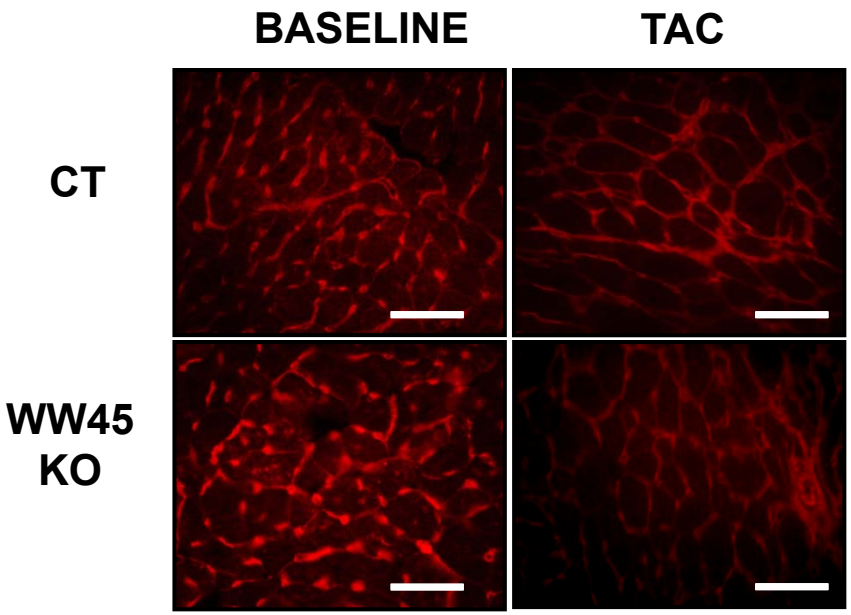


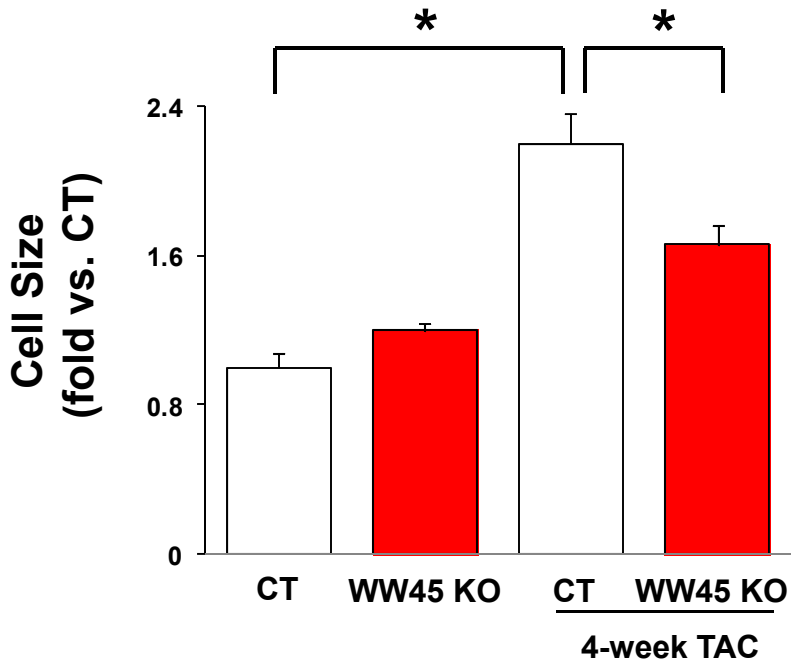


WW45 Deletion does not Induce Hypertrophy but Is Associated with Reduced Cell Size during Pressure Overload

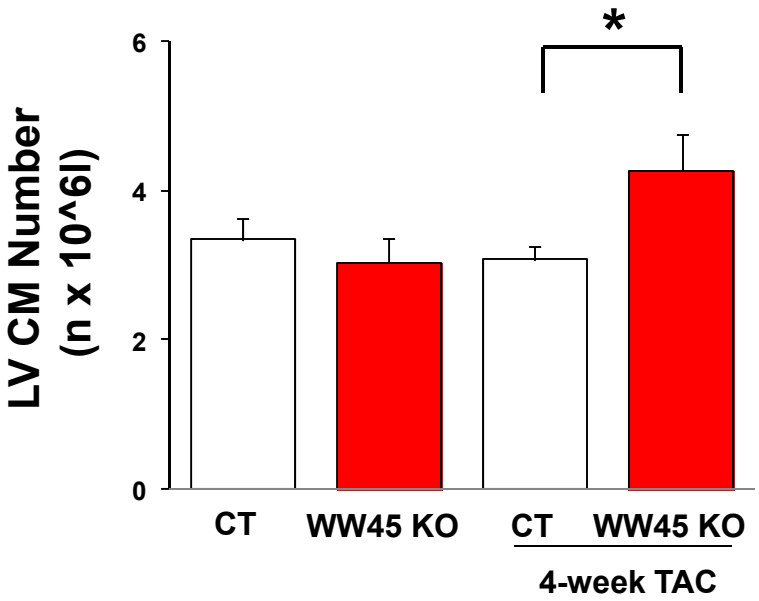


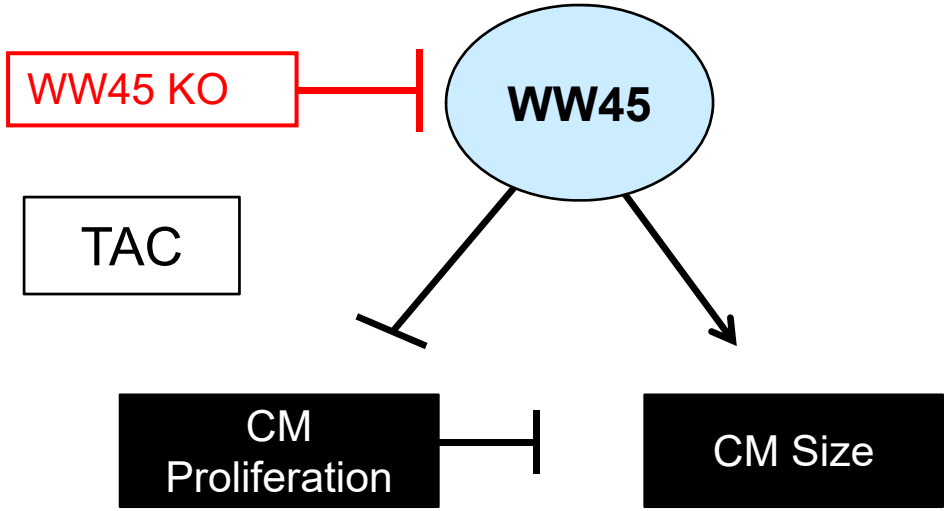


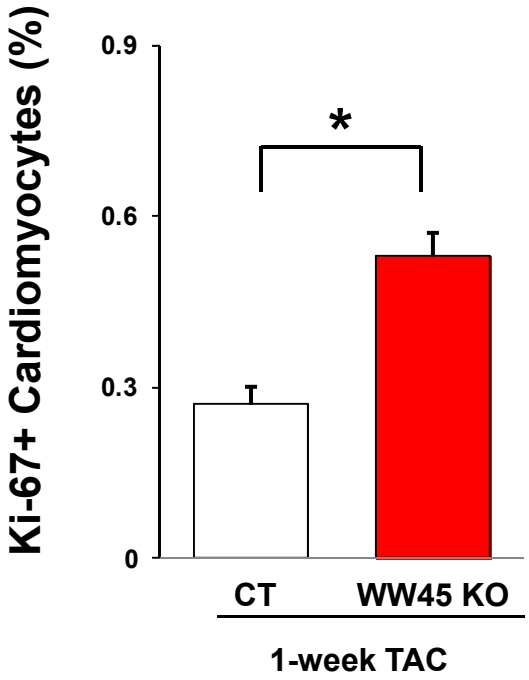


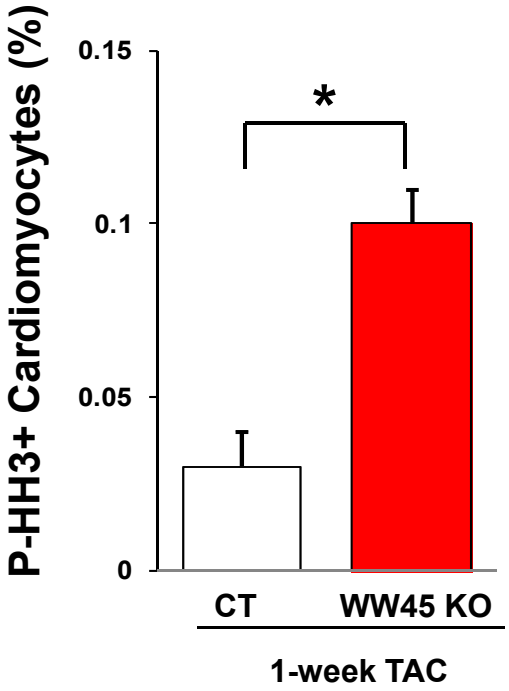


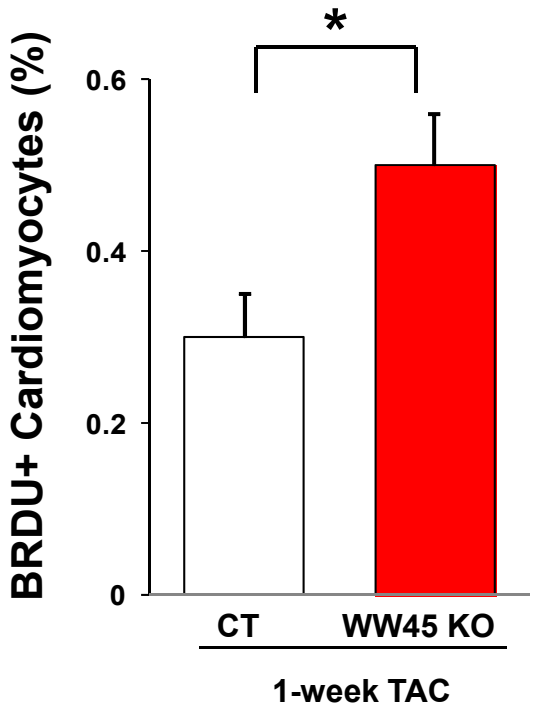
WW45 Restrains CM Proliferation during Pressure Overload



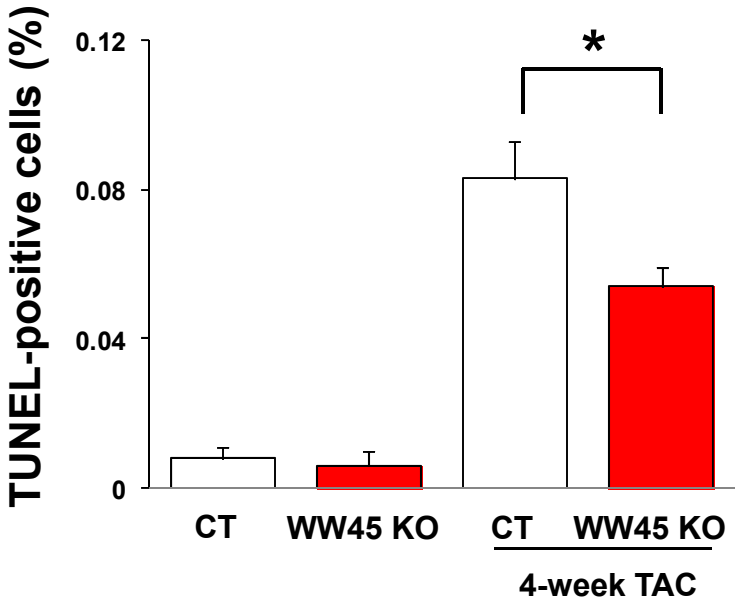


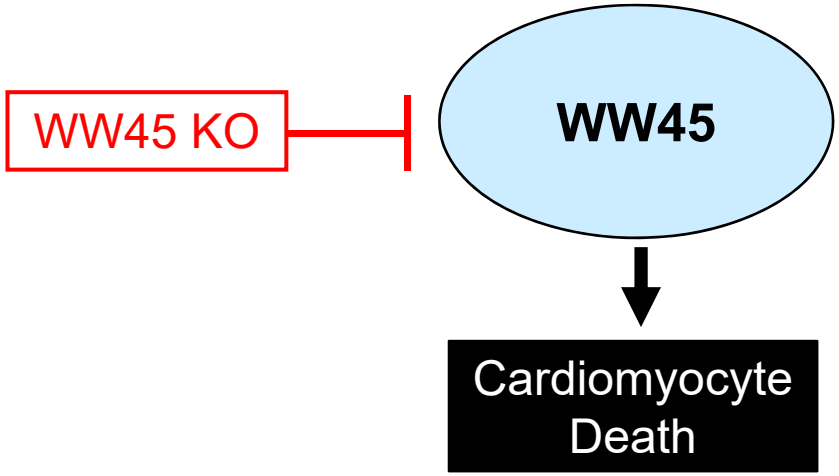


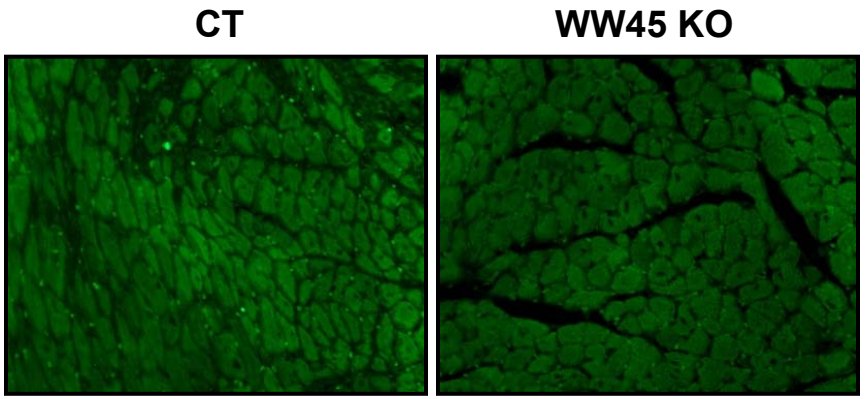




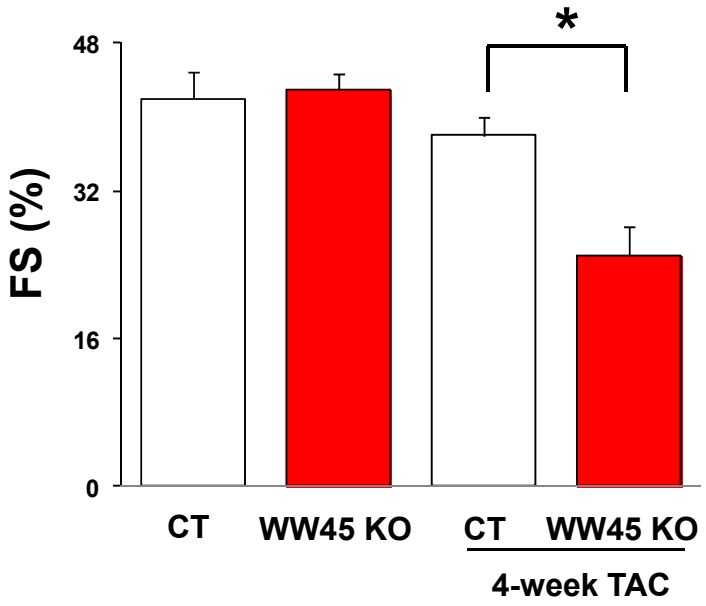
WW45 Deletion Inhibits Apoptosis during Pressure Overload

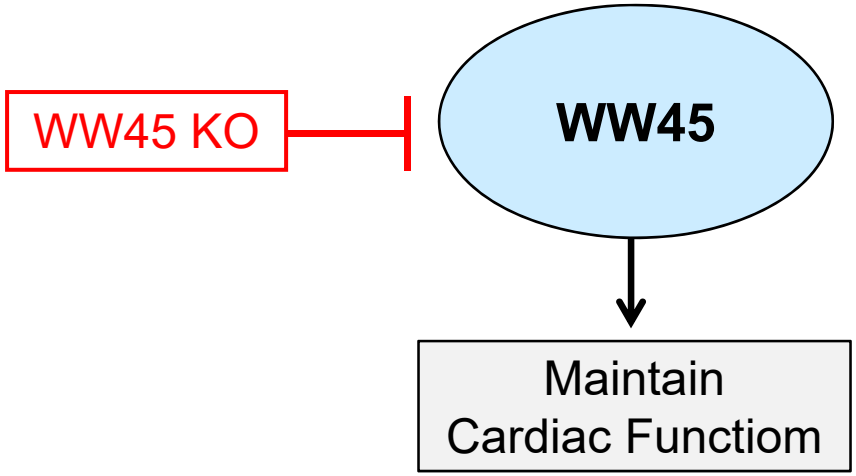


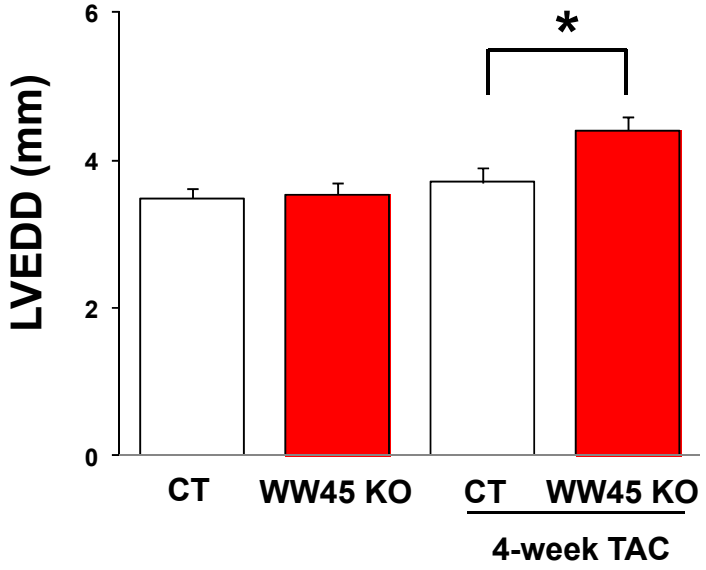


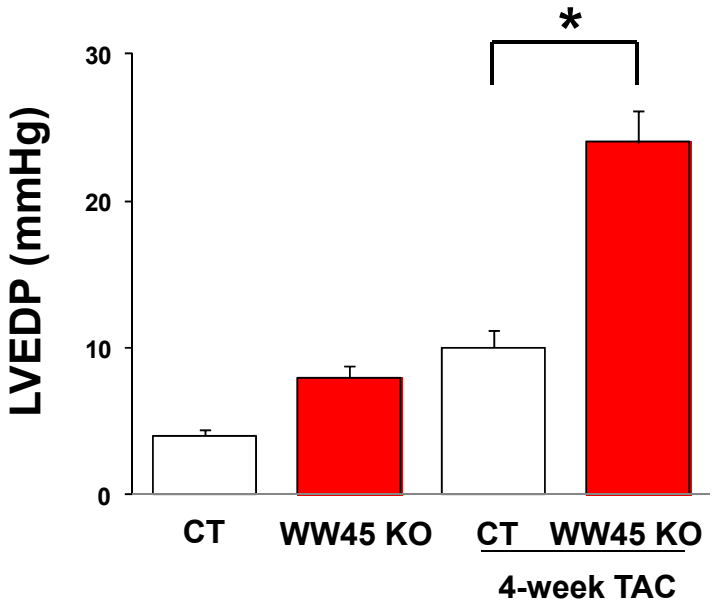


WW45 Deletion is Associated with LV Systolic Dysfunction and Dilation during Pressure Overload

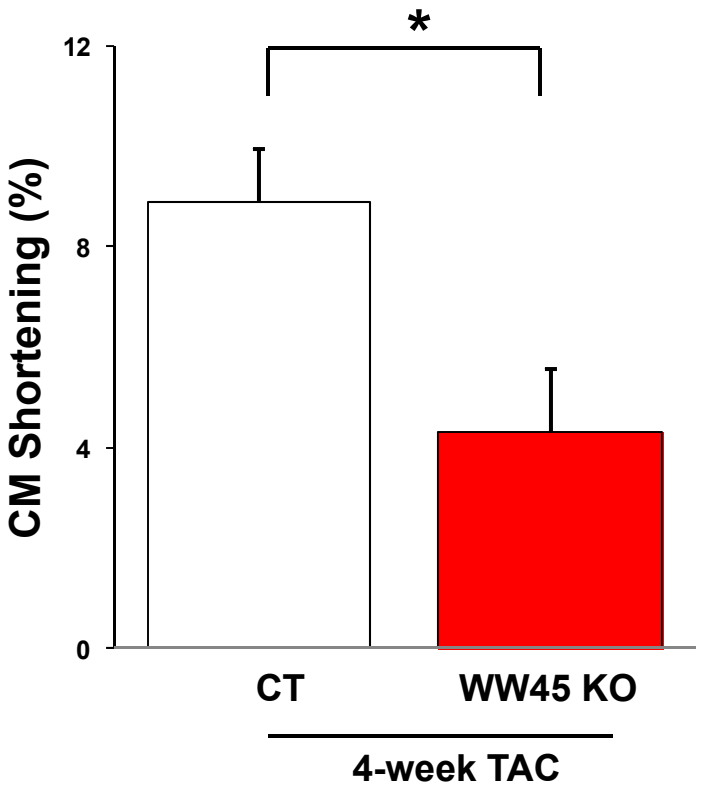


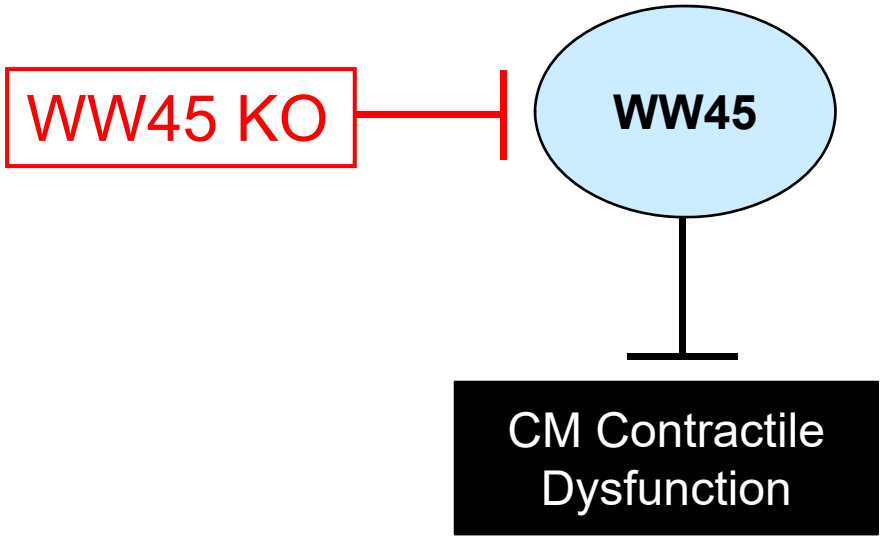




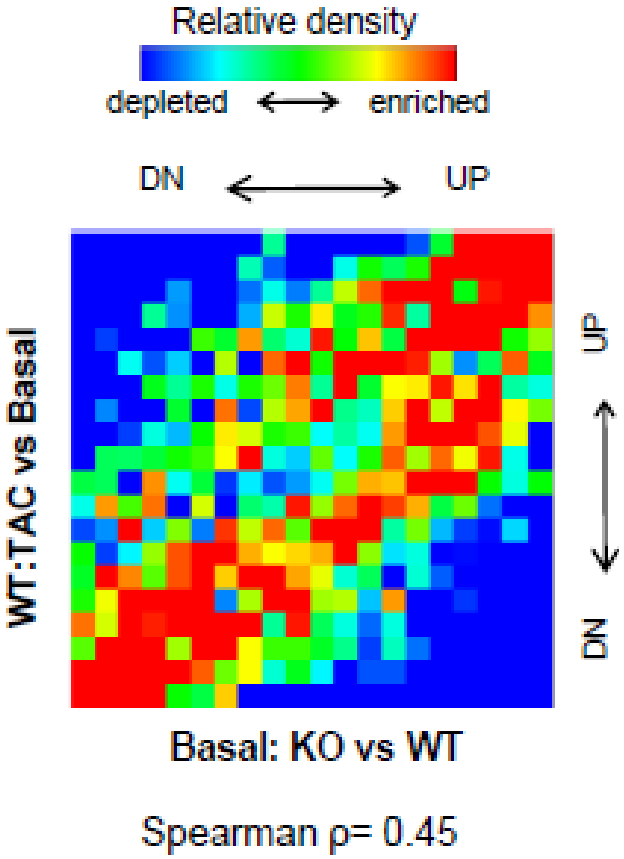


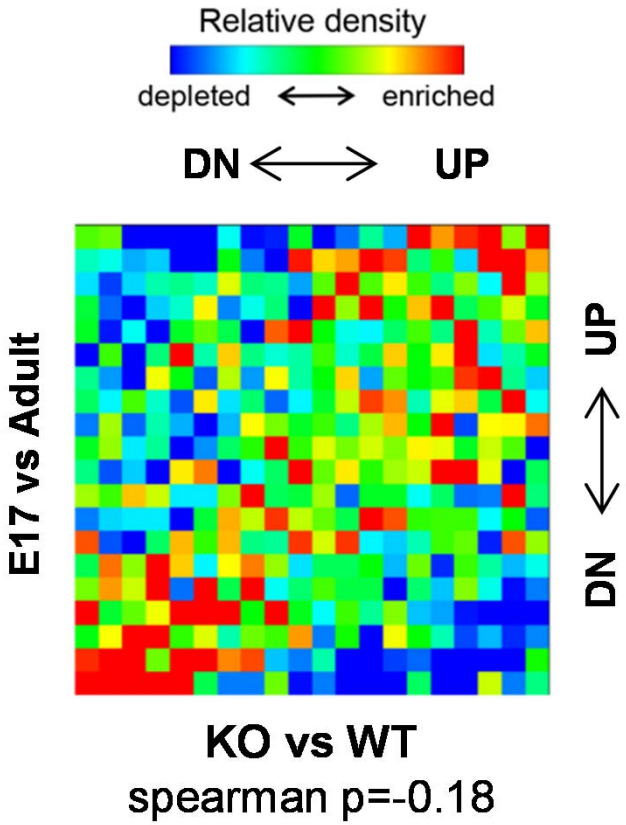
WW45 Deletion is Associated with Reduced Cardiomyocyte Contractility during Pressure Overload



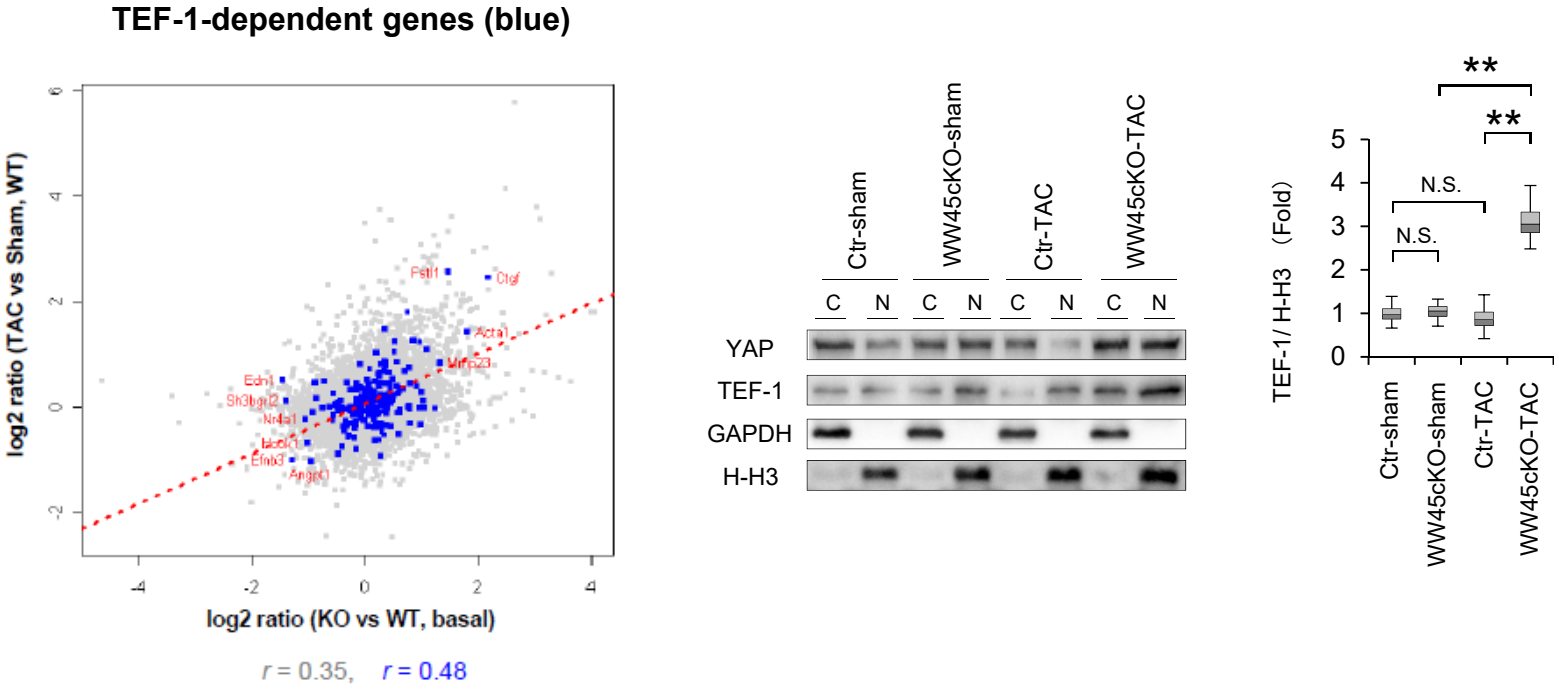


WW45 Disruption Induces a Transcription Profile Similar to Pressure Overloaded and Fetal Heart

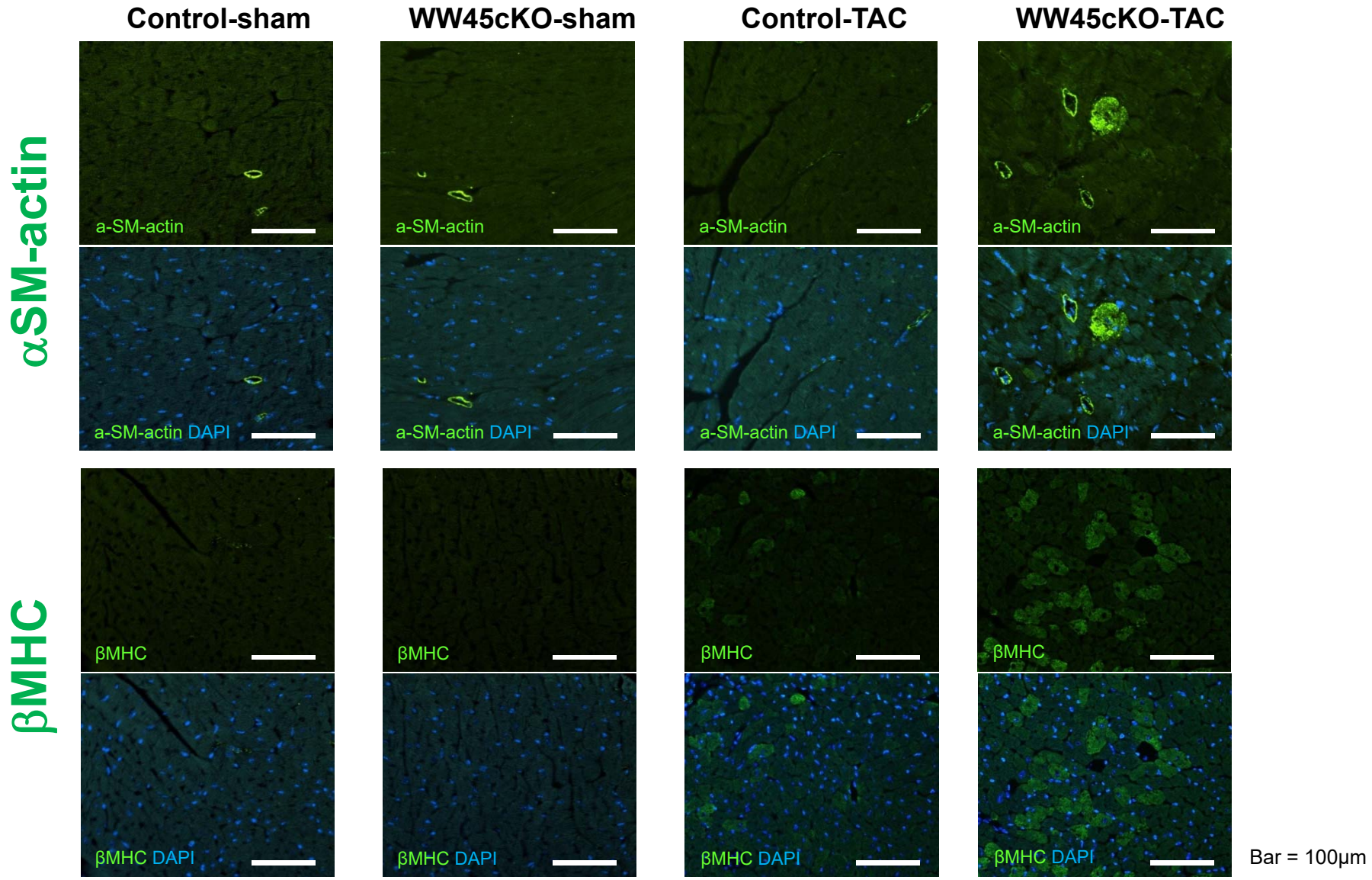




WW45 Disruption Induces a Significant Upregulation of TEF-1-Dependent Genes in the Presence of PO

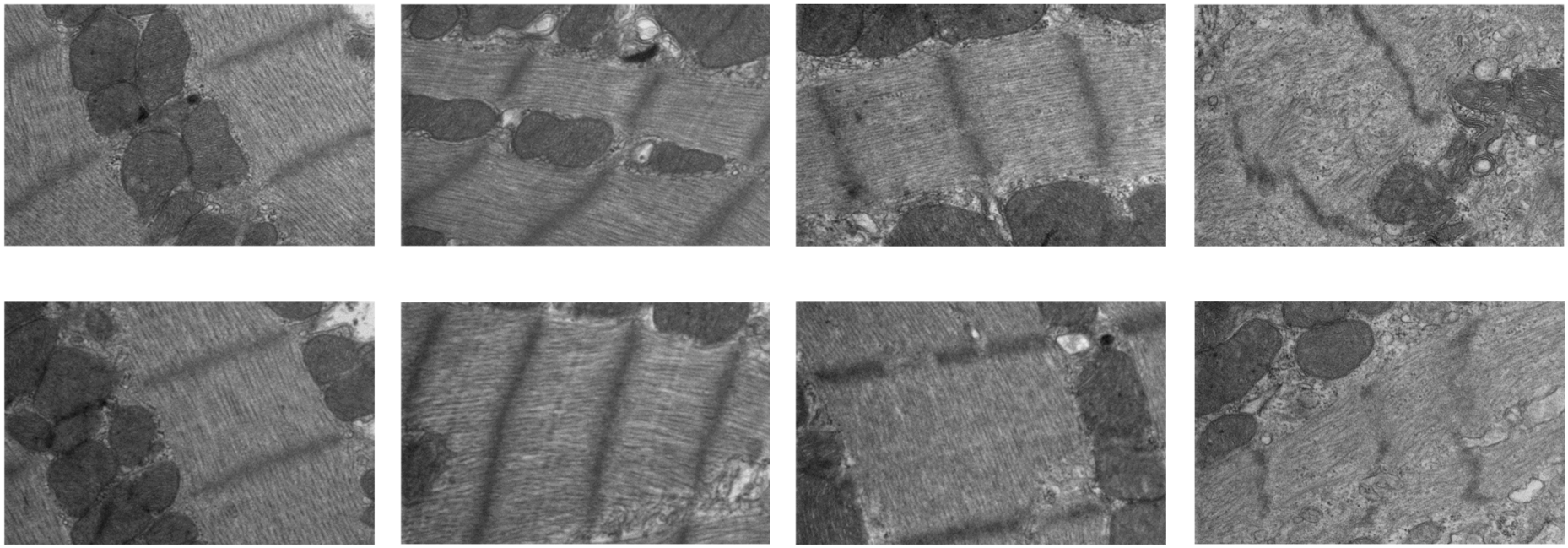


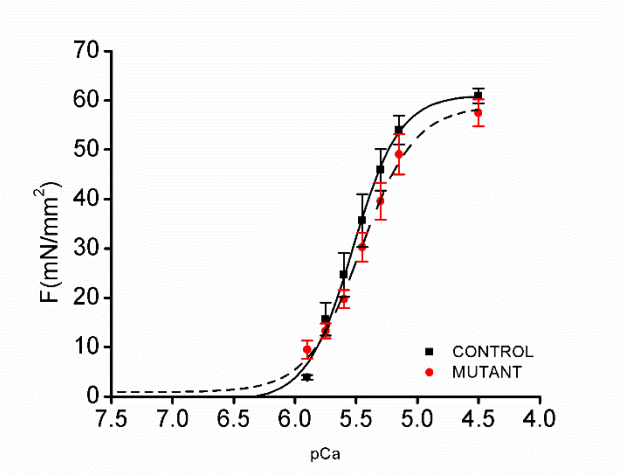
WW45 cKO mice shows dedifferentiated CMs after TAC: re-expression fetal genes (αSM-actin, βMHC)

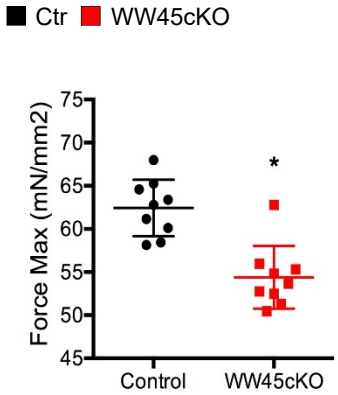


WW45 Disruption Induces Sarcomeric Disarray in Response to Pressure Overload

Control-sham **WW45cKO-sham** **Control-TAC** **WW45cKO-TAC**



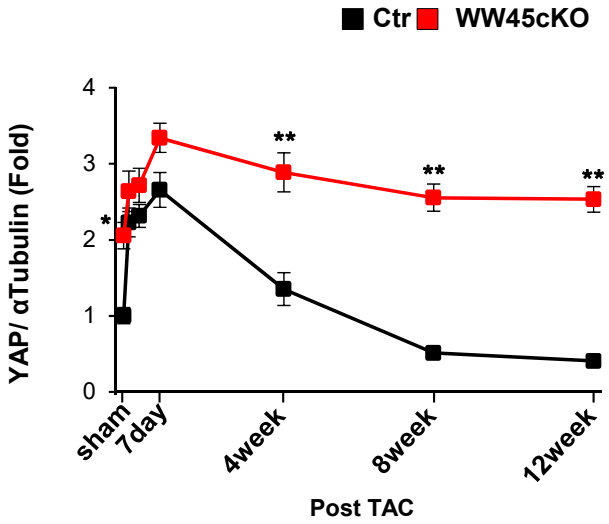




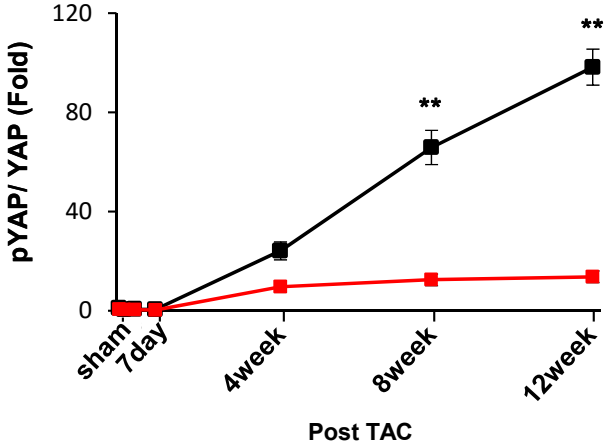
(Dr. S Sadayappan)

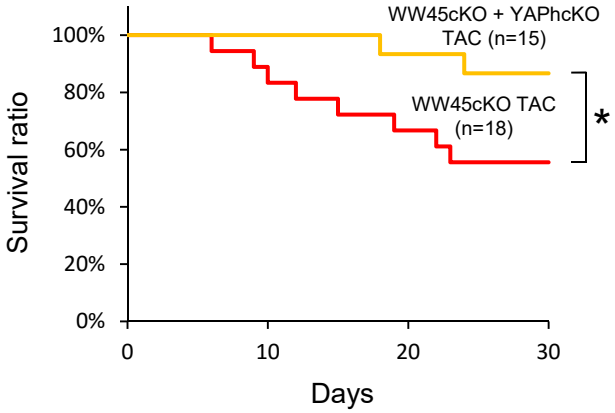
The Hippo pathway is activated during Pressure Overload to prevent sustained activation of YAP and maintain differentiation

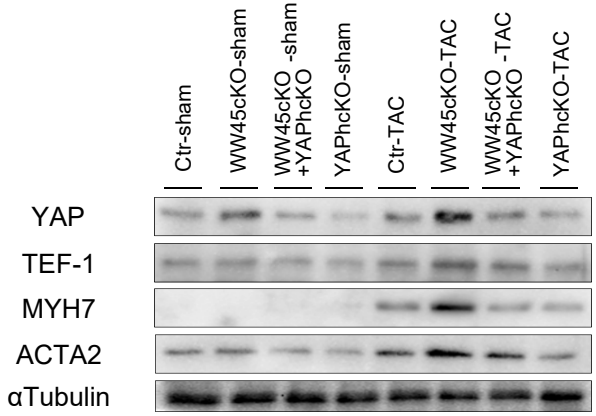
Transient activation of YAP



Time-dependent activation of the Hippo







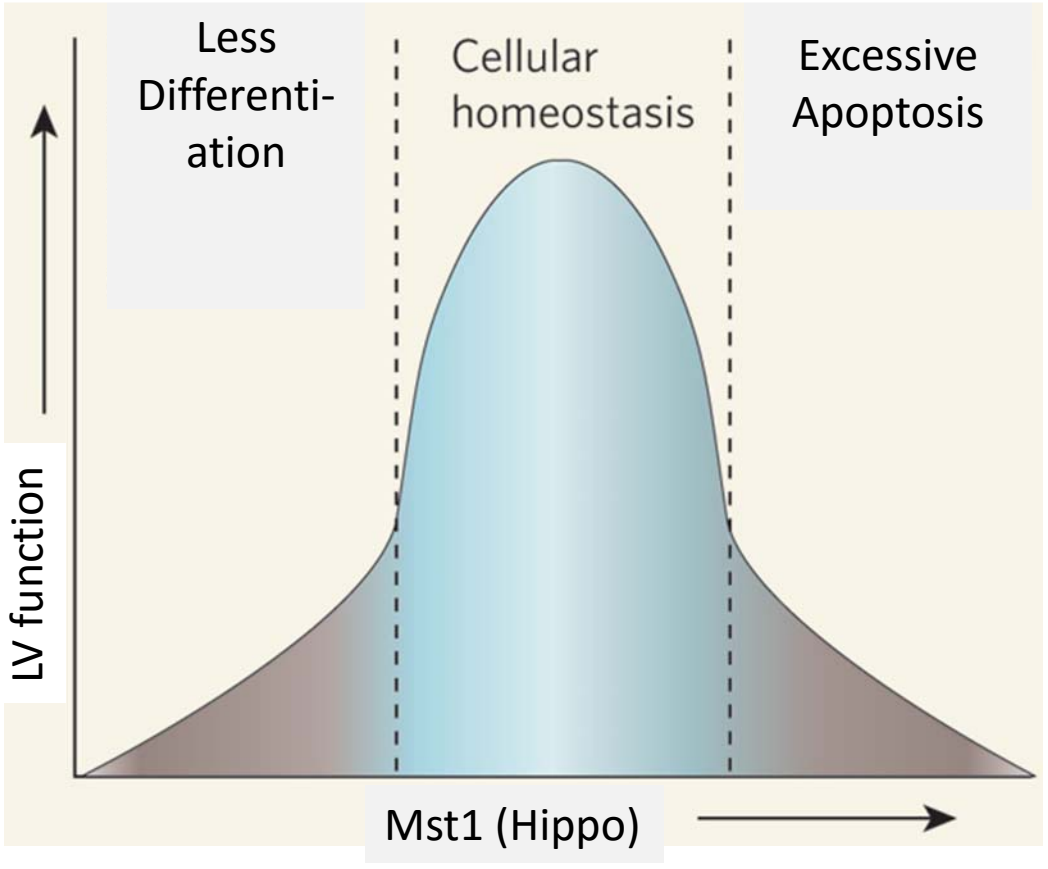
Summary

- **The Hippo pathway is activated by myocardial stress, induces death of cardiomyocytes, and inhibits autophagy, thereby promoting myocardial injury and heart failure.**

- **The Hippo pathway plays an essential role in maintaining differentiation of cardiomyocytes to maintain contraction against pressure overload.**

Dose-dependent functions of the Hippo pathway in the heart

Hippo may exist in the heart to maintain cardiomyocyte differentiation



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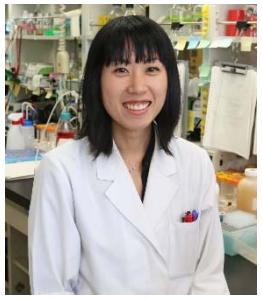
Hippo pathway

Peiyong Zhai
MD PhD

Michinari Nakamura
MD



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Jaemin Byum
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