HIF-1α and mitochondria in cardioprotection induced by adaptation to chronic hypoxia

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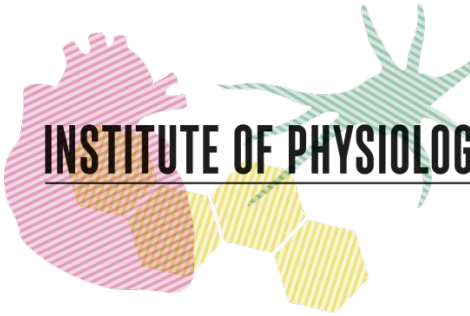


hronic hypoxia (CH)

he extent of I/R injury depends on:

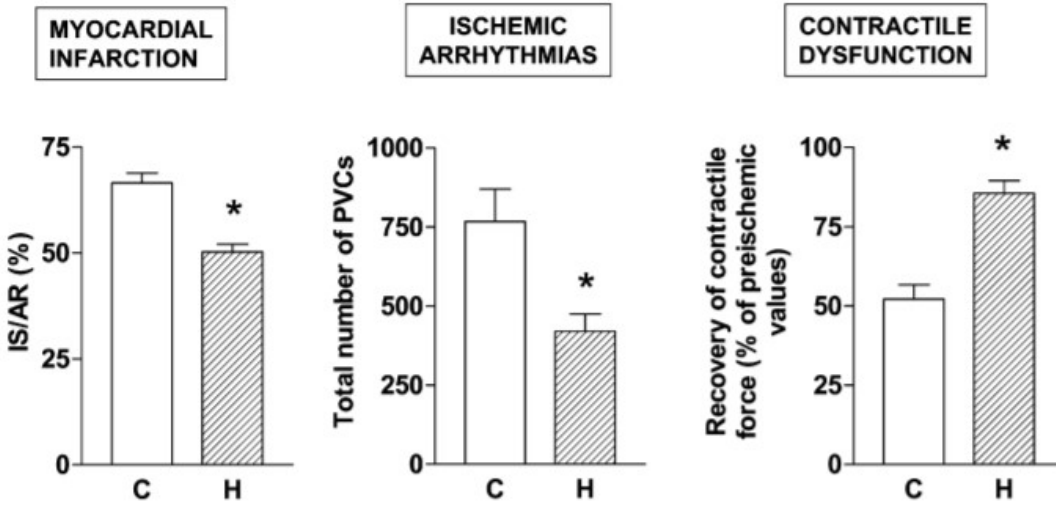
- intensity and duration of ischemic insult
- myocardial tolerance to oxygen deprivation

isproportion between oxygen supply and demand at tissue level

daptation to CH increases myocardial tolerance to acute I/R injury

- myocardial infarct size
- ischemic and reperfusion arrhythmias
- postischemic contractile dysfunction

ong-lasting protection



Ostadal and Kolar, Respir Physiol Neurobiol 2007

ypoxia-inducible factor-1 (HIF-1)

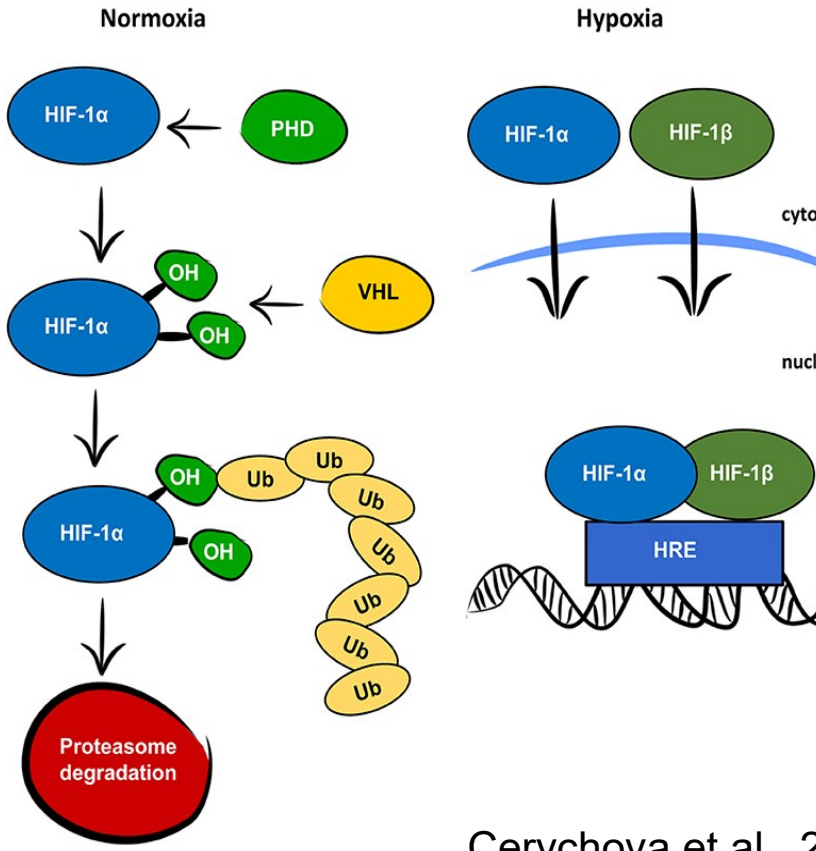
Transcription factor regulating body´s response to hypoxia

>1000 target genes associated with angiogenesis, erytropoiesis, metabolism, cell survival, …

Heterodimer:
- HIF-1α
- HIF-1β

Both subunits are continuously expressed

α-subunit is fastly degraded
in an oxygen-dependent manner

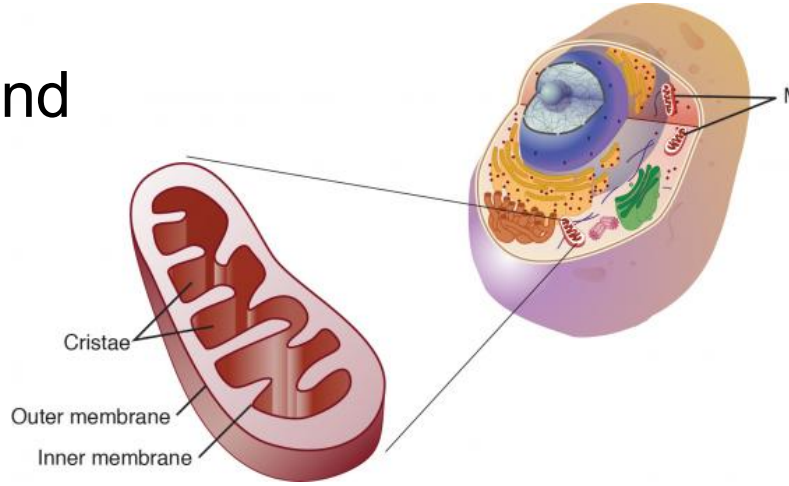


Cerychova et al., 2

itochondria in the heart

Heart is enriched in mt due to its high energy demand

- ATP production
- Calcium and oxygen handling
- Cell signaling
- ROS production



Mitochondrial quality control is crucial for cardiomyocyte homeostasis and surviv

CH alters mt components

- ↑ ROS production
- mK_{ATP} channels
- BK_{Ca} channels
- Mitochondrial dynamics and degradation

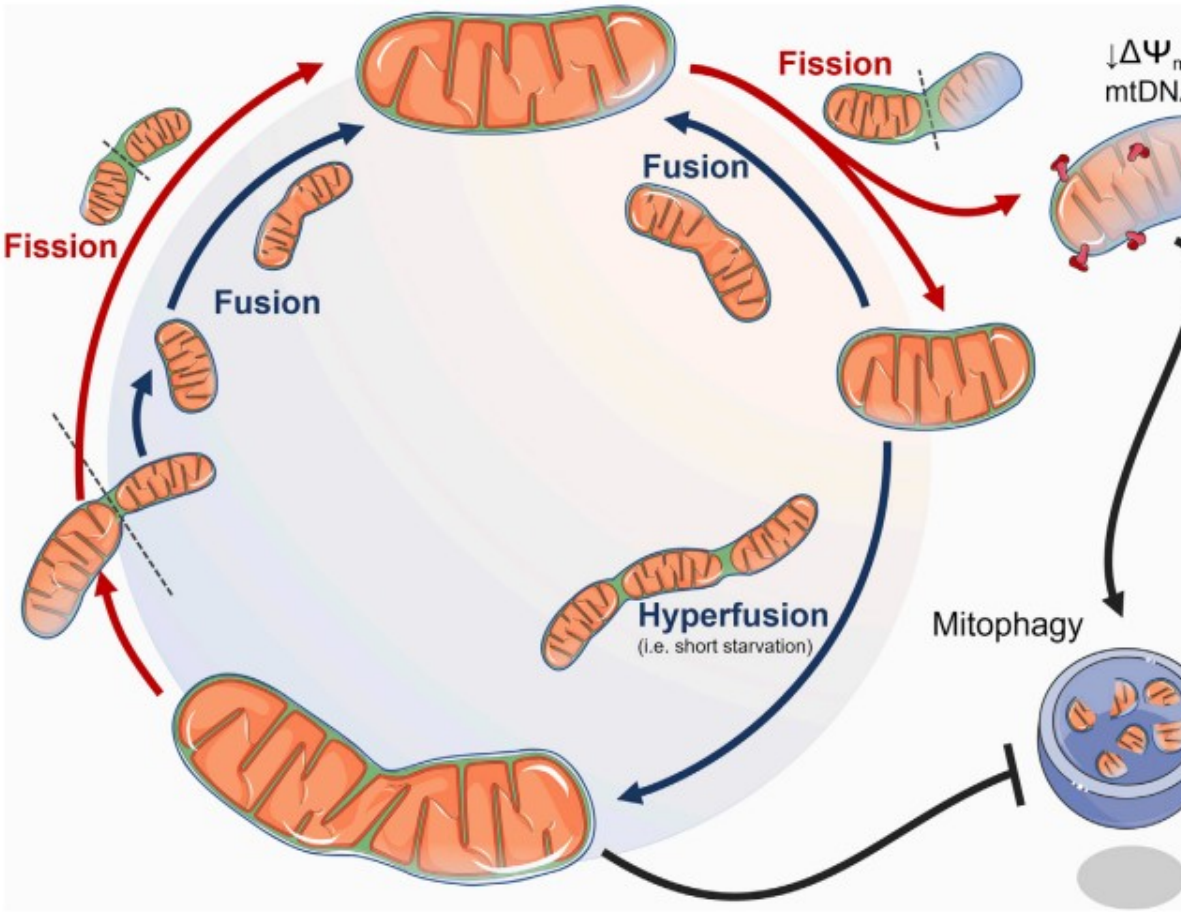
itochondrial dynamics

ynamic networks

usion and fission
mitochondria-shaping proteins
(Mfn1, Mfn2, Opa1, Drp1)

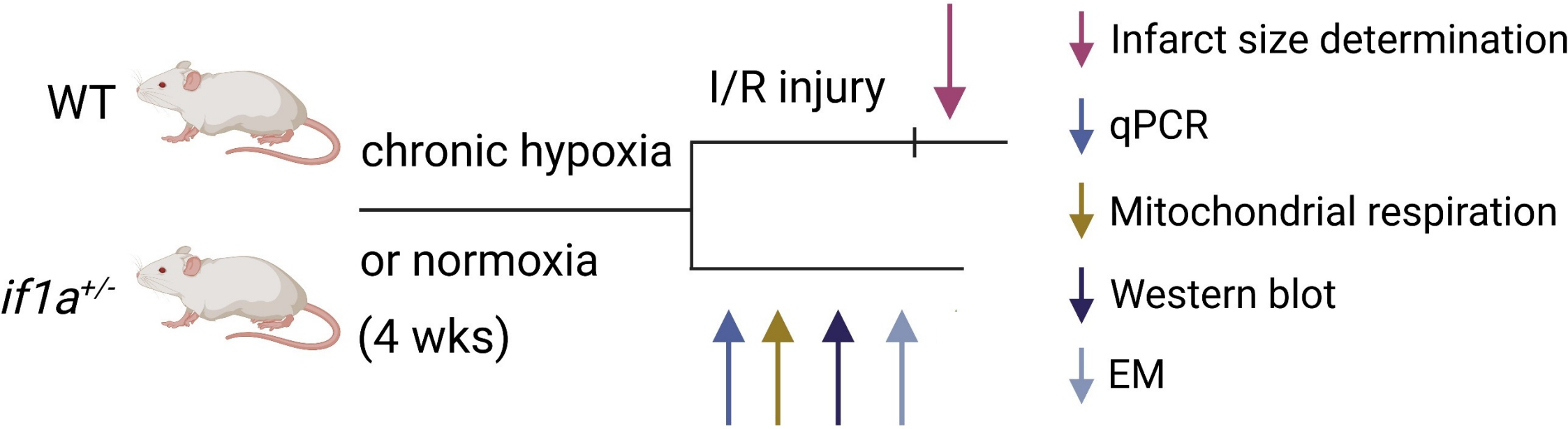
fusion: exchange of genetic material

fission: division, mitophagy



Quintana-Cabrera and Scorrano, Mol Cell 2

ethodology



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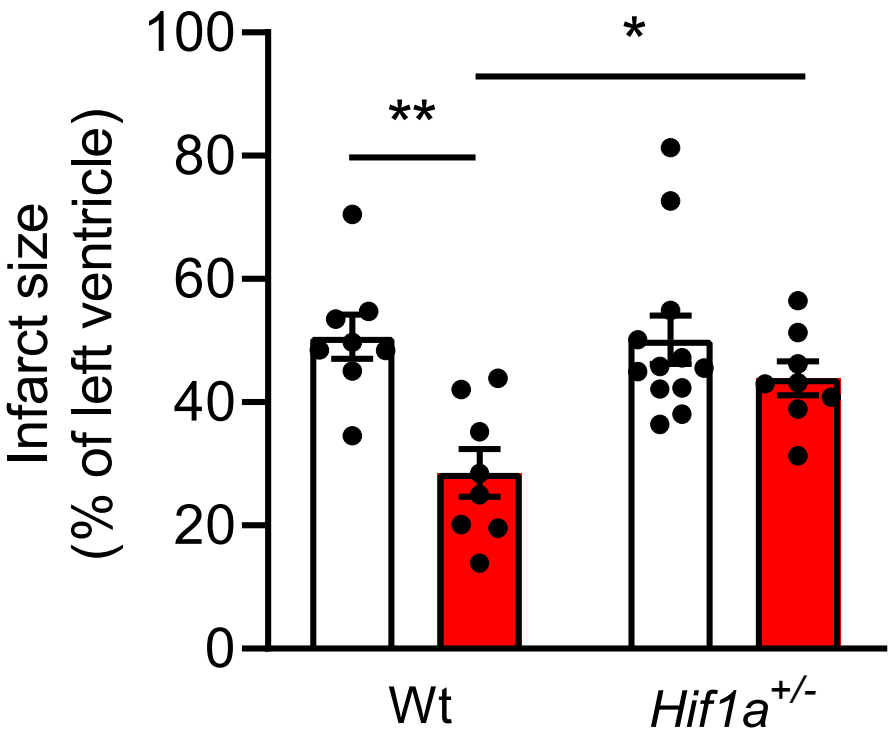
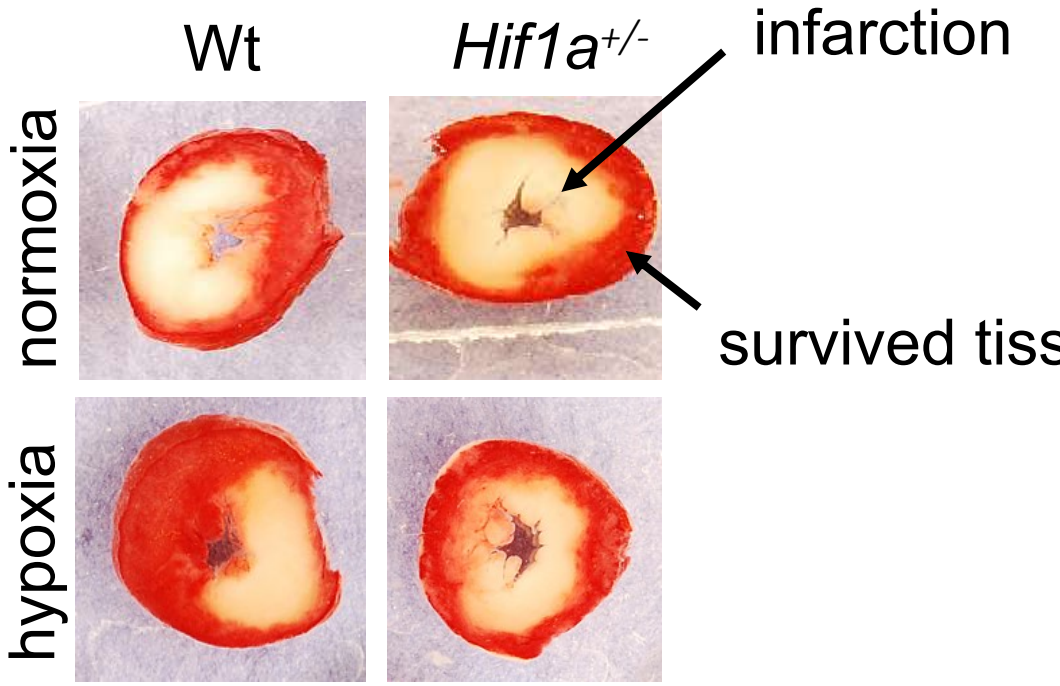
rtial *Hif1a* deficiency inhibited CH-induced cardioprotection

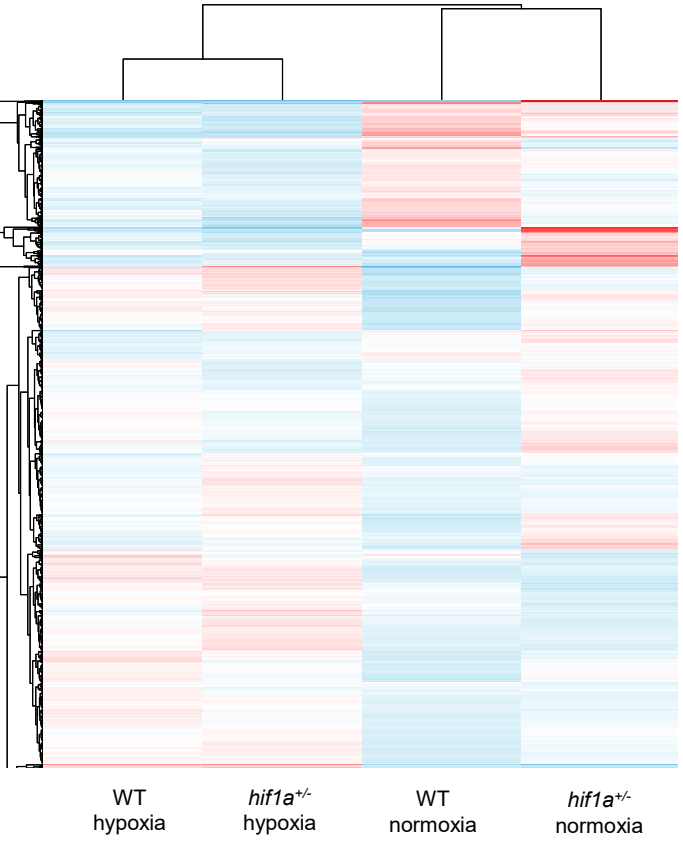


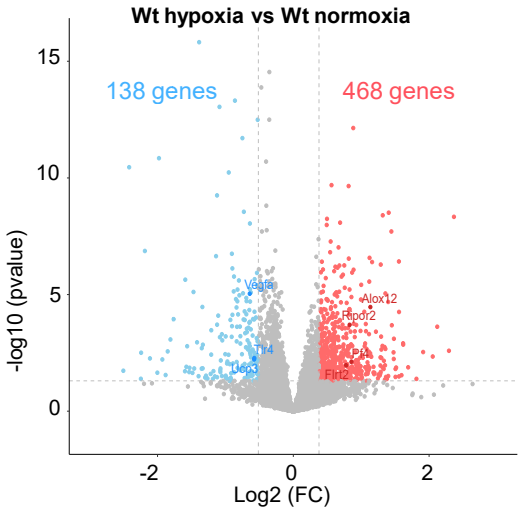


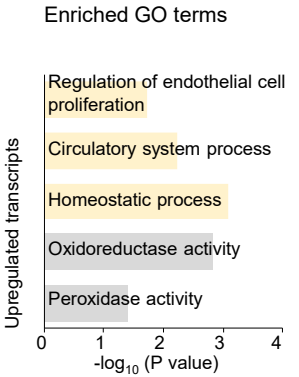
normoxia

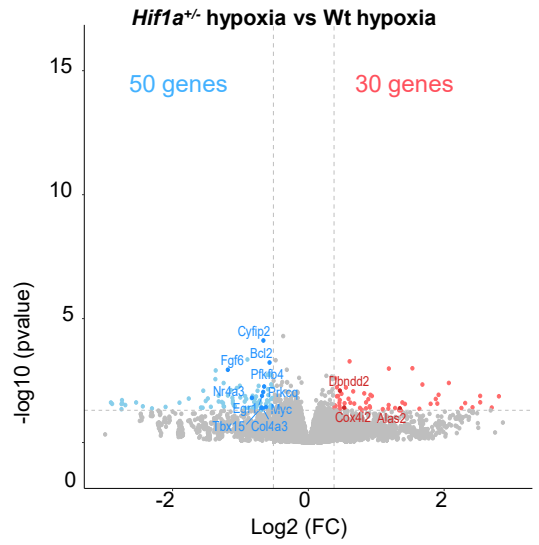
hypoxia

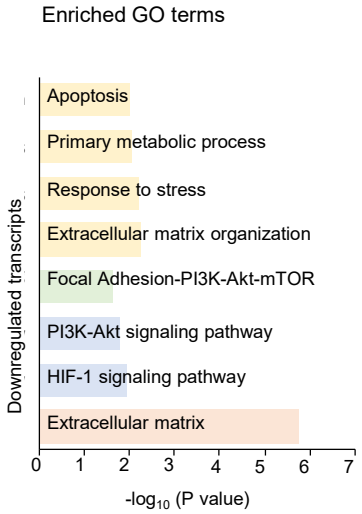
H induced changes in the transcriptome of cardiomyocytes



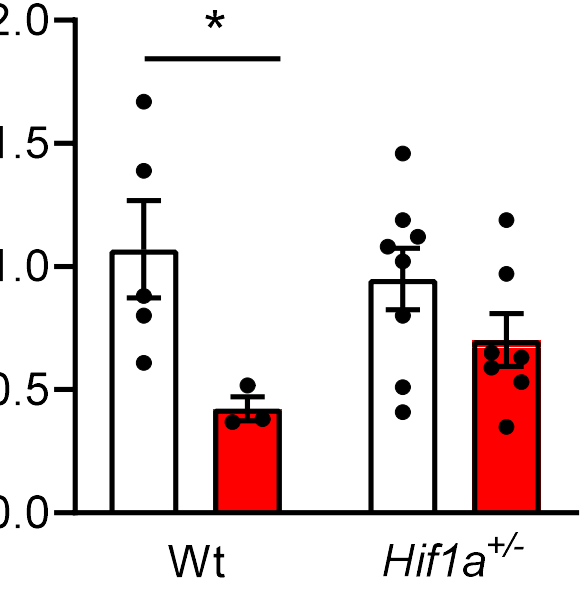


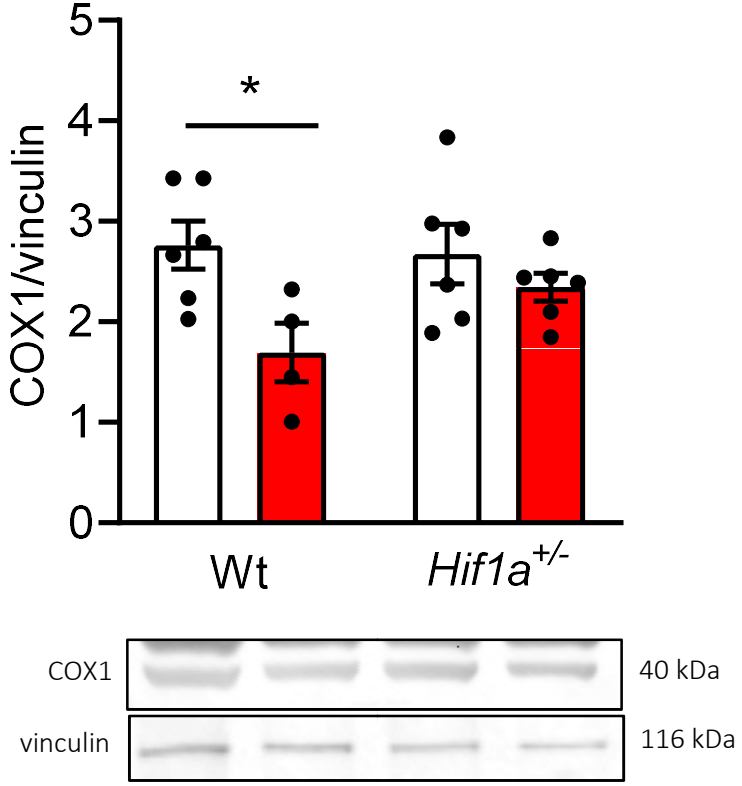


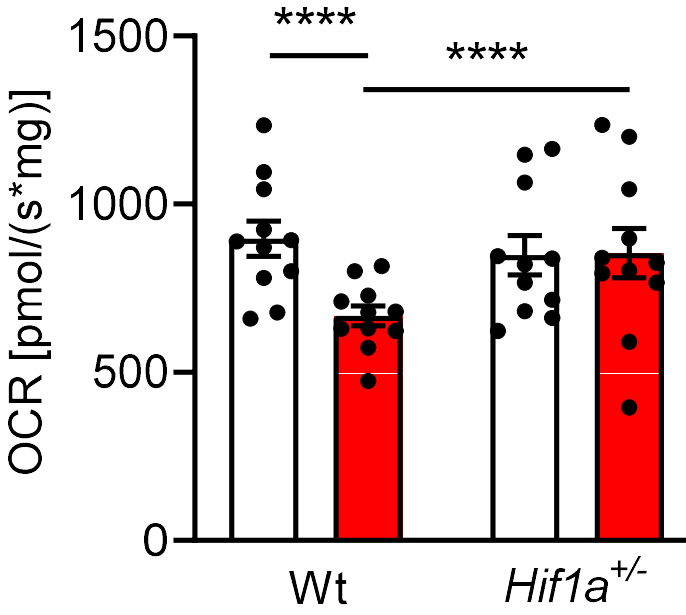




H reduced mitochondrial content and altered its function



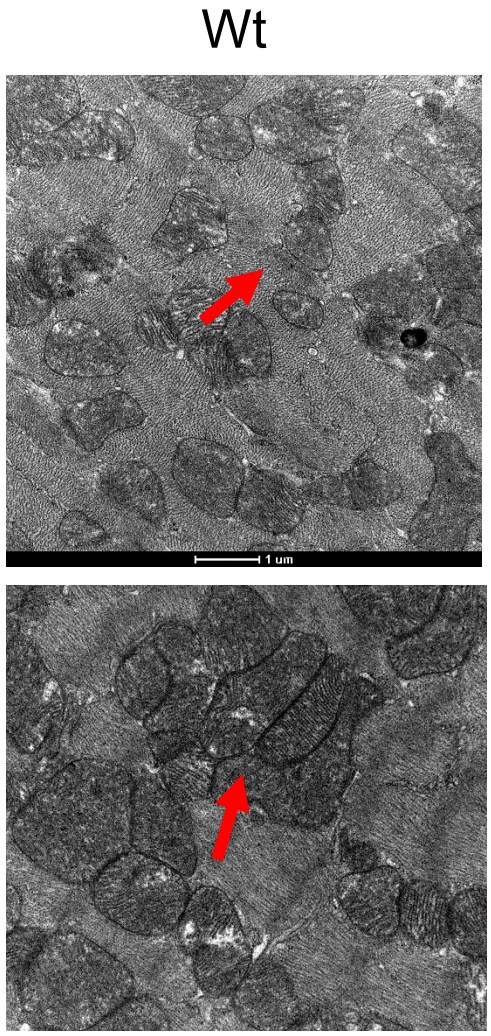


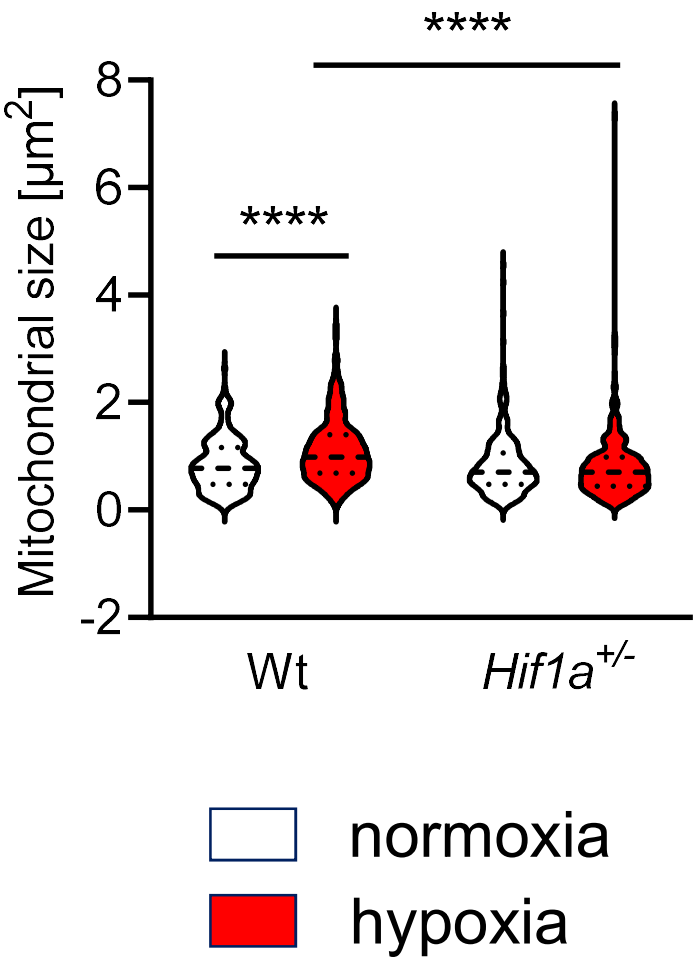


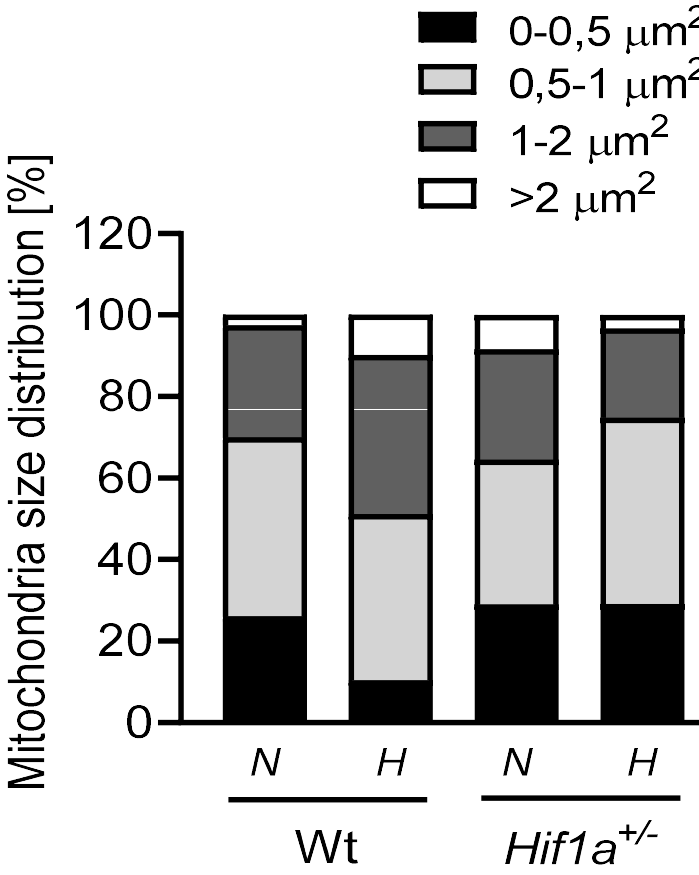
normoxia

hypoxia

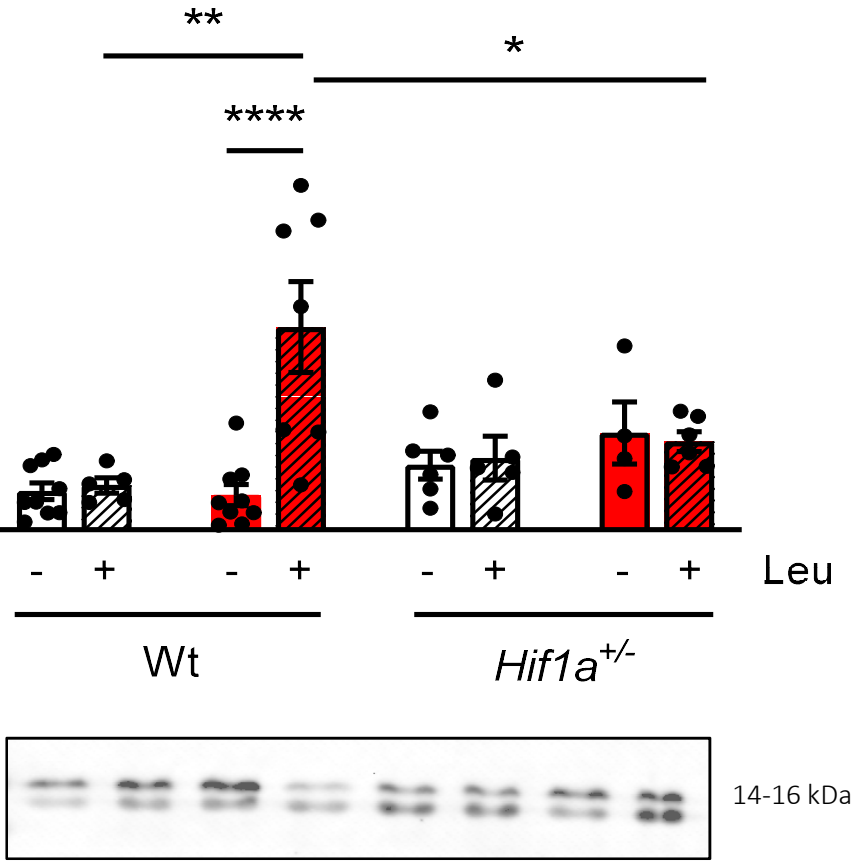
H altered mitochondrial ultrastructure

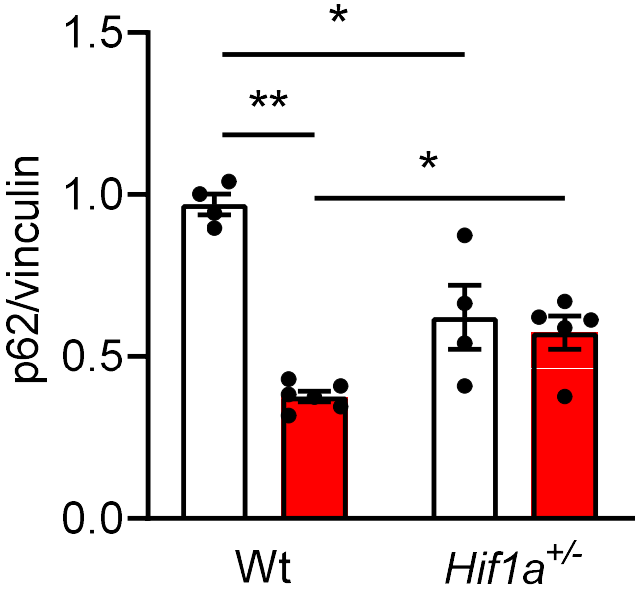


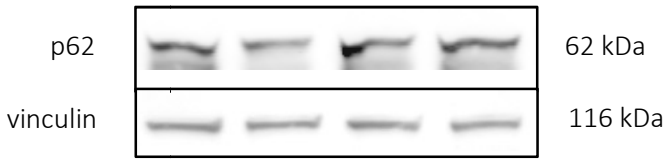


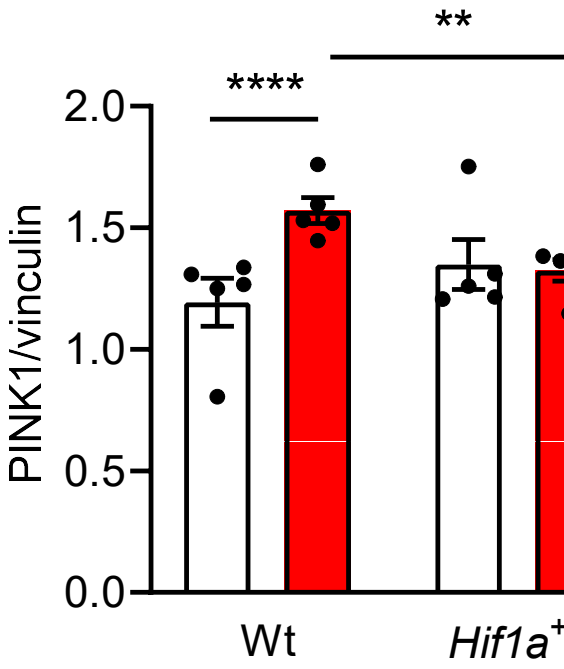


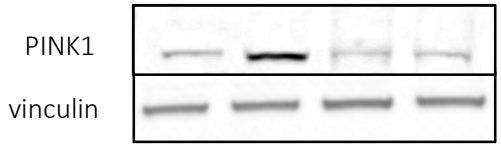
H induced autophagic flux

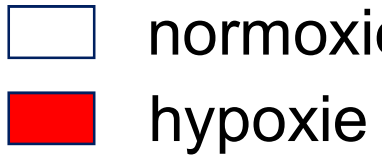




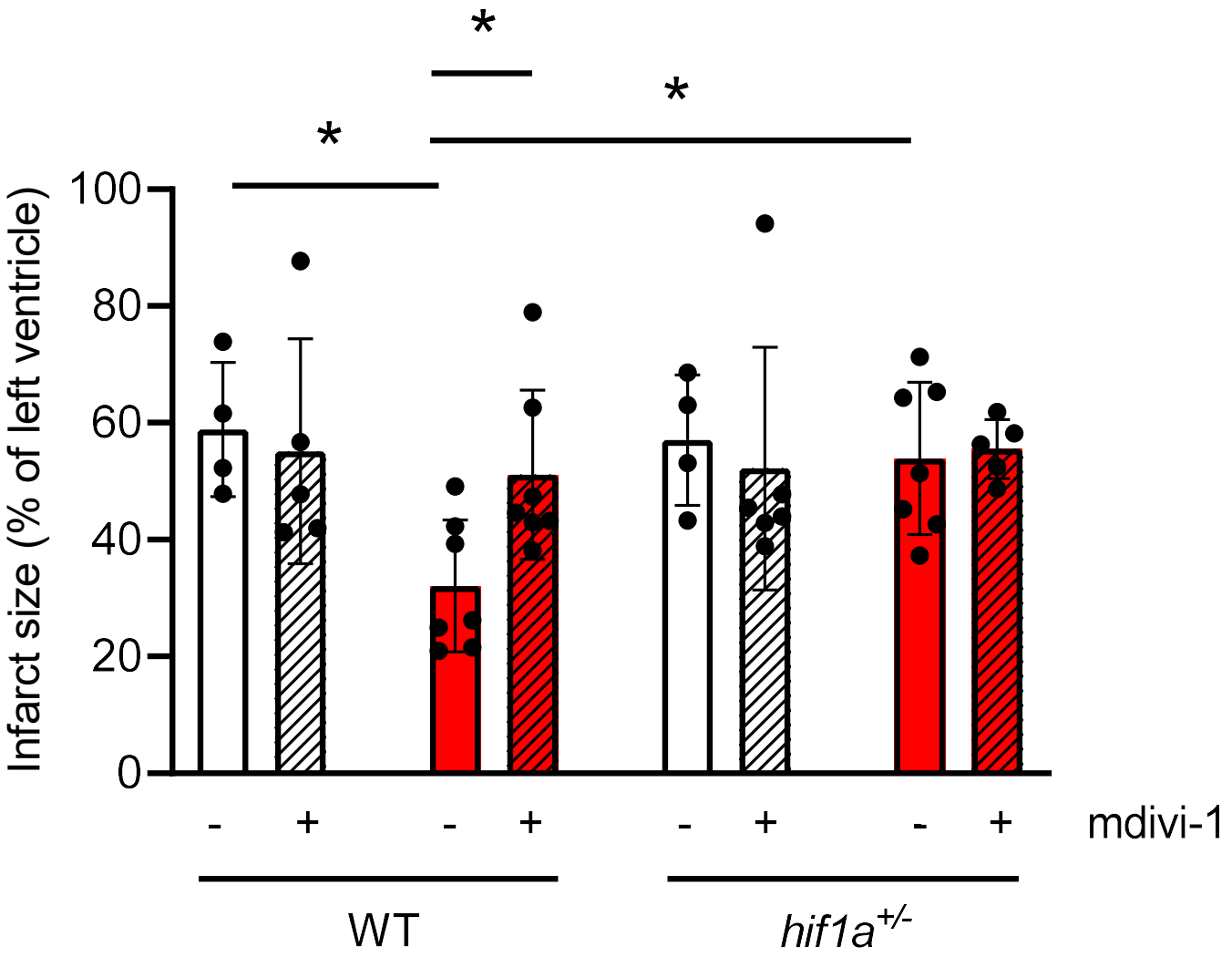








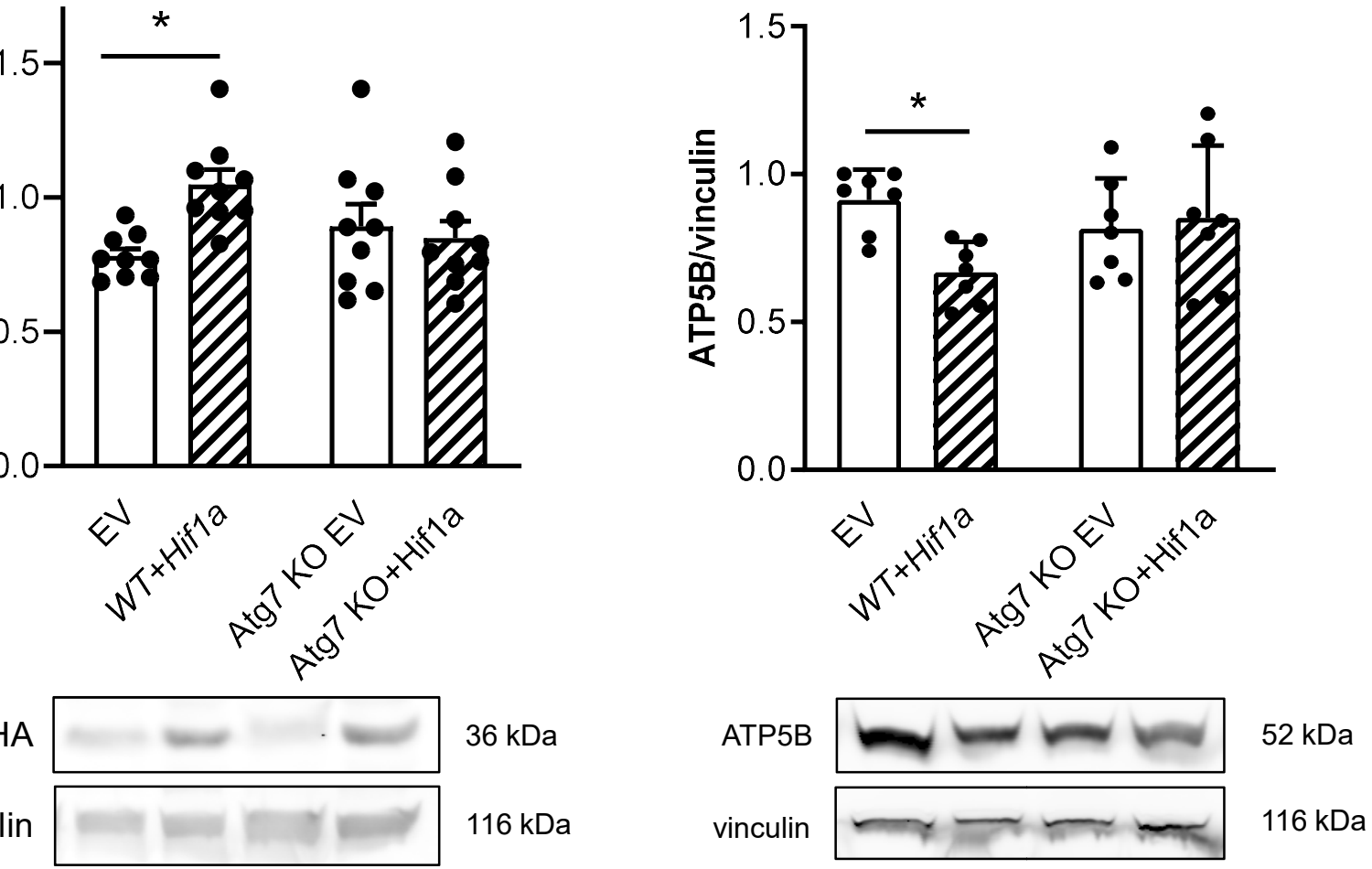
F-1α-activated mitophagy was necessary for CH-induced cardioprotection



mdivi-1:
- Mitochondrial fission inhibitor
- 25 mg/kg, i.p.

normoxia
hypoxia

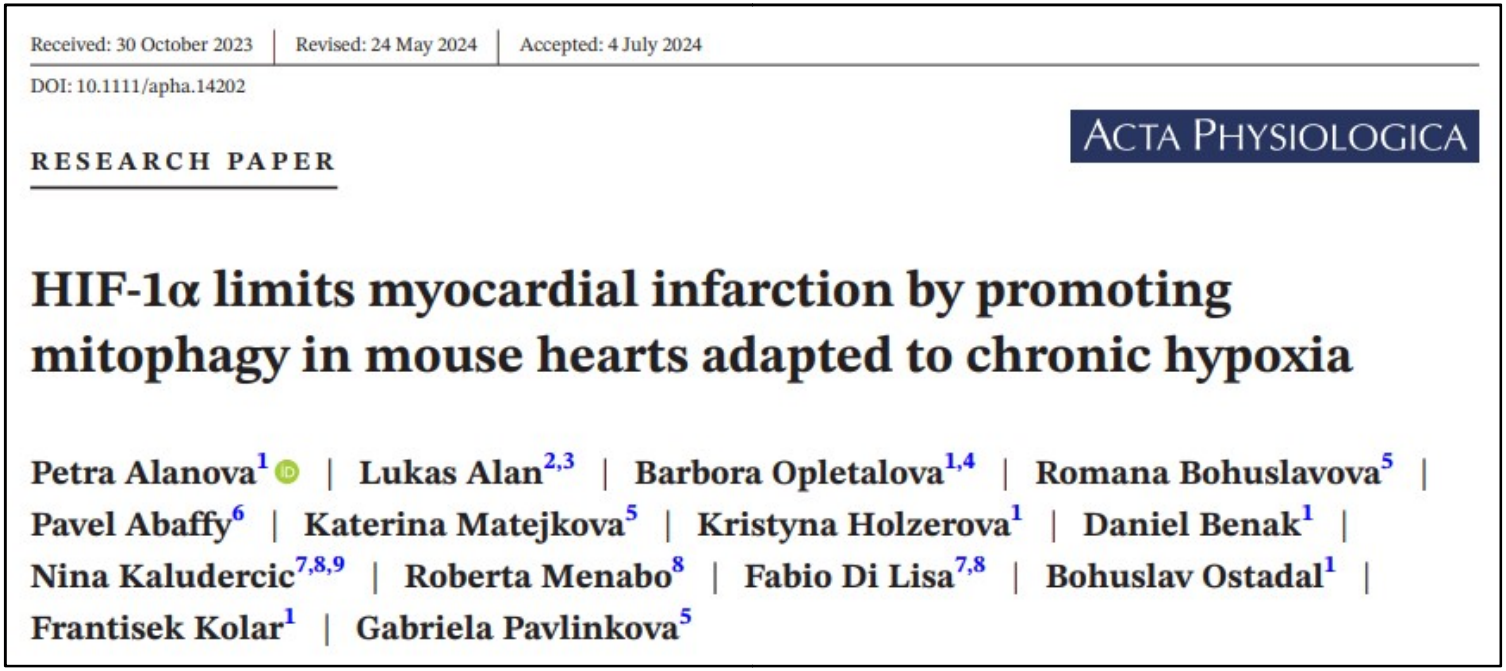
echanism verified *in vitro*



- AC16 cell line
- CRISPR-Cas9 → *Atg7* knock (KO)
- ATG7 - key autophagy protei
- Transfection
  - empty vector (EV)
  - *Hif1a* plasmid (resistant to prolyl-hydroxylases degrada

onclusion

HIF-1α enhances degradation of possibly harmful mitochondria by activating mitophagy and thus, boosts the development of the cardioprotective phenotype



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ACTA PHYSIOLOGICA

RESEARCH PAPER

HIF-1α limits myocardial infarction by promoting mitophagy in mouse hearts adapted to chronic hypoxia

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