Mitochondria-ER interplay in the regulation of metabolic flexibility

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icdm International Congress of Diabetes & Metabolism 2017

Conflict of interest disclosure

None

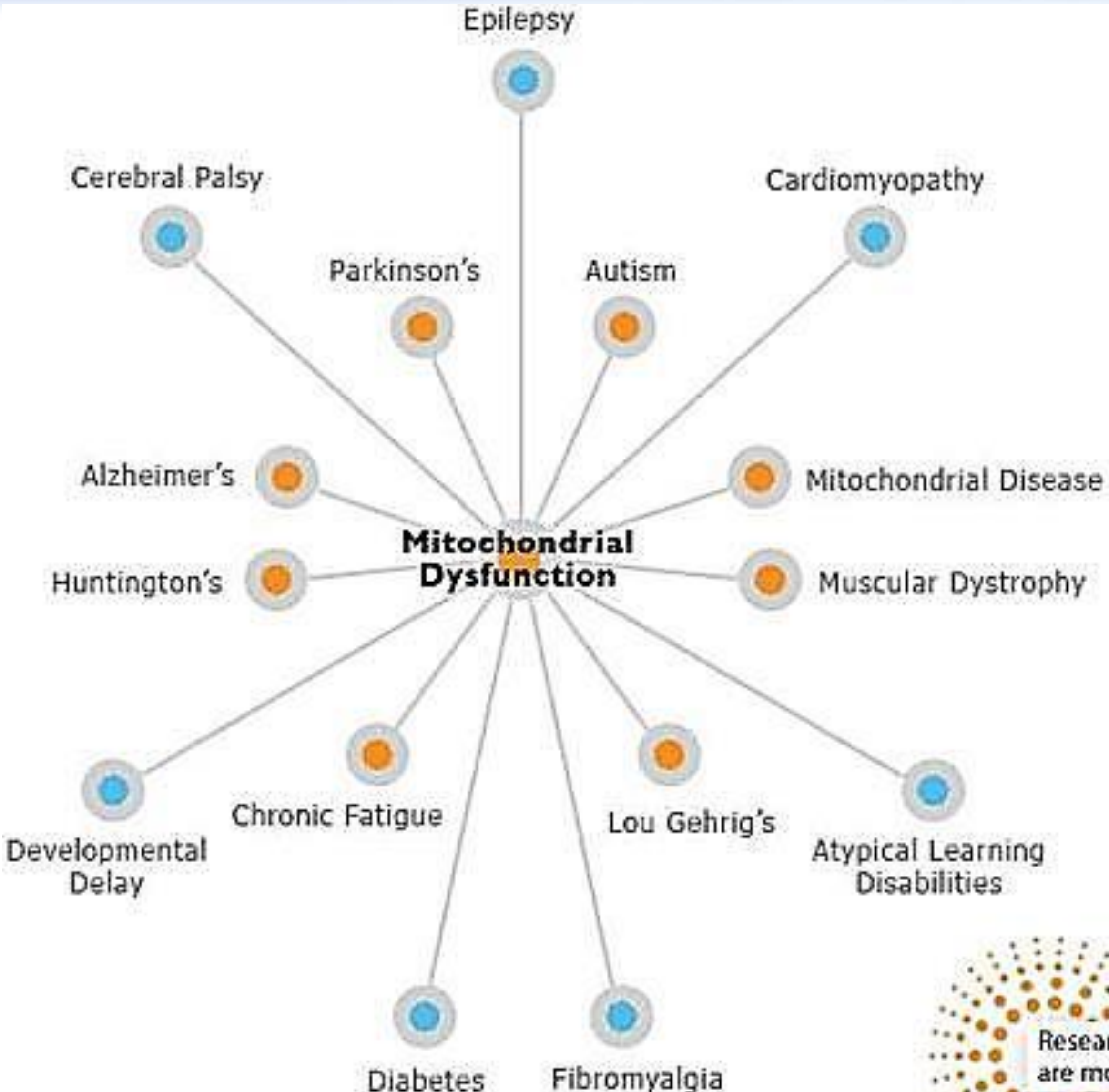
Committee of Scientific Affairs

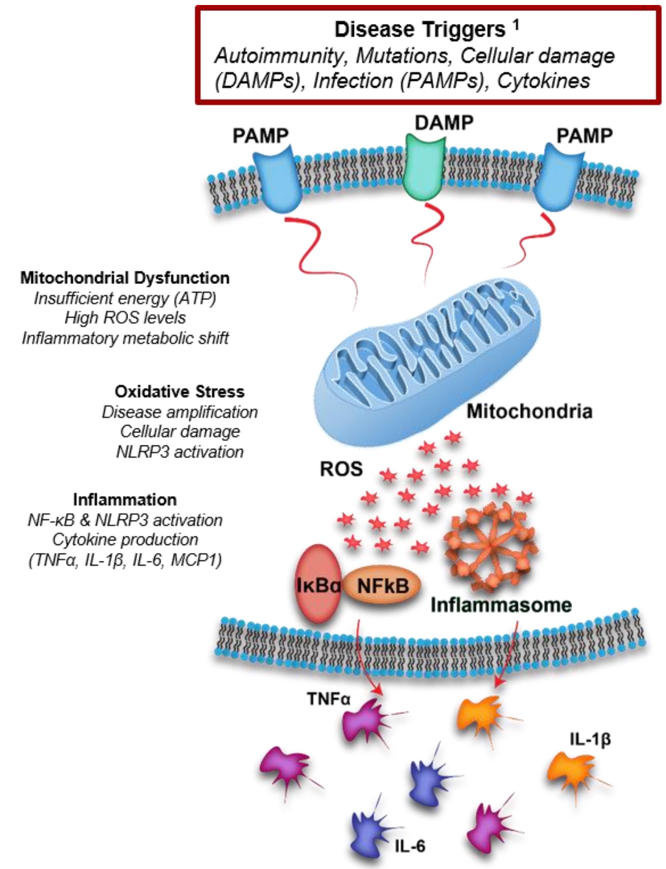
Mitochondria, "the Powerhouse" of the Cells

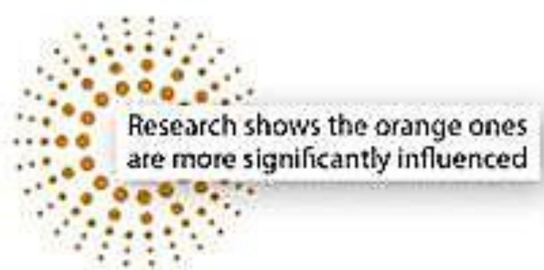
- ATP (energy)
- ROS (stress)
- Biosynthesis
- Ca2+ signaling
- Stemness
- Apoptosis

From Salk institute

Mitochondrial dysfunction and Diseases







Fast, Present and Future Research Trends in mitochondria

Mitochondrial Dysfunction

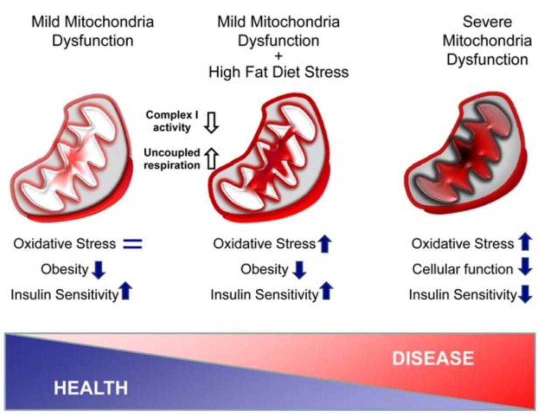
- Mitochondrial ROS
- Mito membrane potential
- Mito-mediated Cell death
- mtDNA mutation

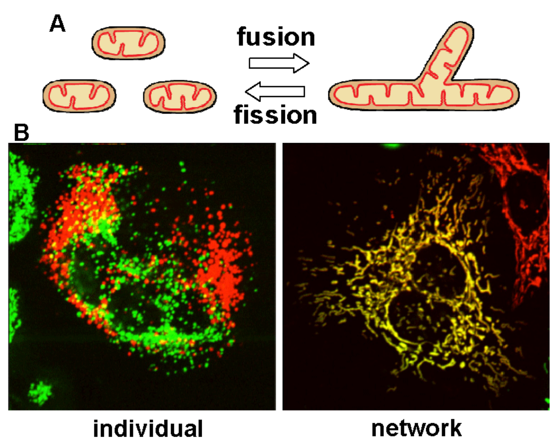
Mitochondrial Dynamics

- Fission/fusion dynamics
- Mitophagy
- Mito-Biogenesis
- Mitochondrial trafficking

Organellar Interaction

- MAM
- Mito-ER
- Mito-Peroxisome
- Mito-nuclear Retrograde signaling



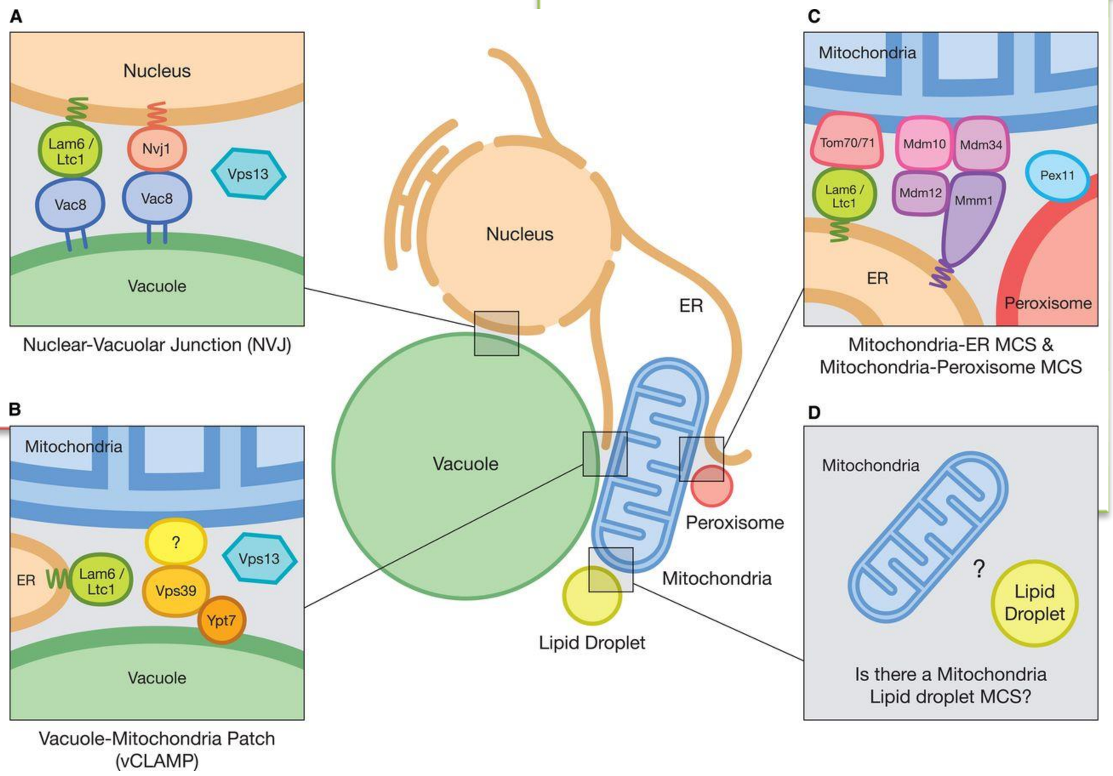


Fast, Present and Future Research Trends in mitochondria

Mitochondrial Dysfunction

Mitochondrial Dynamics

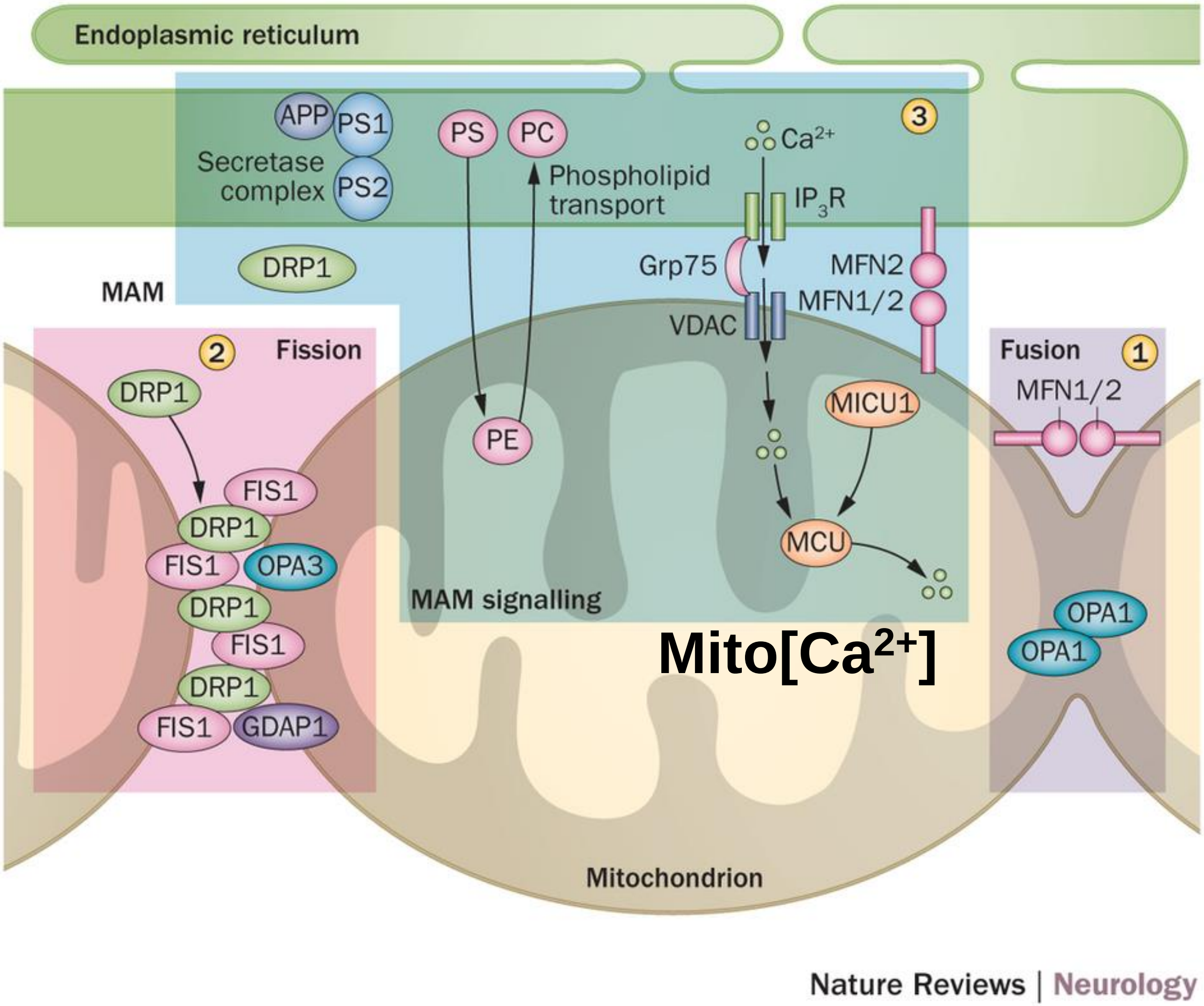
Organellar Interaction



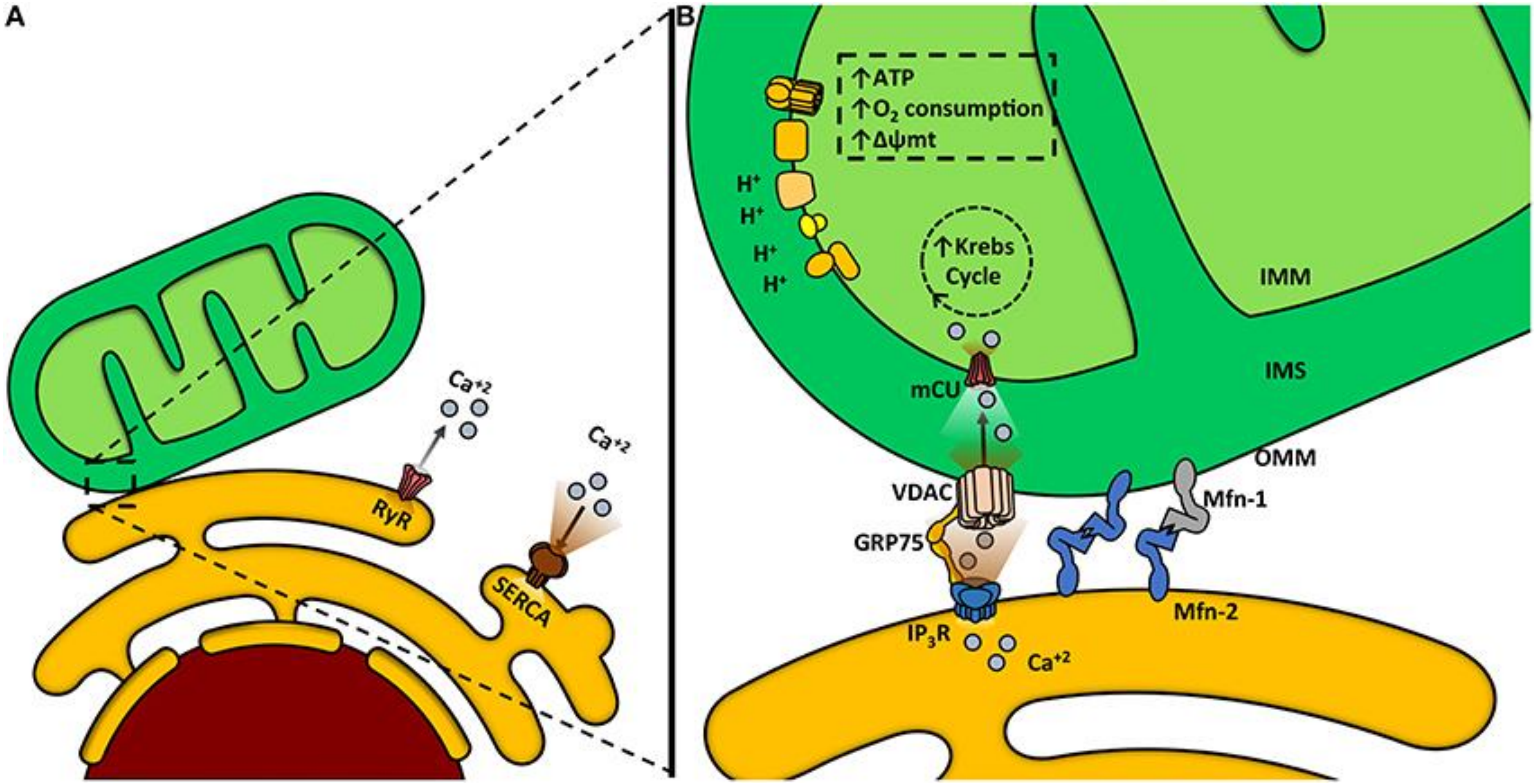
- MAM
- Mito-ER
- Mito-Peroxisome
- Mito-nuclear Retrograde signaling

ERMCS : ER and mitochondrial contact site

Mitochondria uptake Calcium from ER

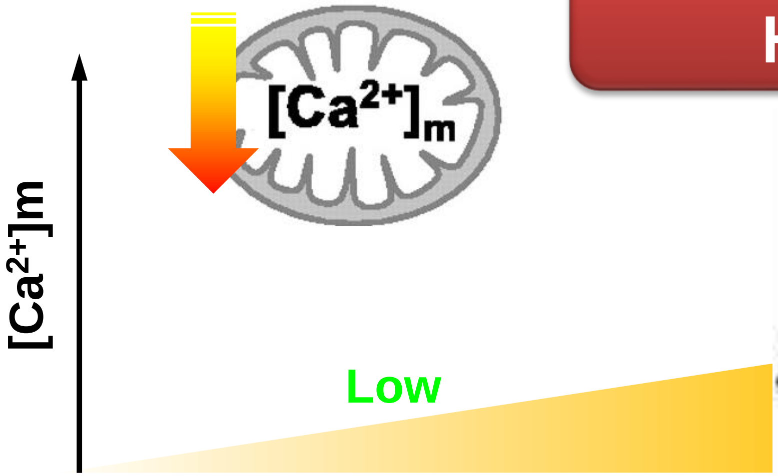


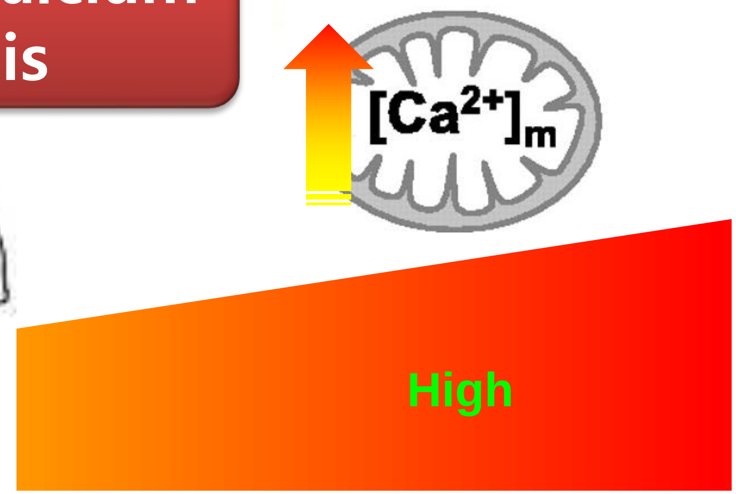
Calcium Reservoir in Cell


A
Ca+2
Ca+2
RyR
SERCA
B
↑ATP
↑O2 consumption
↑Δψmt
H+
H+
H+
H+
↑Krebs
Cycle
IMM
IMS
OMM
mCU
VDAC
GRP75
Mfn-1
Mfn-2
IP3R
Ca+2

Differential decoding of mitochondrial Ca^{2+}

Mitochondrial Calcium Homeostasis





- Limit the enzyme activities of TCA cycle
- Low ATP production

- Reduced Cell function

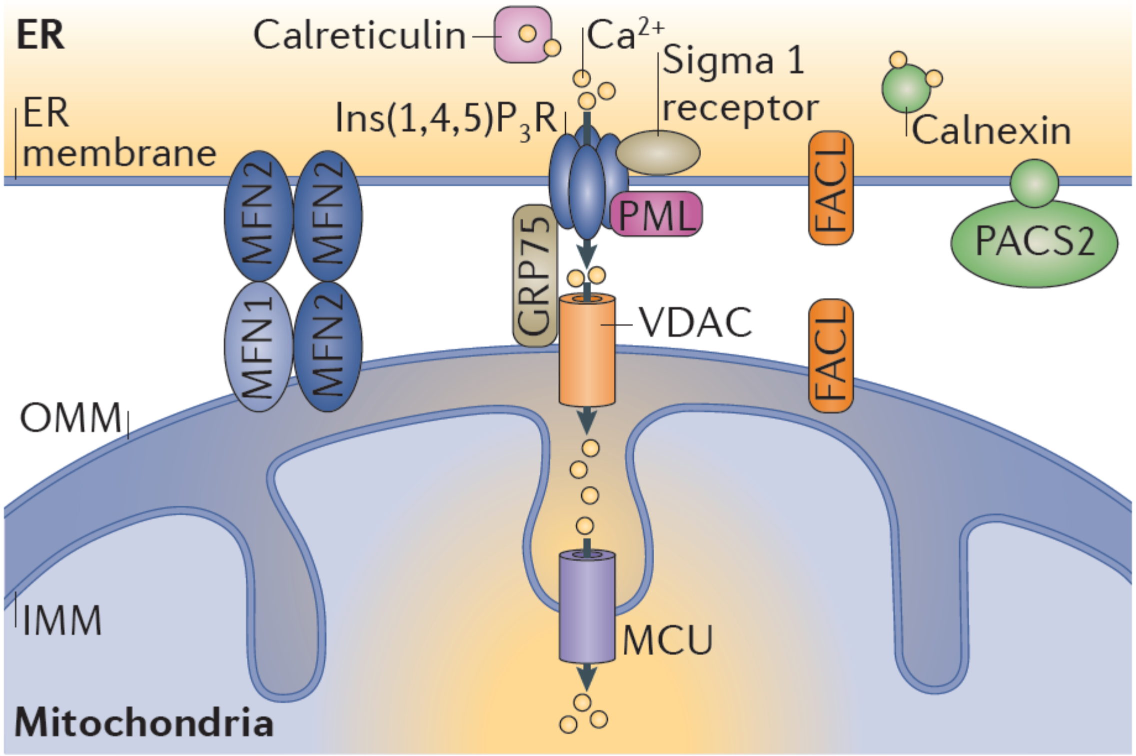
"Healthy" ATP production

- High mito-membrane potential ($\Delta\psi m$)
- High mito-ROS

- Mitochondria-mediated Cell death

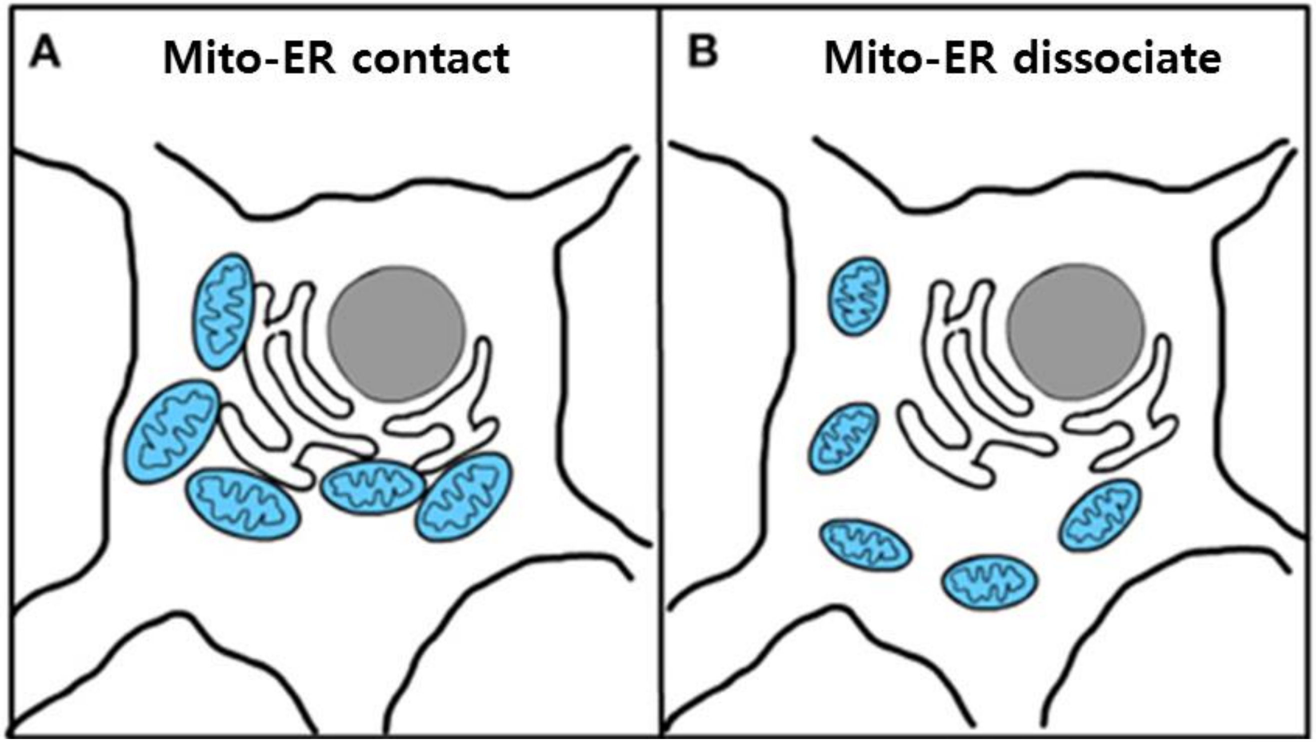
Mitochondria uptake calcium from ER via ERMCS

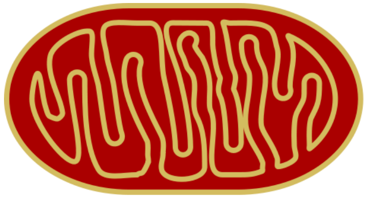
Build up of ERMCS (ER mitochondria contact site)

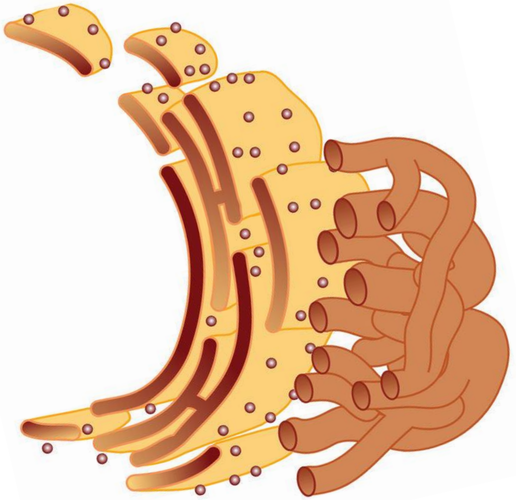


- ✓ **Mitofusin1/2 homo- heterodimer : physical linker**
- ✓ **IP3R(ER)-GRP75(linker)-VDAC(mito)-MCU1 : Calcium path**

Dynamic interaction between Mitochondria & ER

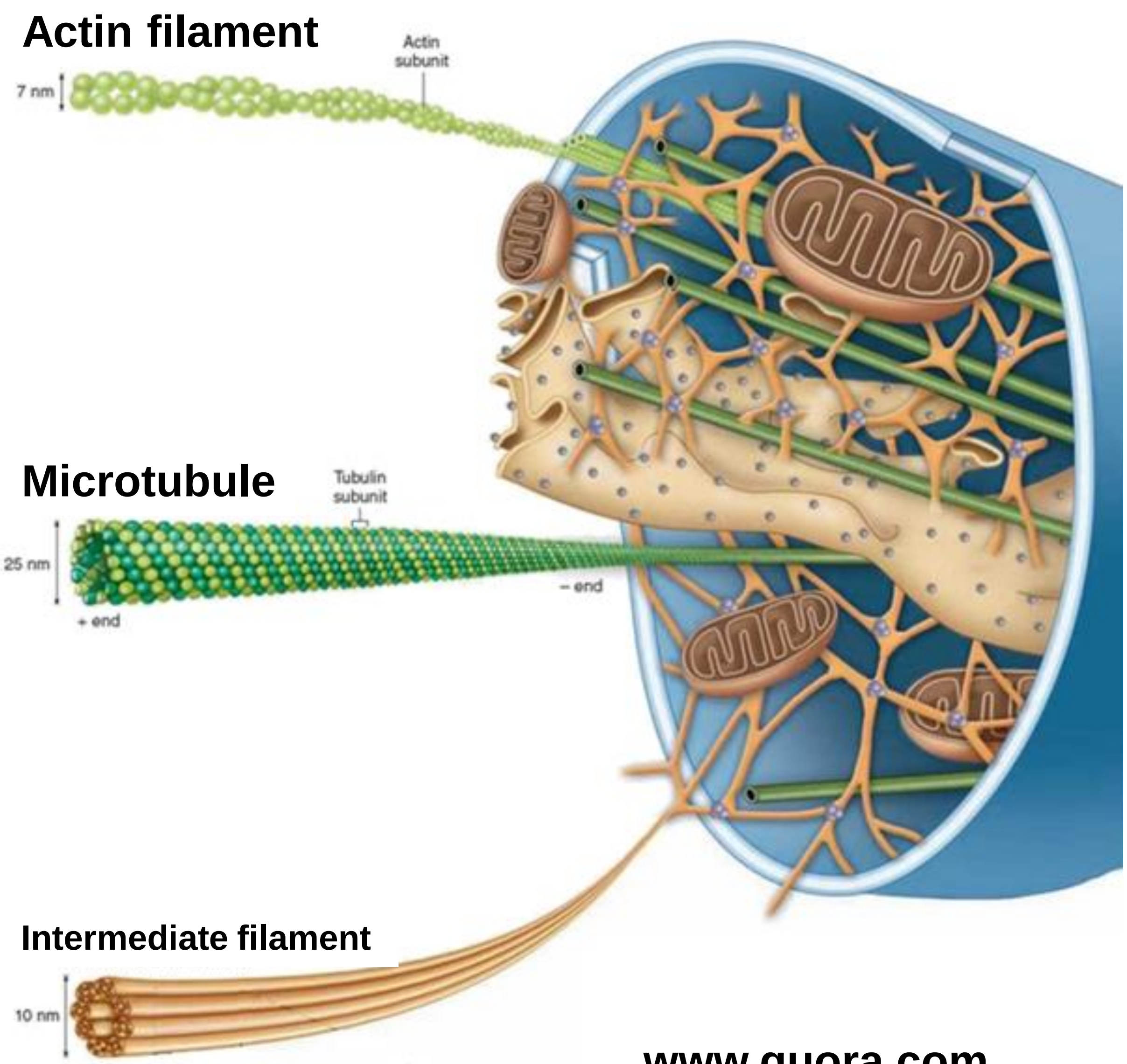


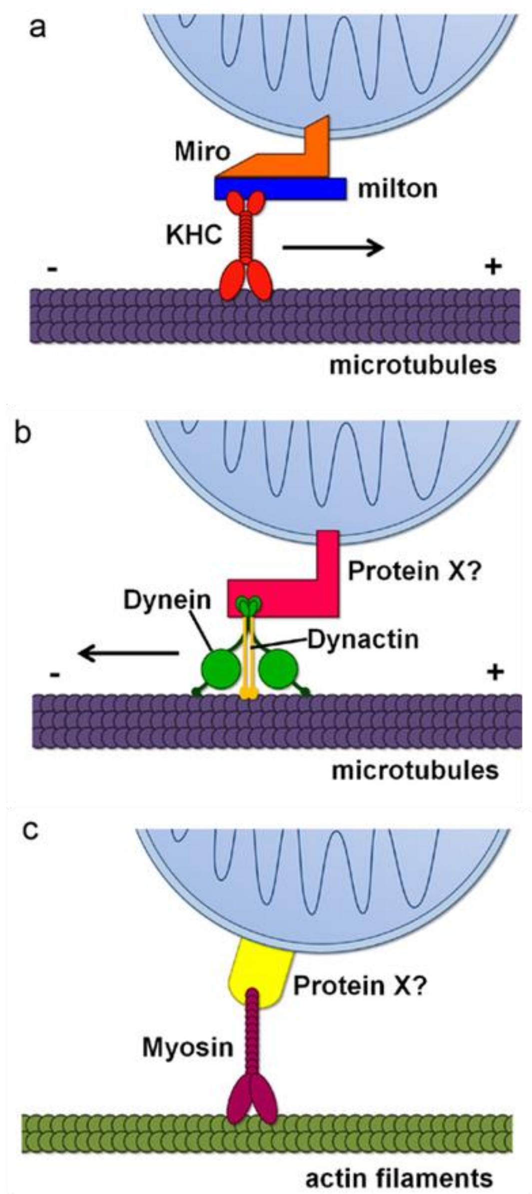




How to regulate ER mitochondrial tethering ??

Cytoskeleton mediated Mitochondrial Transporting

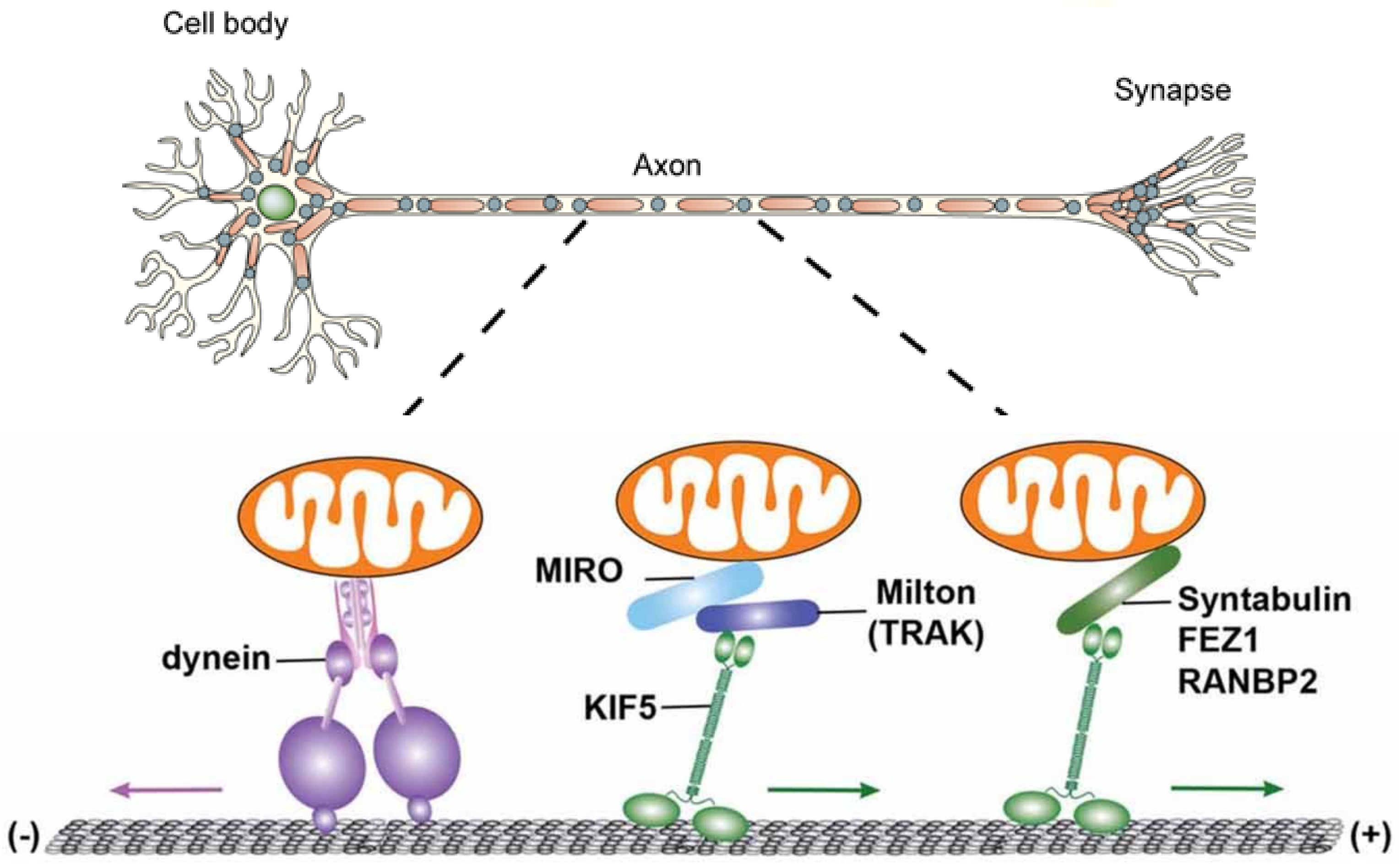




www.quora.com

Miro : Mitochondria trafficking regulator in neuron

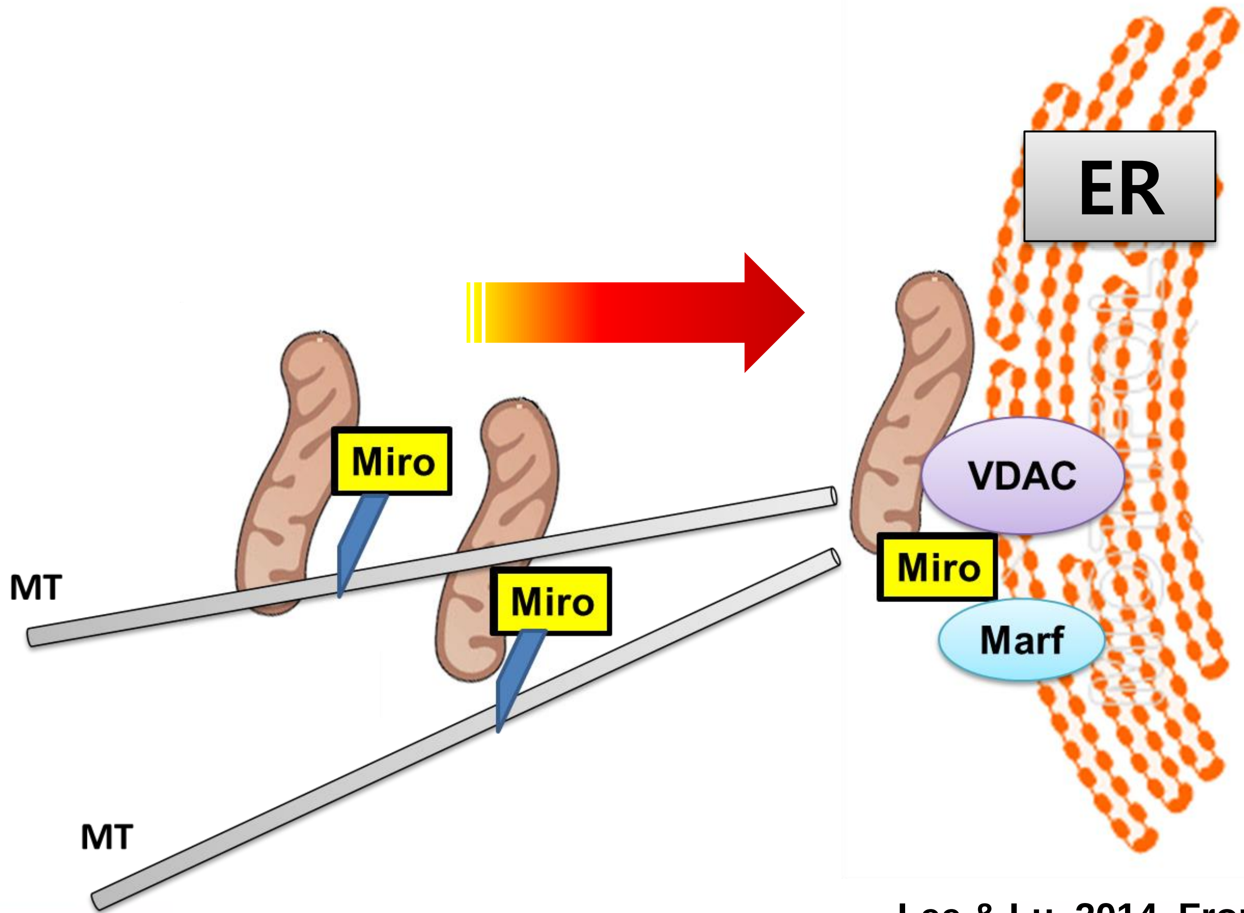
Miro (mitochondrial Rho)



Wang and Schwarz, 2011, Cell

Myriad roles of Miro : Calcium regulator?

- Miro contains two GTPase & two Calcium binding EF hand domains.
- Miro is an adaptor molecule in mitochondrial transport complex

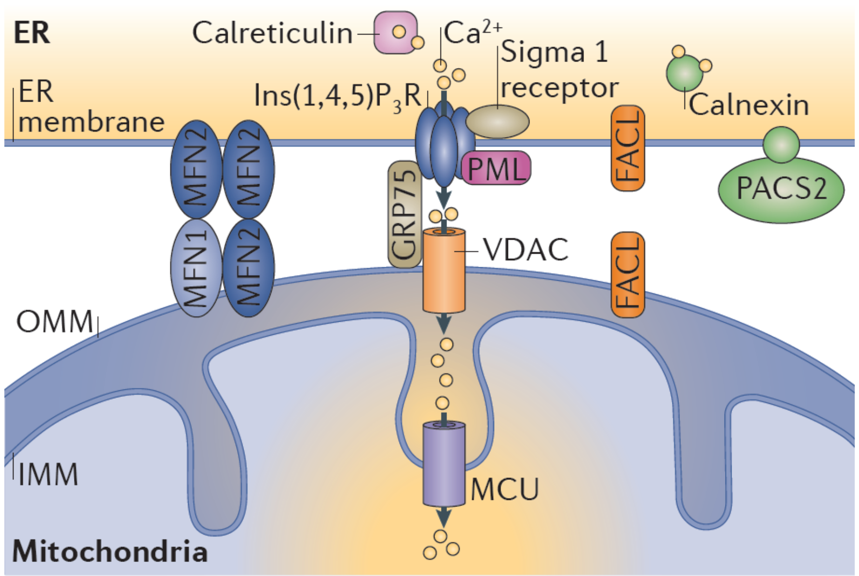


Tang, 2016, Cells

Lee & Lu, 2014, Frontier in Neuroscience

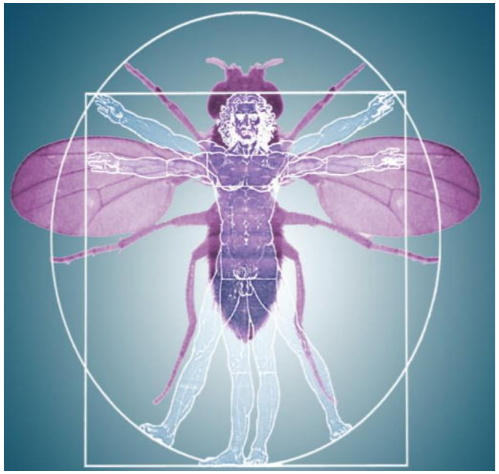
Mitochondria uptake calcium from ER via ERMCS

Build up of ERMCS (ER mitochondria contact site)



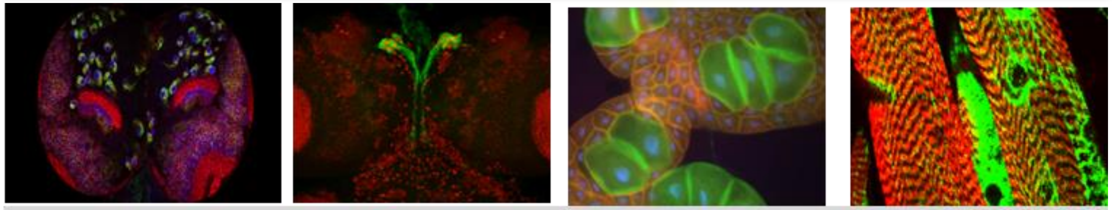
	Mammals	Fly
Calcium channels	IP3R	Itp-r83A
	VDAC	Porin
	GRP75	Hsc70-5
	MCU1	dMCU1
Tethering linker	Mitofusin1	Marf
	Mitofusin2	Marf
Mitochondrial movement	Rhot1	Miro

Drosophila tool kit for organelle dynamics



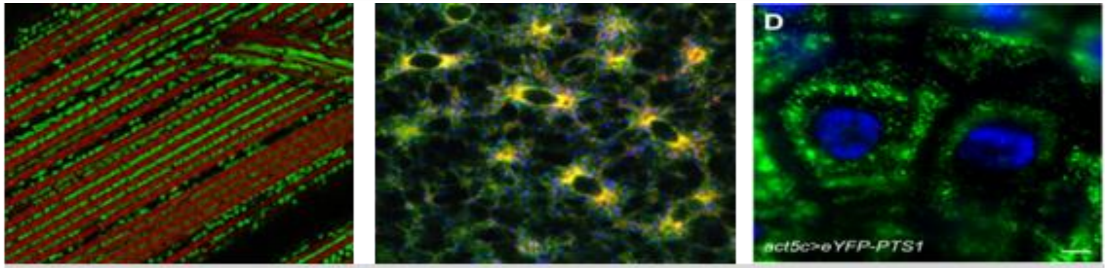
- ✓ Gal4/UAS system
- ✓ Tissue specific Gal4 drivers
- ✓ Target gene GOF & LOF lines
- ✓ Genome wide RNAi lines
- ✓ CRISPR/Cas9 system
- ✓ Organelle marker Transgenic

Tissue-specific gene regulation



NSC | IPC | Fat body | Muscle

Organelle dynamics and bioenergetics

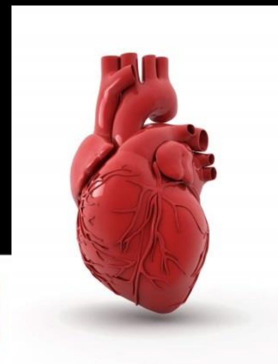


mitochondria | ER | peroxisome

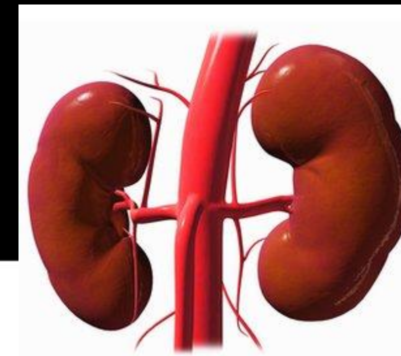
Drosophila counterparts of mammalian tissues

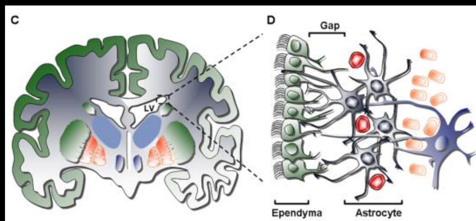
Tatar, Post and Yu, 2014

heart

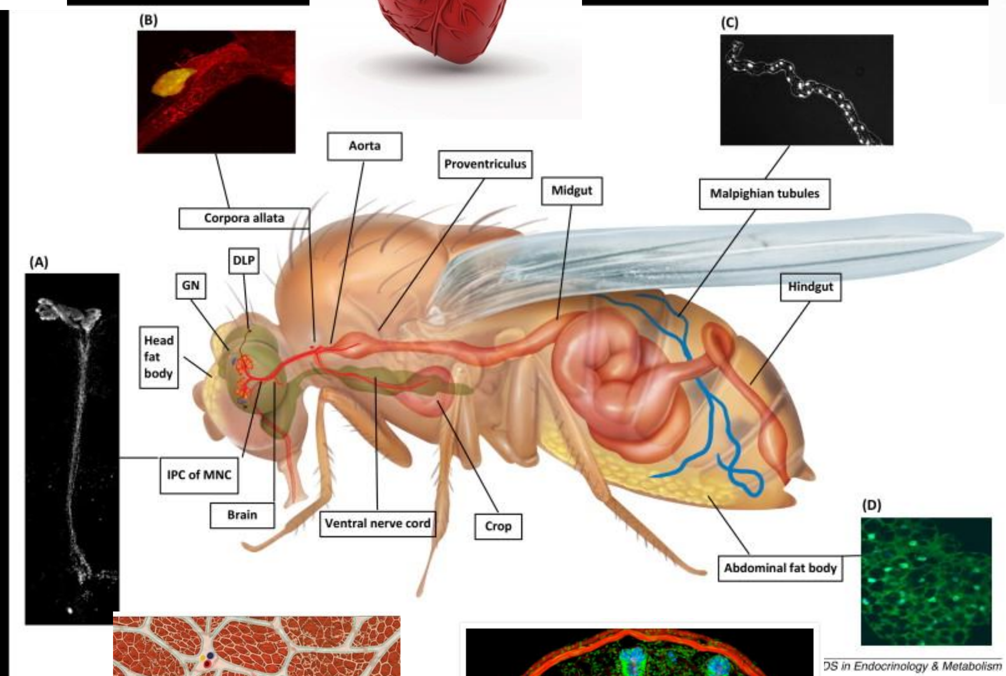


kidney

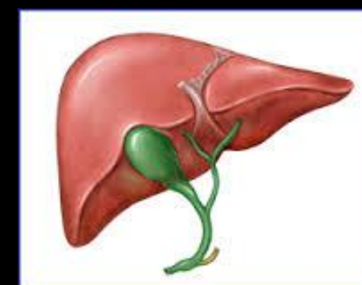




Brain/NSC

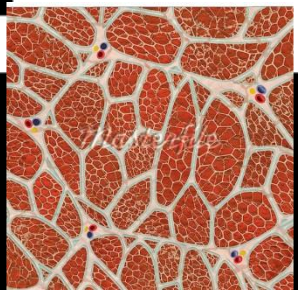


adipocyte

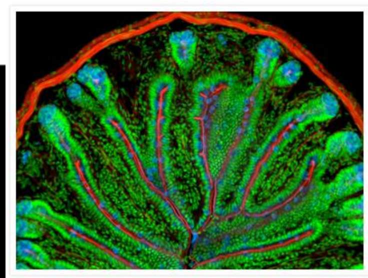


Liver

Pancreatic β cell



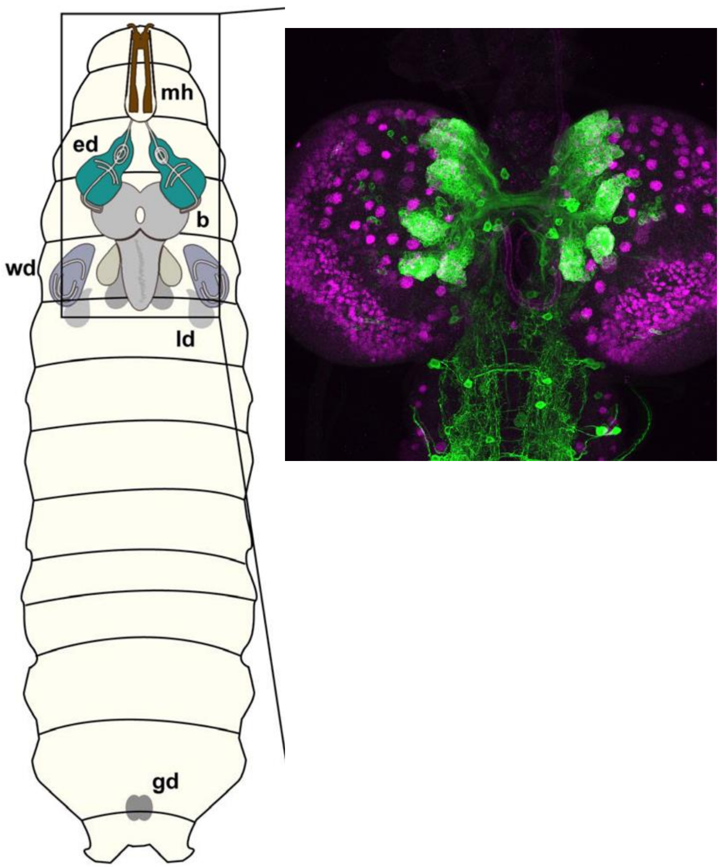
Muscle

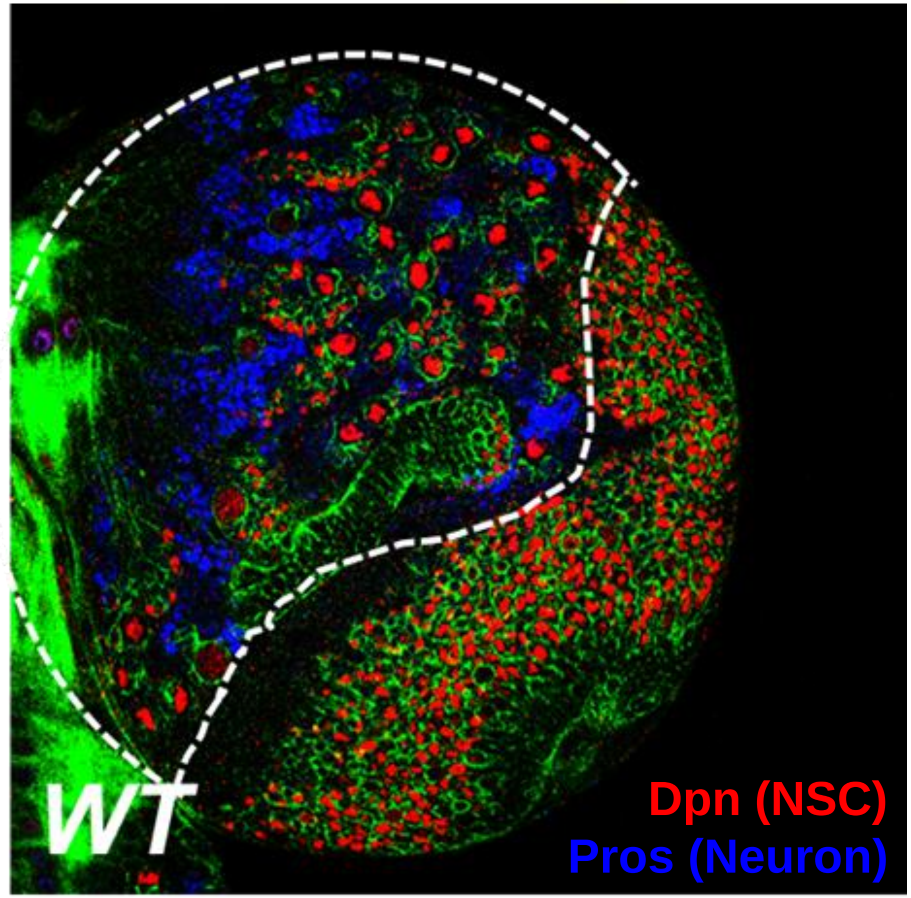


GI tract

Drosophila Model for Neural stem cell

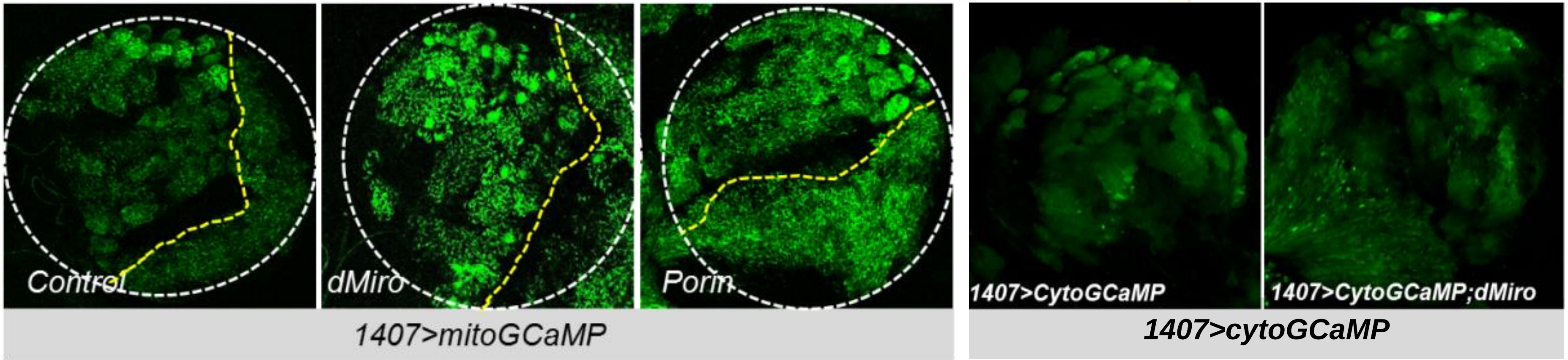
- NBs are similar to mammalian NSCs in lineage hierarchy, including the presence of transit-amplifying intermediate progenitors (IPs).



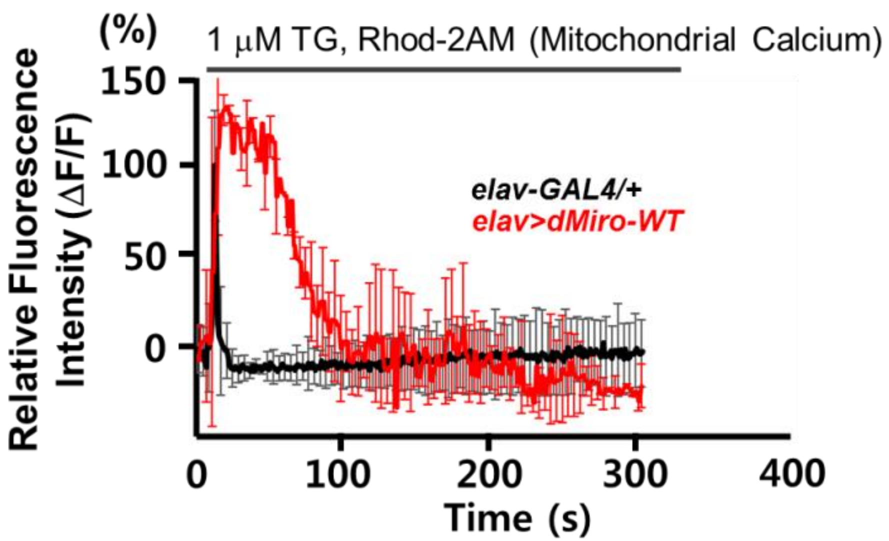


Approximately ~90 type I and 8 type II NB exist in larval brain hemisphere

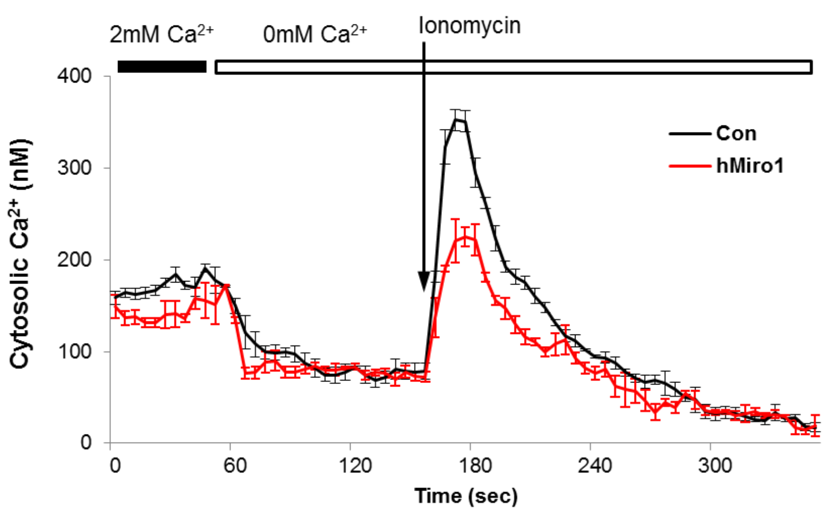
Miro regulates mitochondrial Ca2+ homeostasis



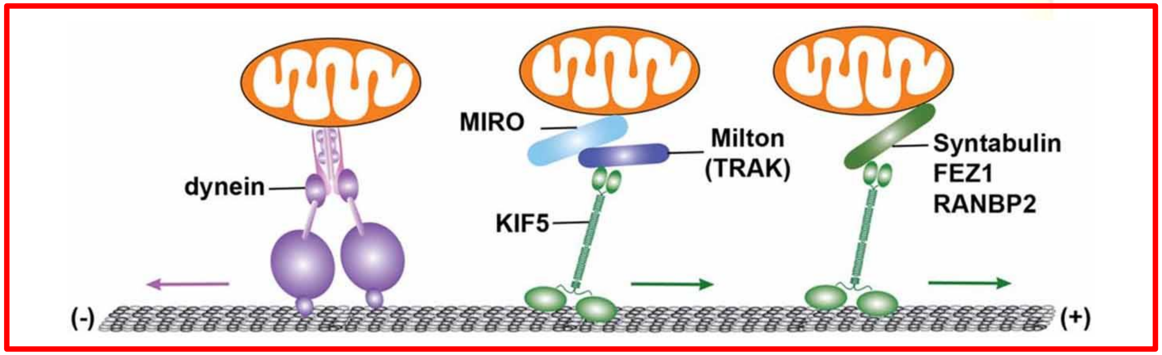
$Ca^{2+}_{[Mito]}$

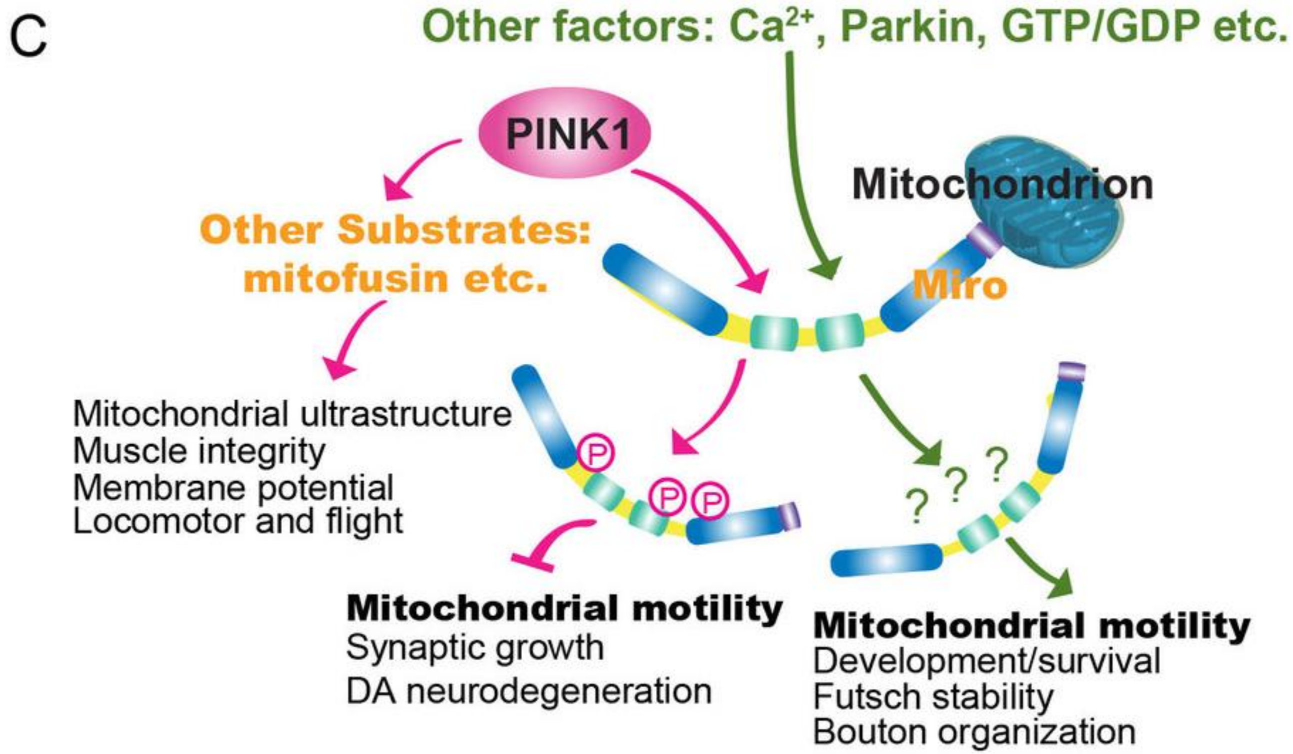


$Ca^{2+}_{[ER]}$



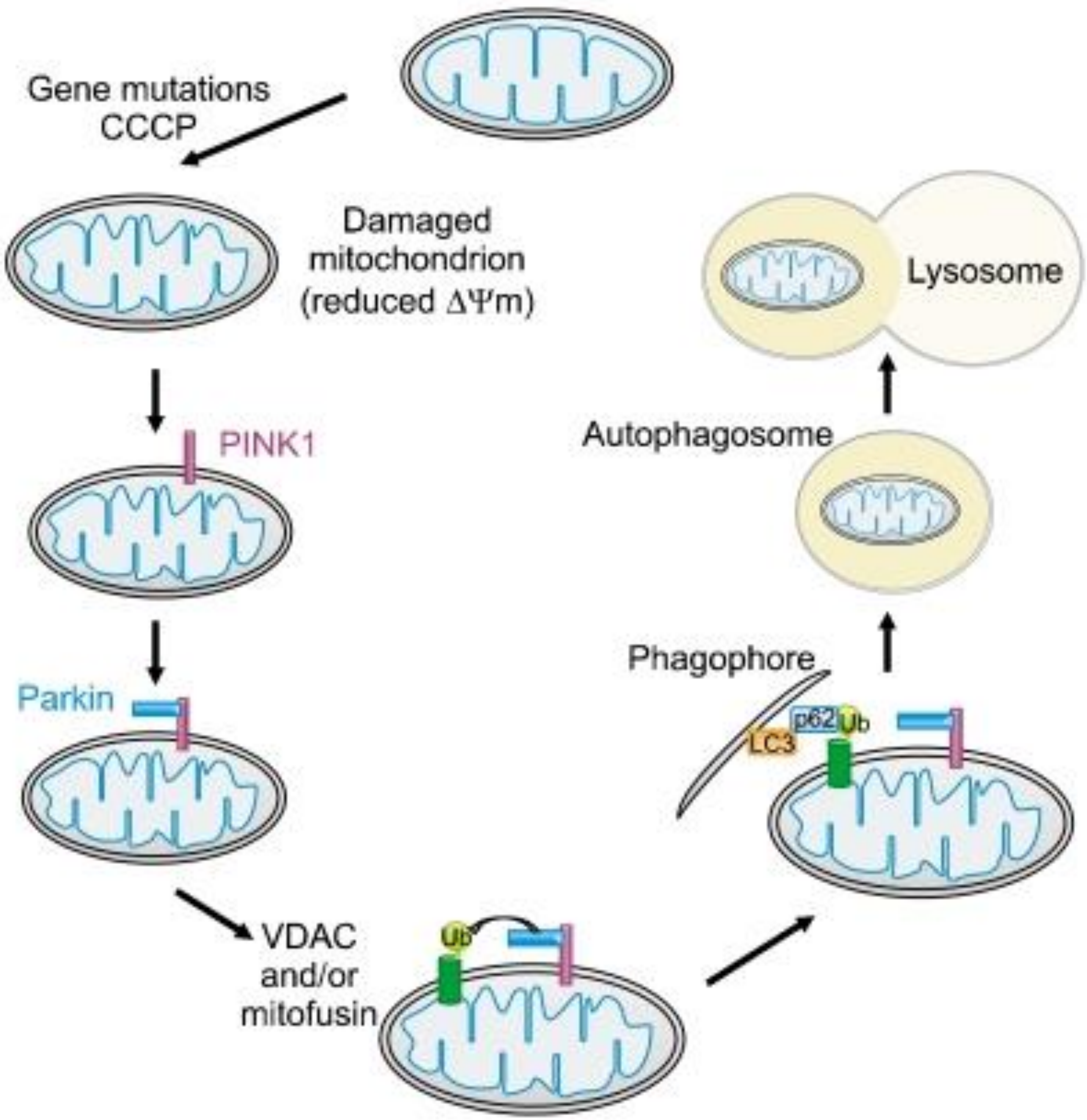
Mitochondrial motility controlled by phospho-code of Miro



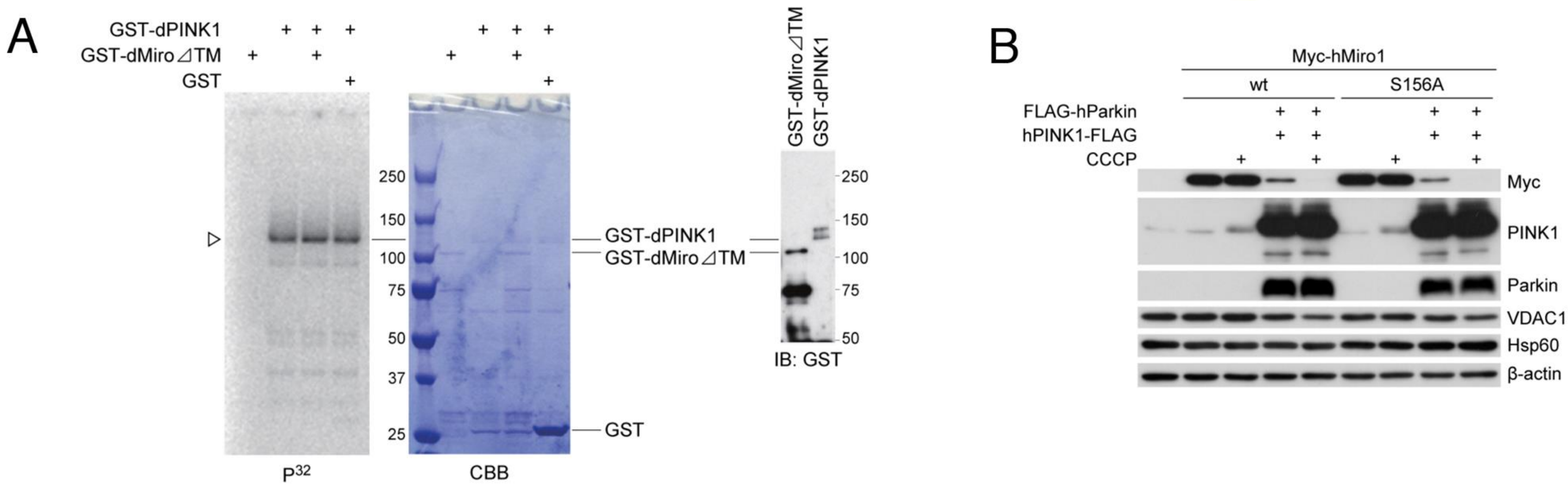


Tsai et al, 2014, Sci Rep

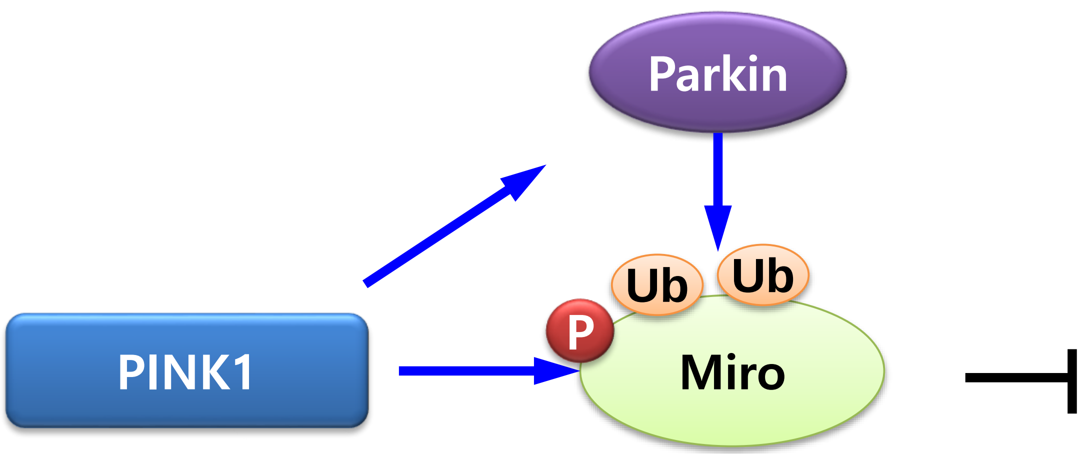
Parkinson's disease gene PINK1 is involved In clearance of damaged mitochondria by mitophagy

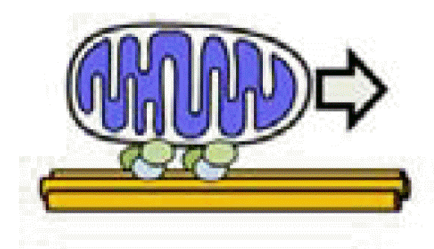


Phosphorylation of Miro by PINK1 on S156



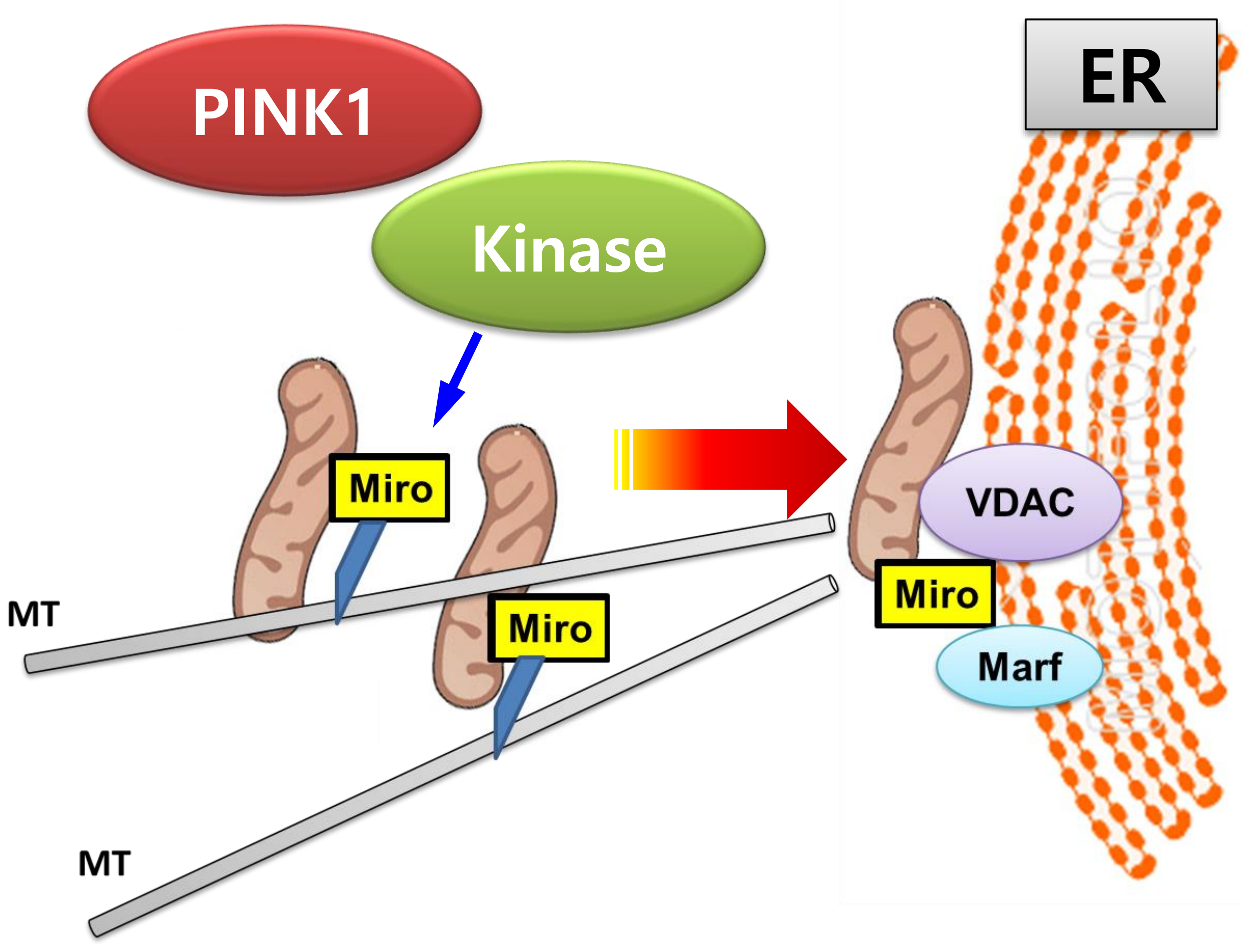
Liu et al., Plos Genetics, 2012
Wang et al., Cell, 2011





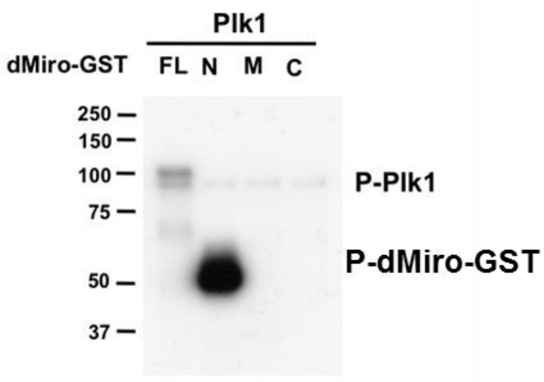
mitochondrial trafficking

Does Miro activity regulate by Kinase?

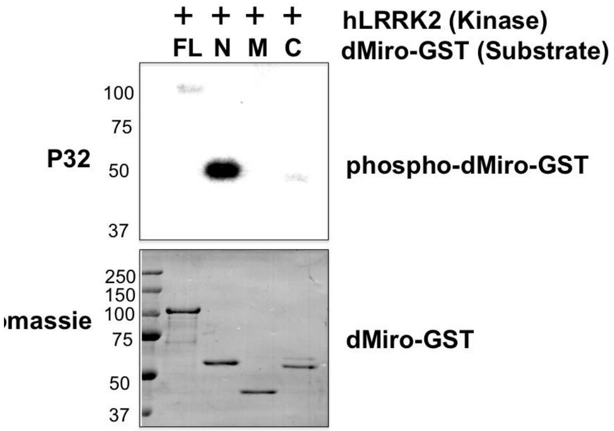


Miro-regulating Kinases

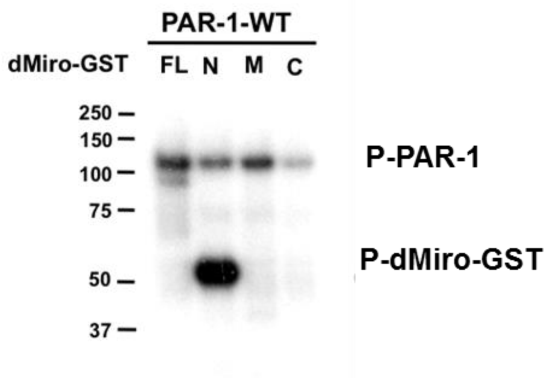
PLK1

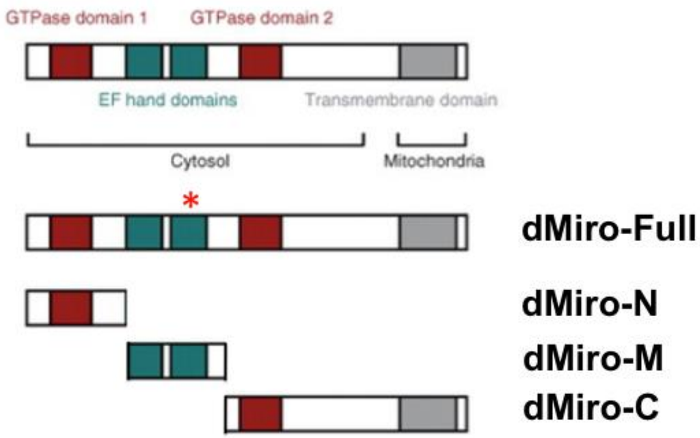


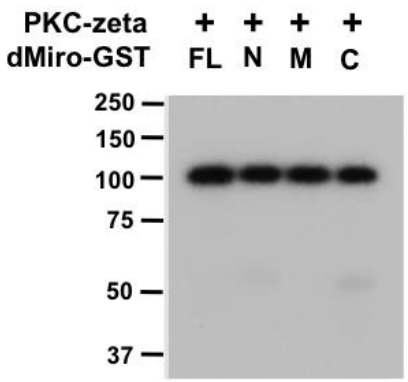
hLRRK2



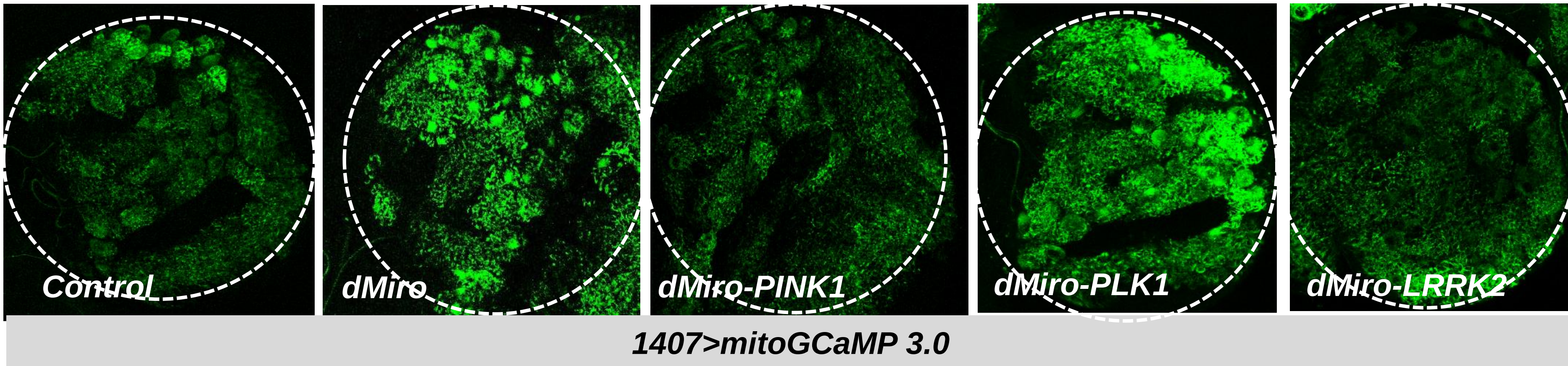
PAR-1

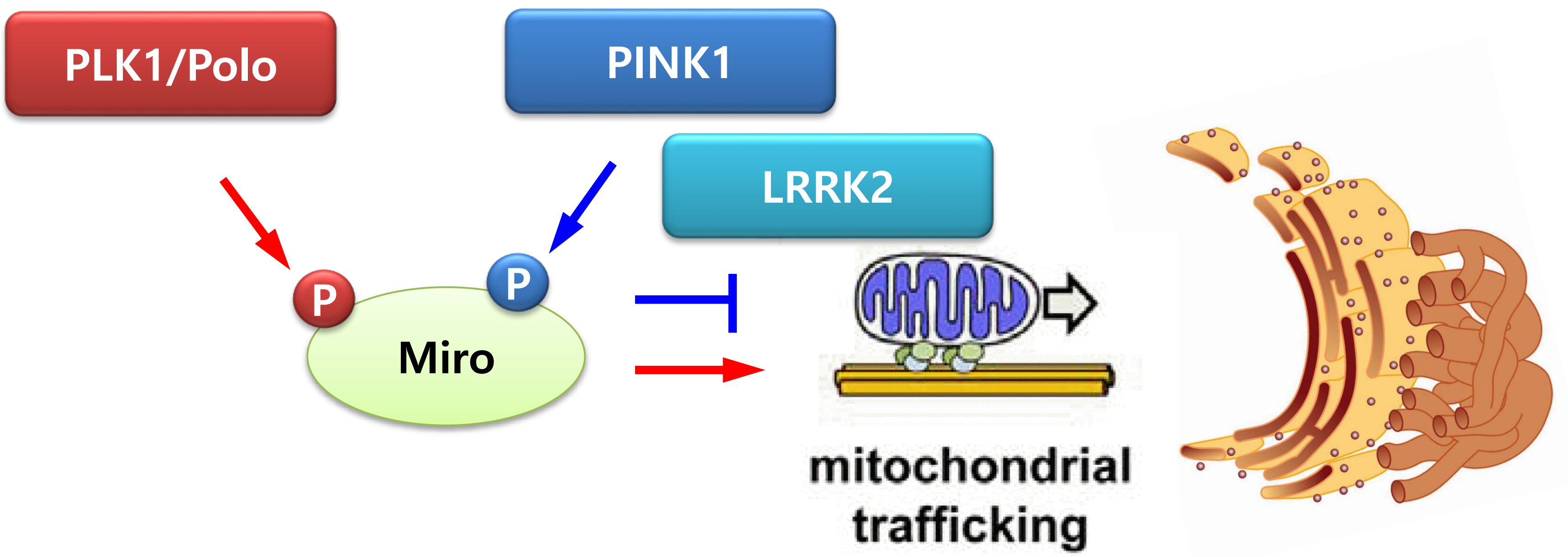




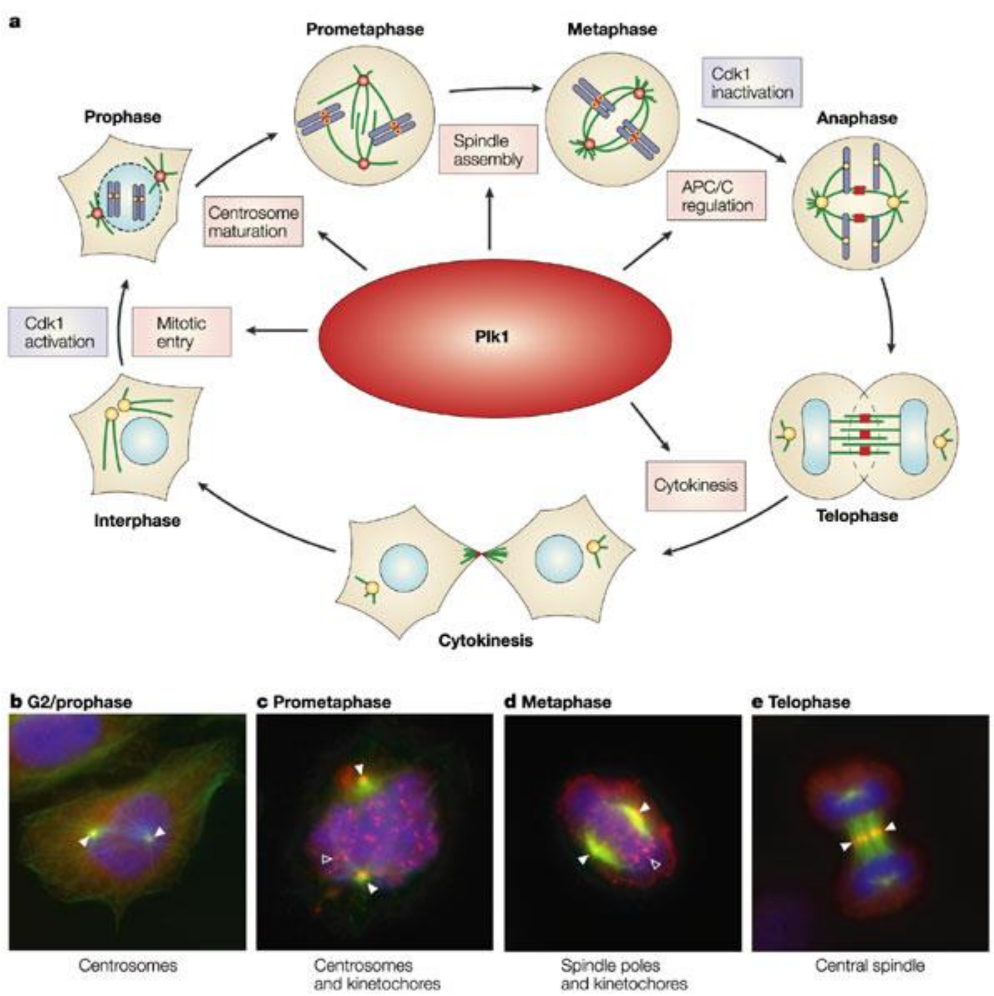


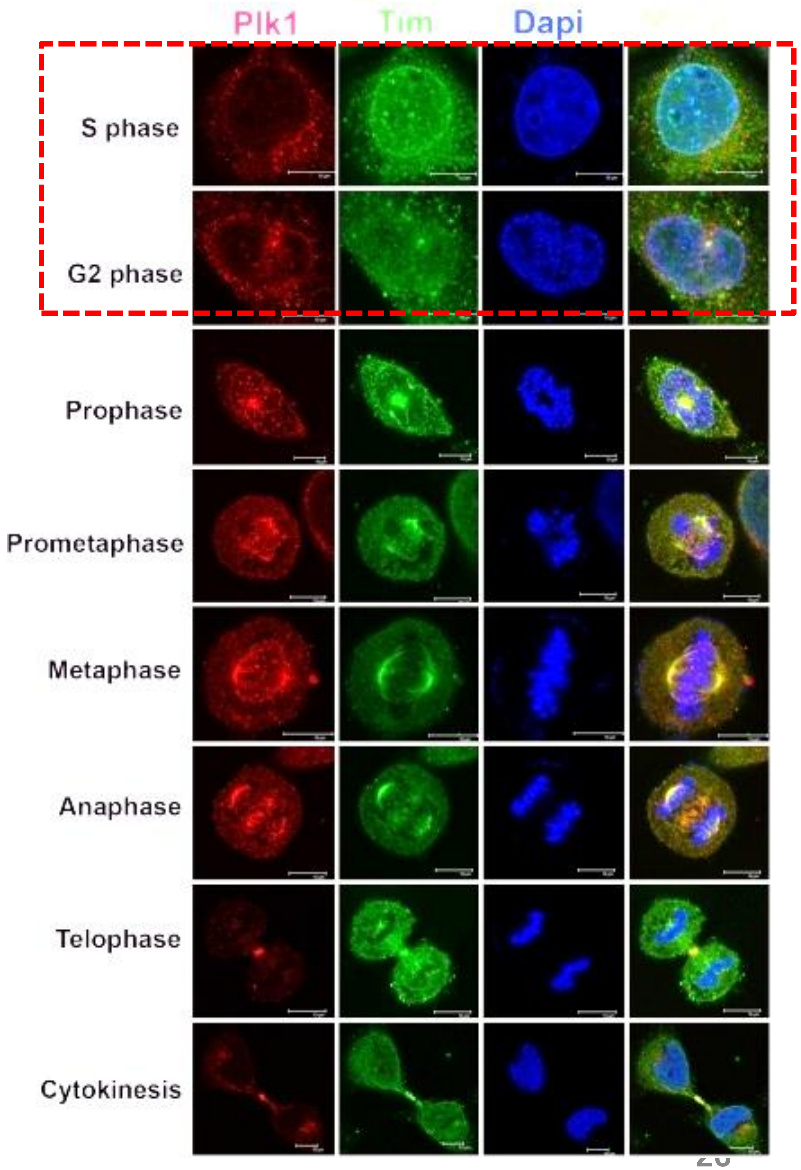
Miro-regulating Kinase : PLK1





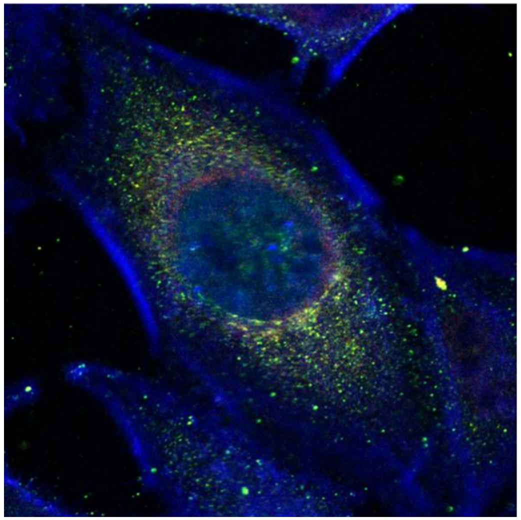
PLK1 localized in mitochondria during G phase



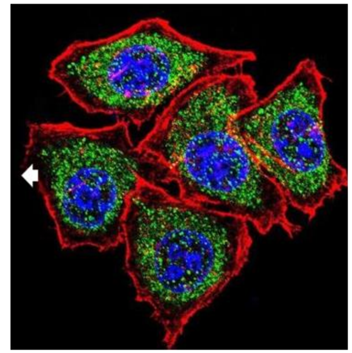


PLK1 localized in mitochondria during G phase

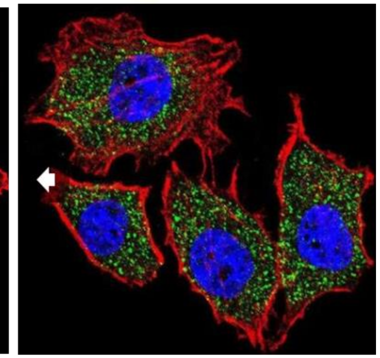
PLK1 MCU1 F-actin



PLK1 DAPI F-actin

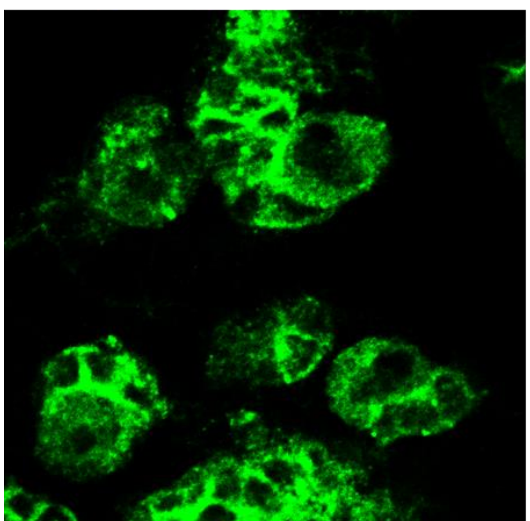


HeLa Cell

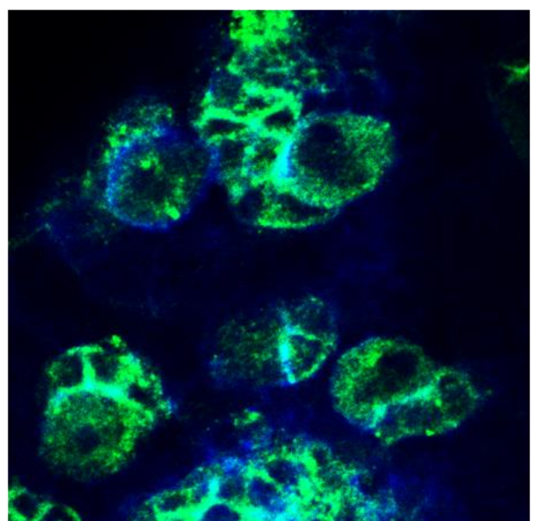


U251 glioma cells

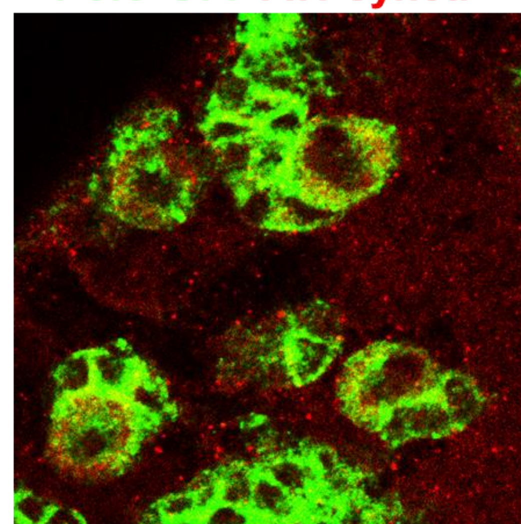
Polo-GFP



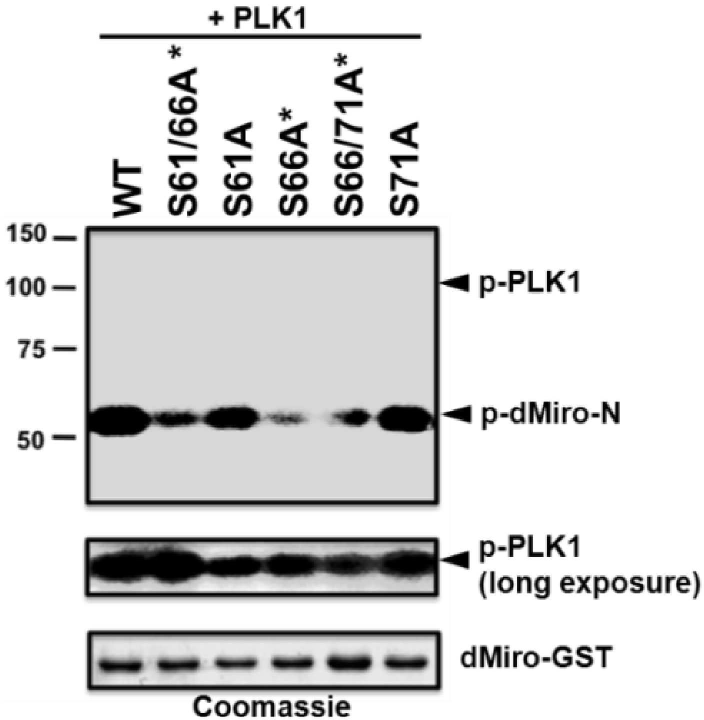
Polo-GFP F-actin

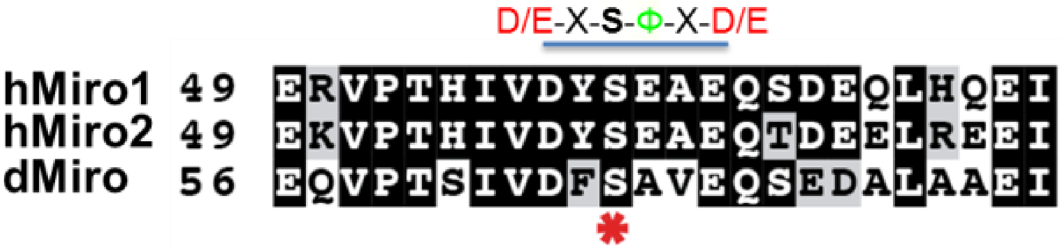


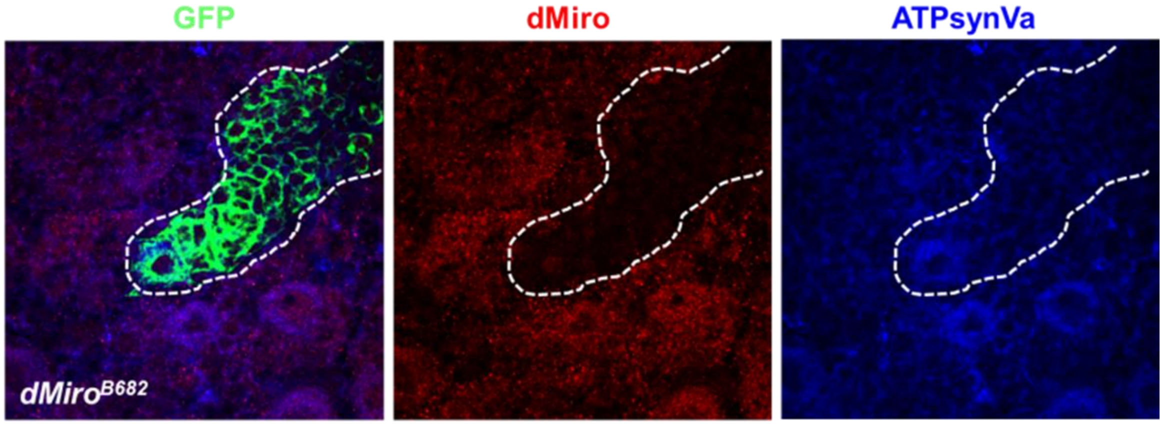
Polo-GFP ATPsyn5a

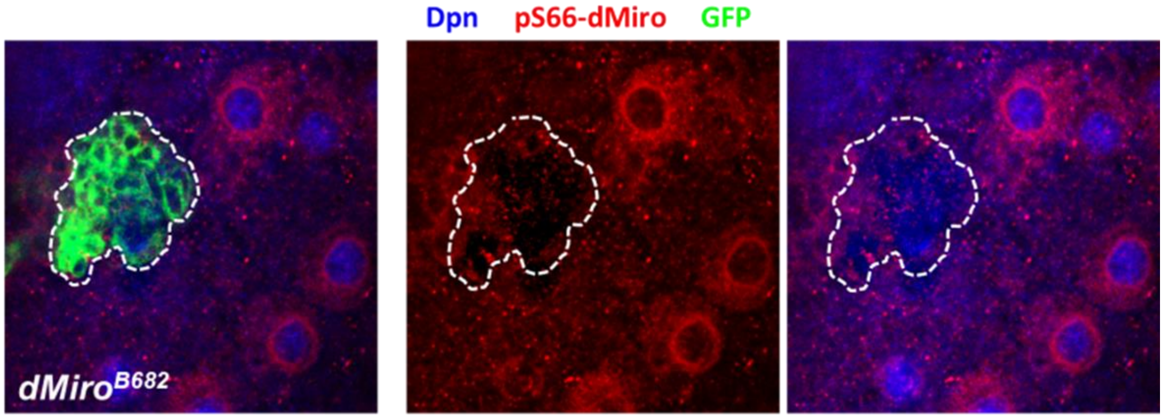


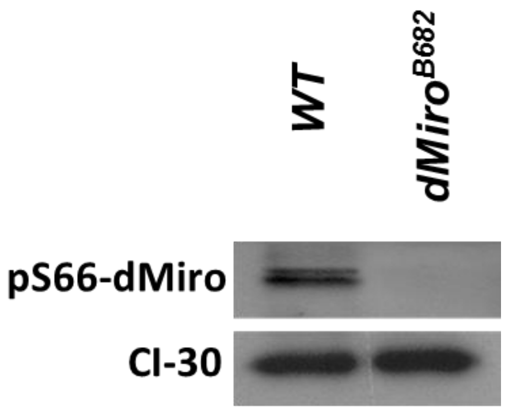
Polo-Phosphorylated Miro enriched in ER-mito contact sites



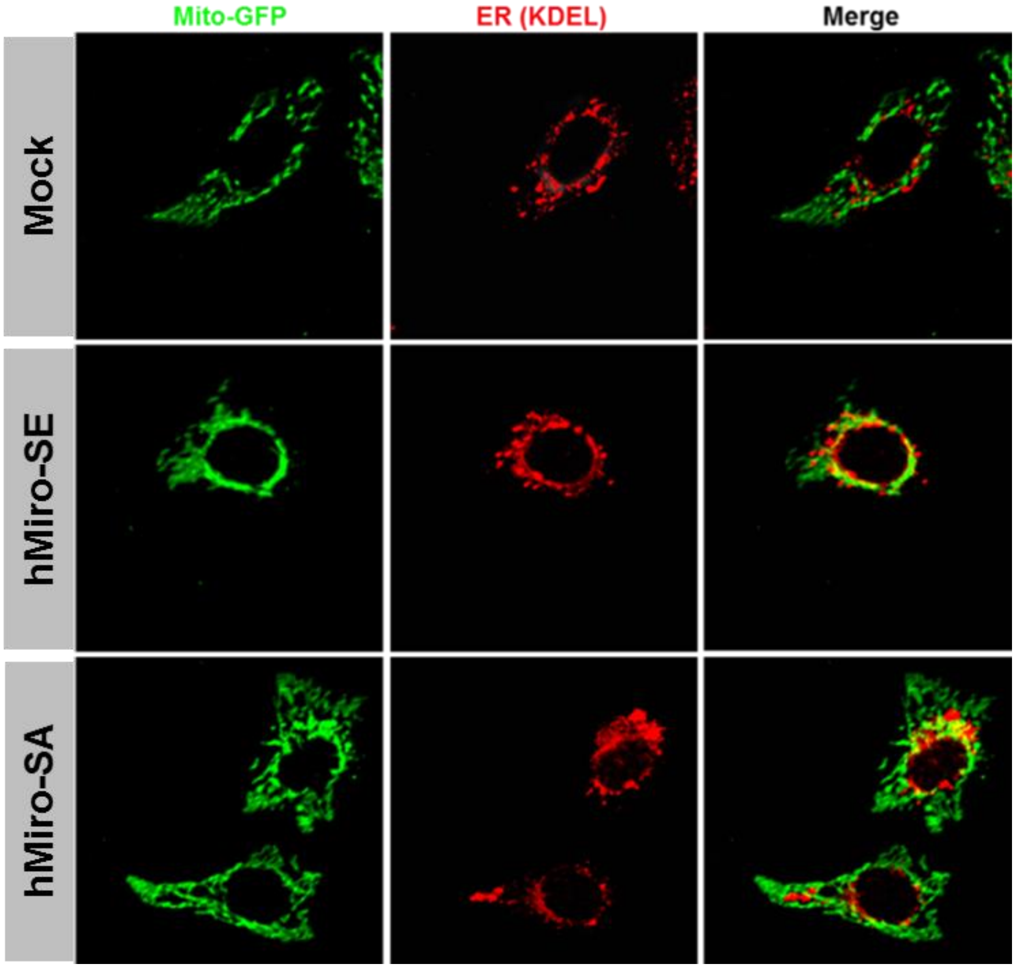


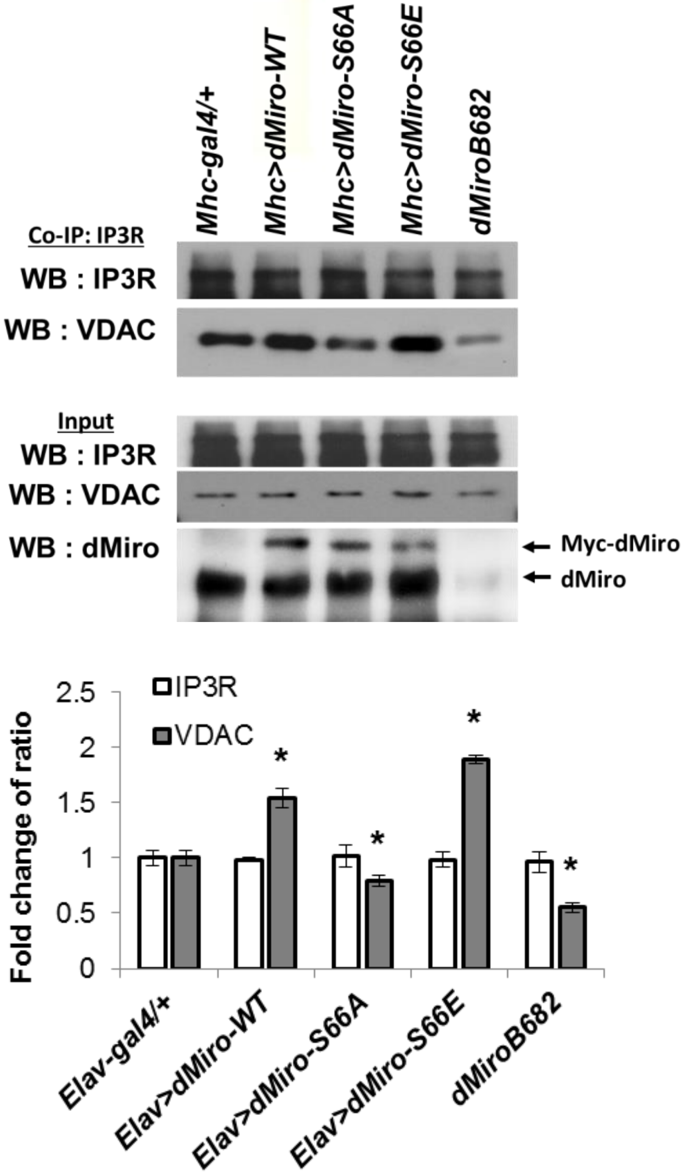






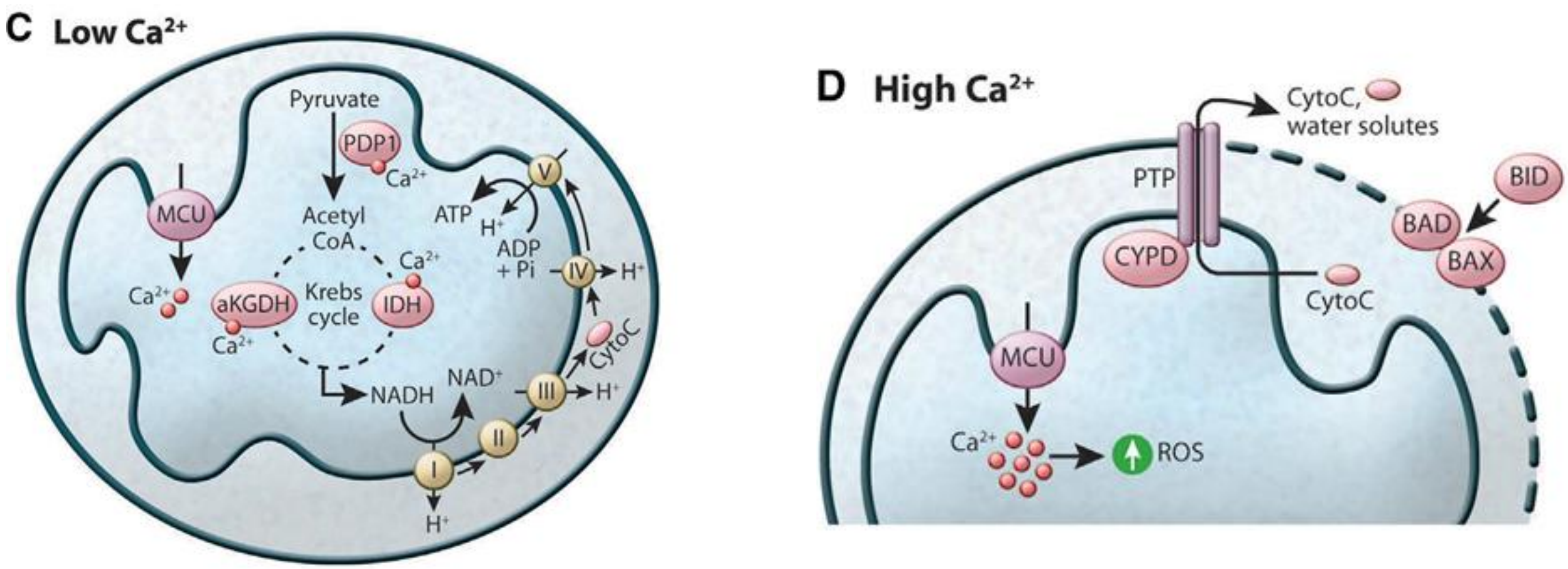
PLK1-Miro regulates ER-mitochondrial interaction





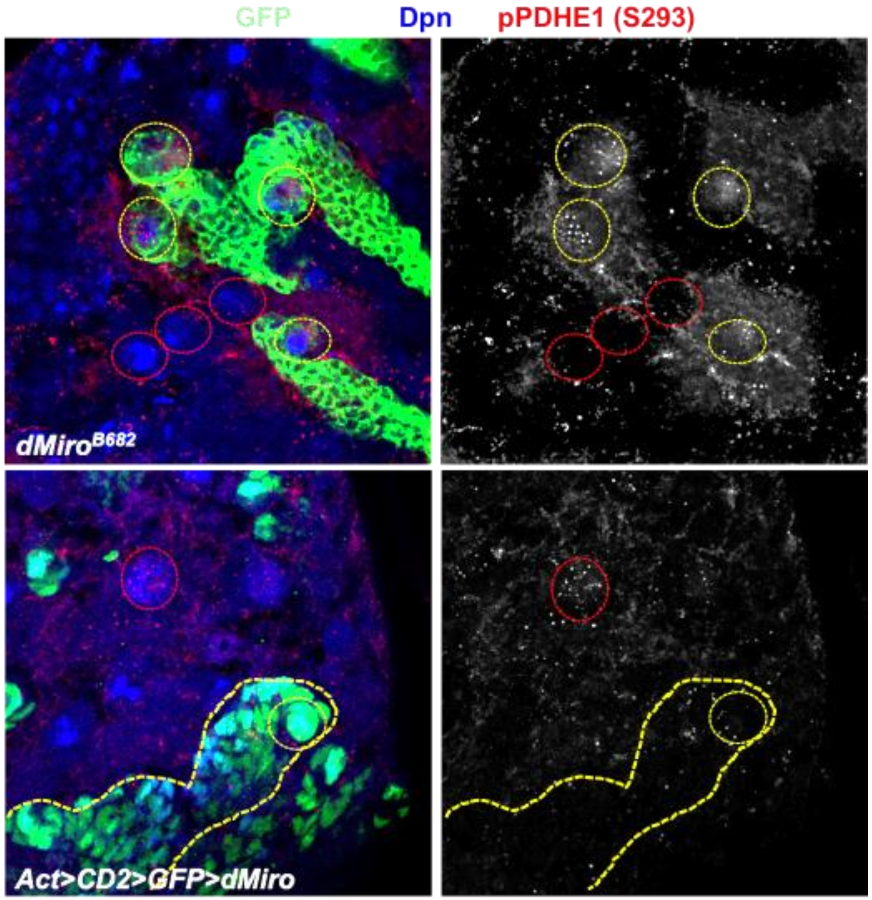
Metabolic readouts of mitochondrial Calcium

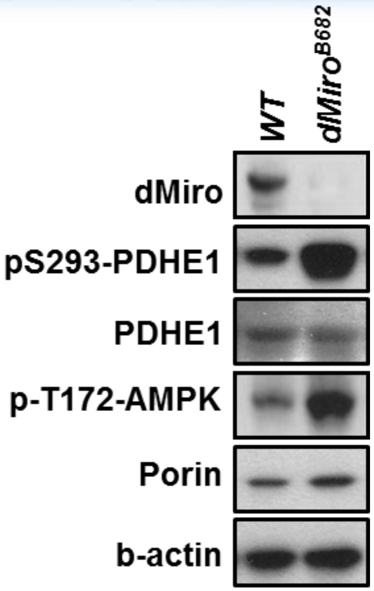
- ✓ Low Ca^{2+}[mito] indicators : phosphor-AMPK, phosphor-PDHE1, low ATP
- ✓ High Ca^{2+}[mito] indicators : mitochondria-mediated cell death including mito-ROS, cleaved Caspase-3, cytochrome c release, mitochondrial aggregation, mitochondrial membrane potential

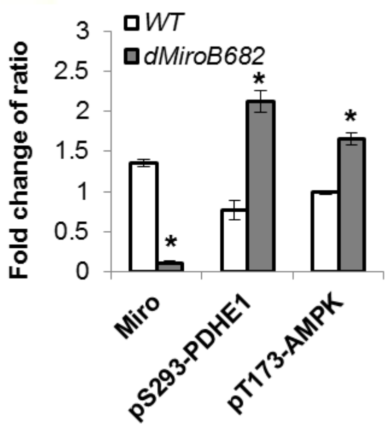


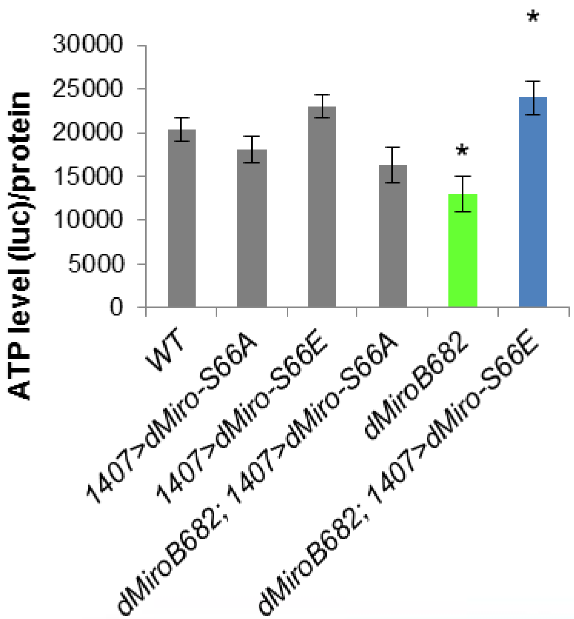
Arruda and Hotamisligil, 2015, Cell Metabolism

Miro KO mutant lead mitochondrial metabolic defect

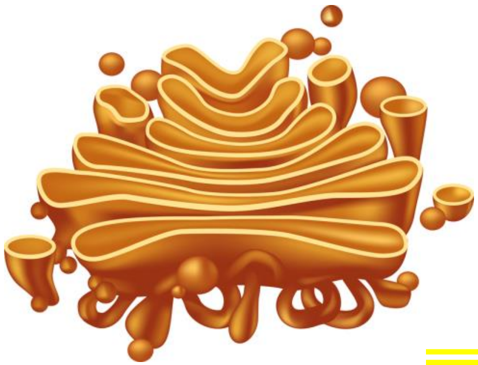








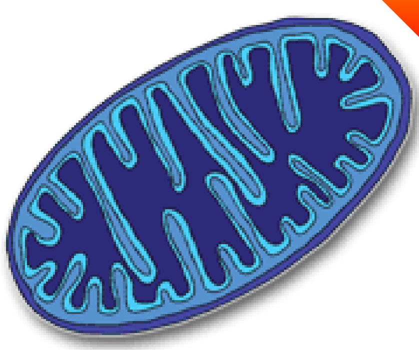
Miro-ER calcium imbalance induced cell dysfunction



Endoplasmic reticulum

ER [Ca^{2+}] loss → ER stress

ROS → Mito-ER-mediated Cell death



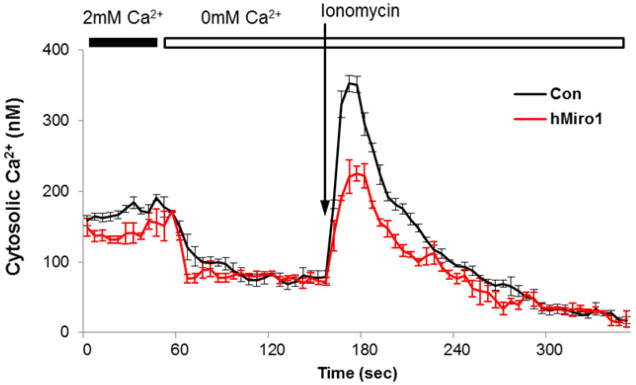
Mitochondria

Mito [Ca^{2+}] Overload → Mitochondrial dysfunction

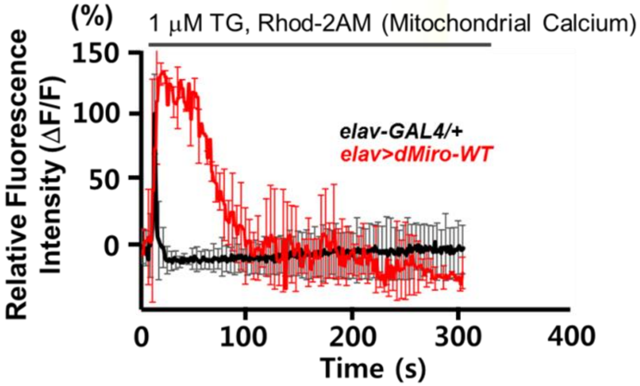
Lee et al, 2016, Developmental Cell
Arruda and Hotamisligil, 2015, Cell Metabolism

Miro Overexpression lead mitochondrial dysfunction

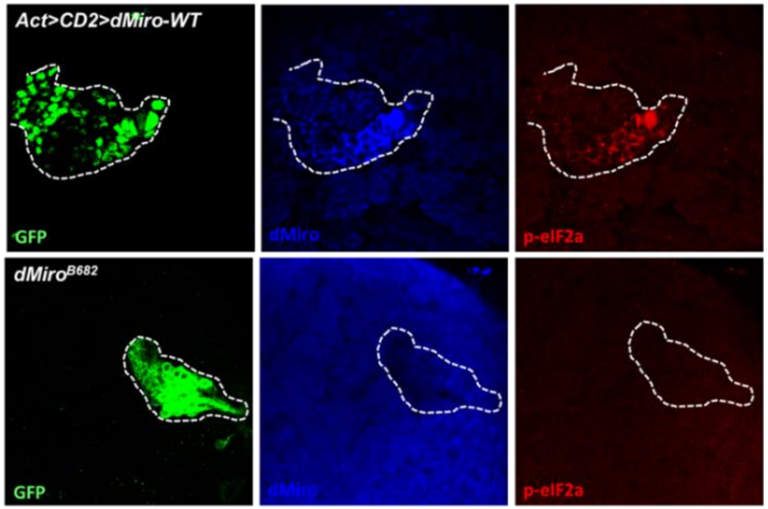
$Ca^{2+}_{[ER]}$



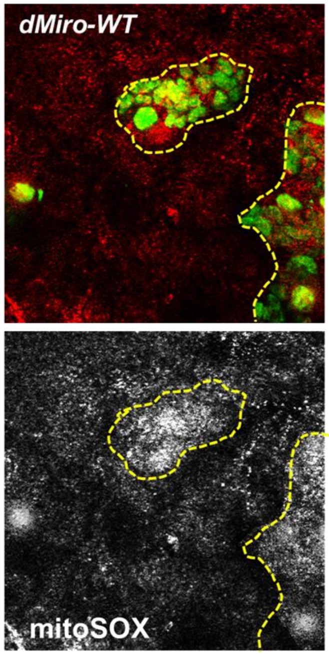
$Ca^{2+}_{[Mito]}$



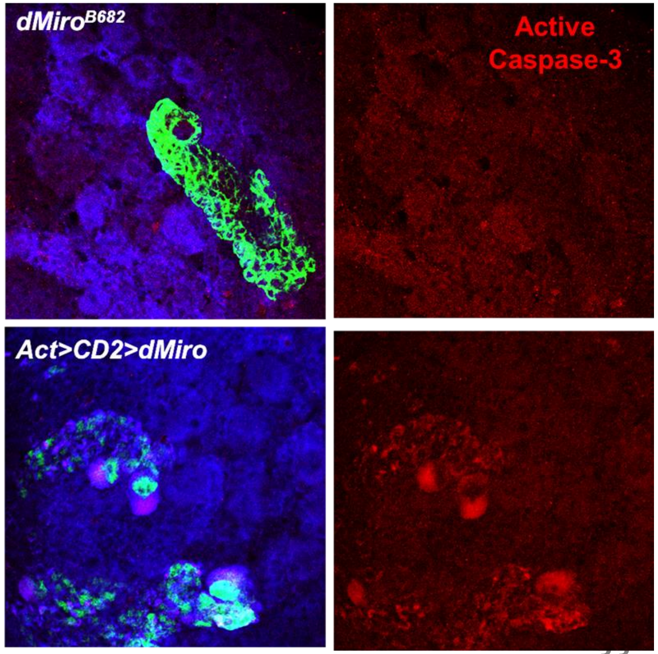
ER stress



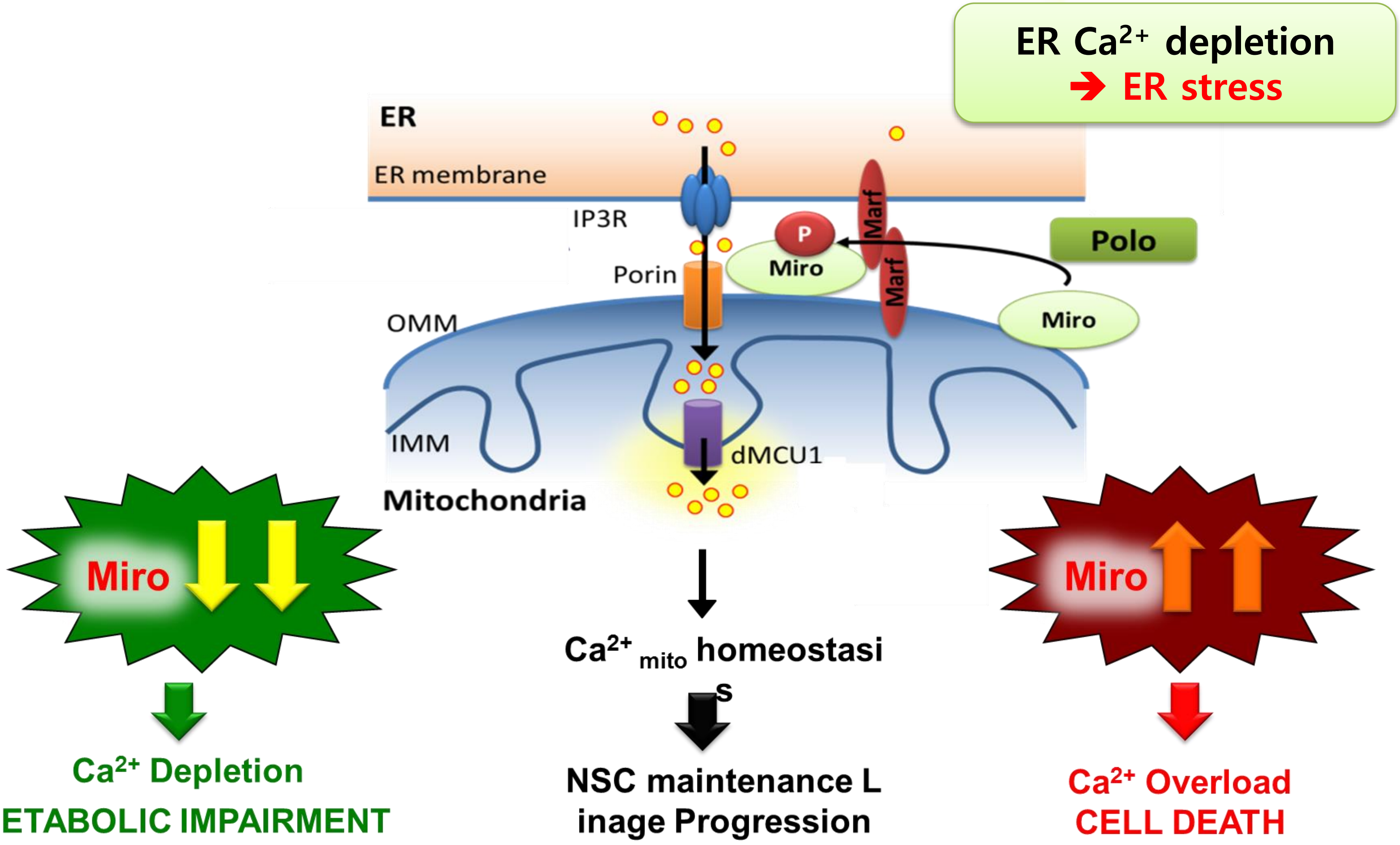
Mitochondrial ROS



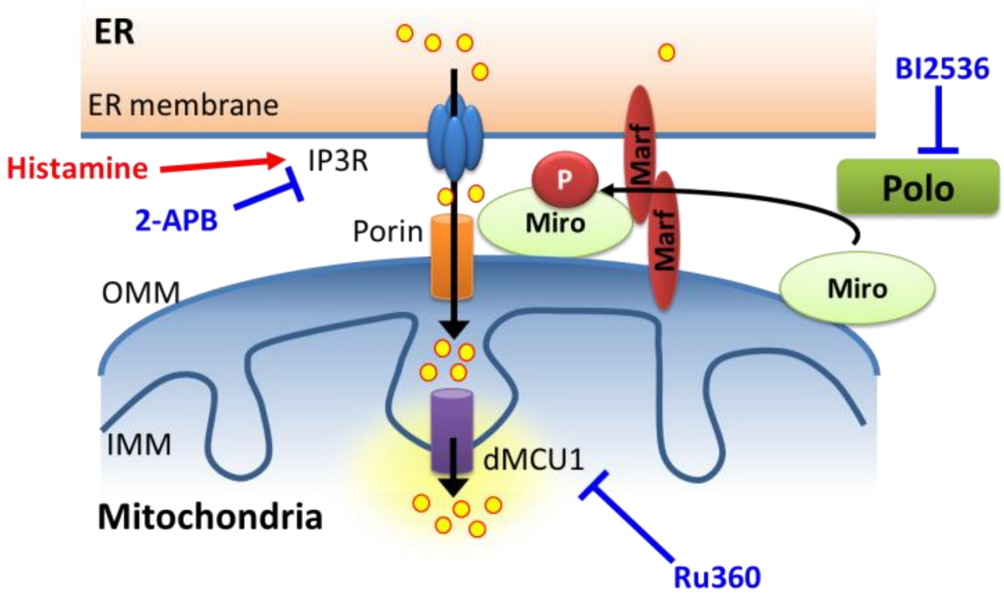
Mitochondrial-mediated cell death

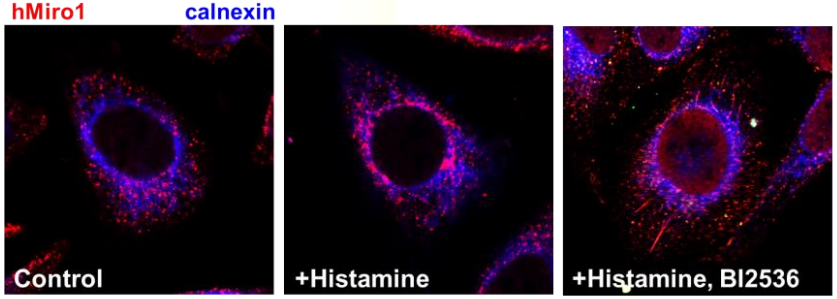


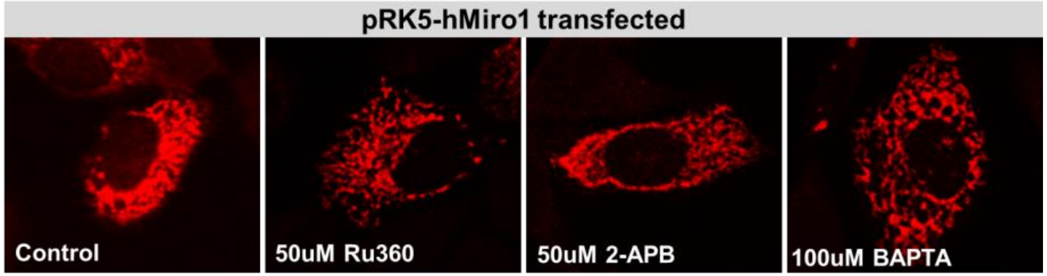
PLK1-Miro regulates Mito-Calcium Homeostasis



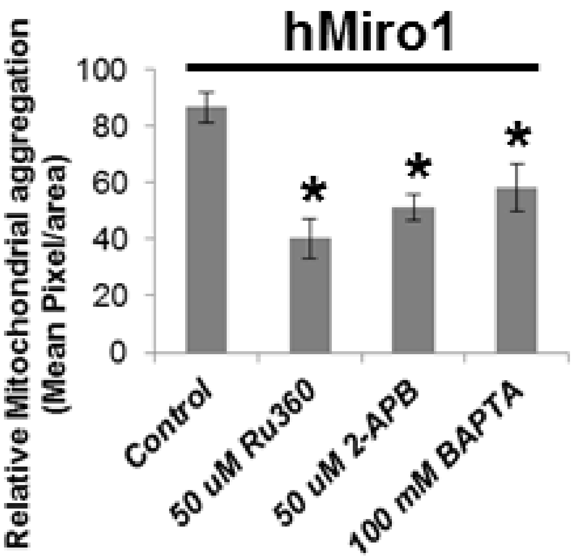
Increased Mito[Ca^{2+}] led to Mitochondrial aggregation



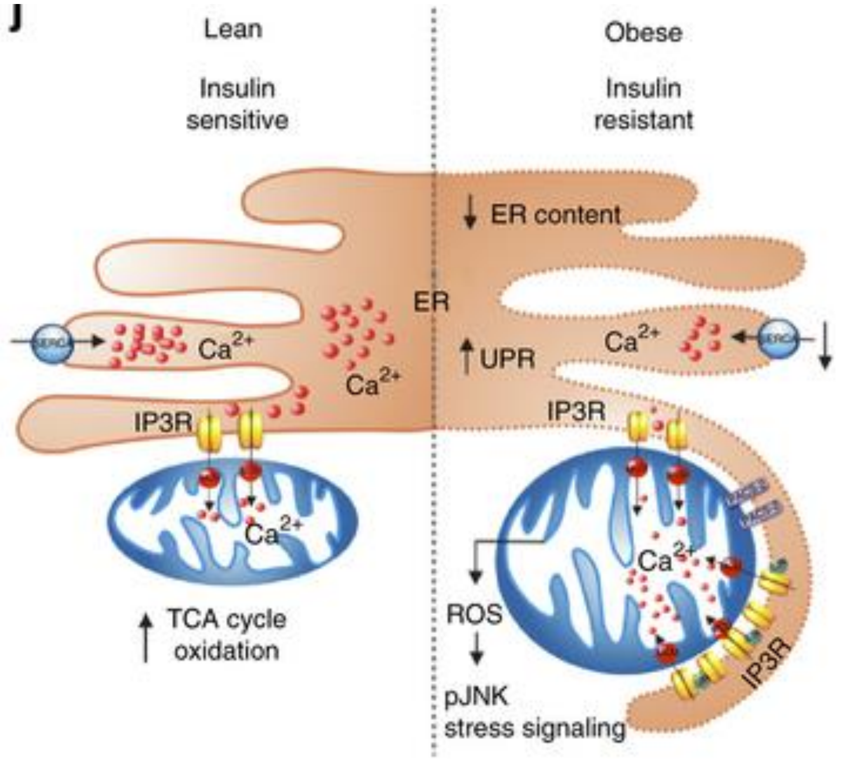


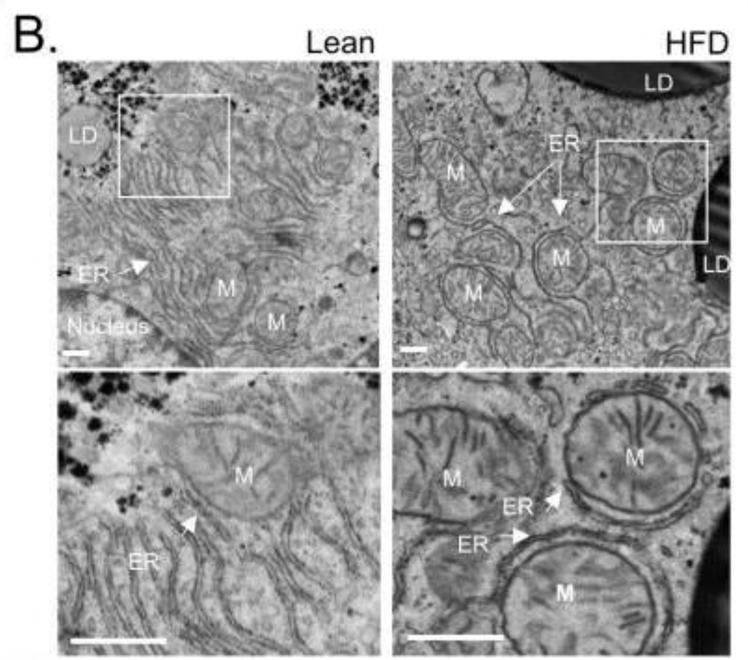


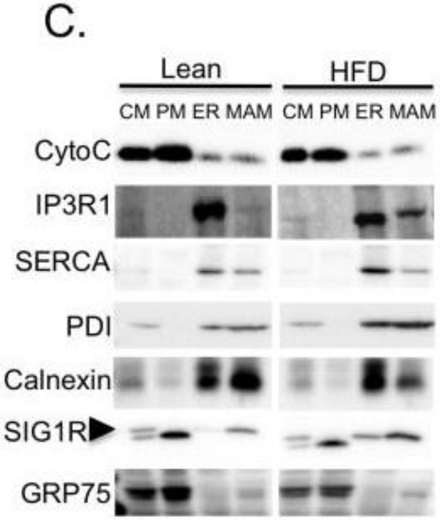
Myc-dMiro



Increased MAM in Obese condition, leading to Ca^{2+} overload into mitochondria and ER stress

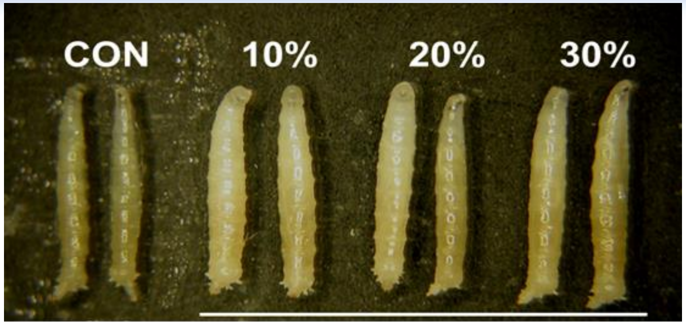






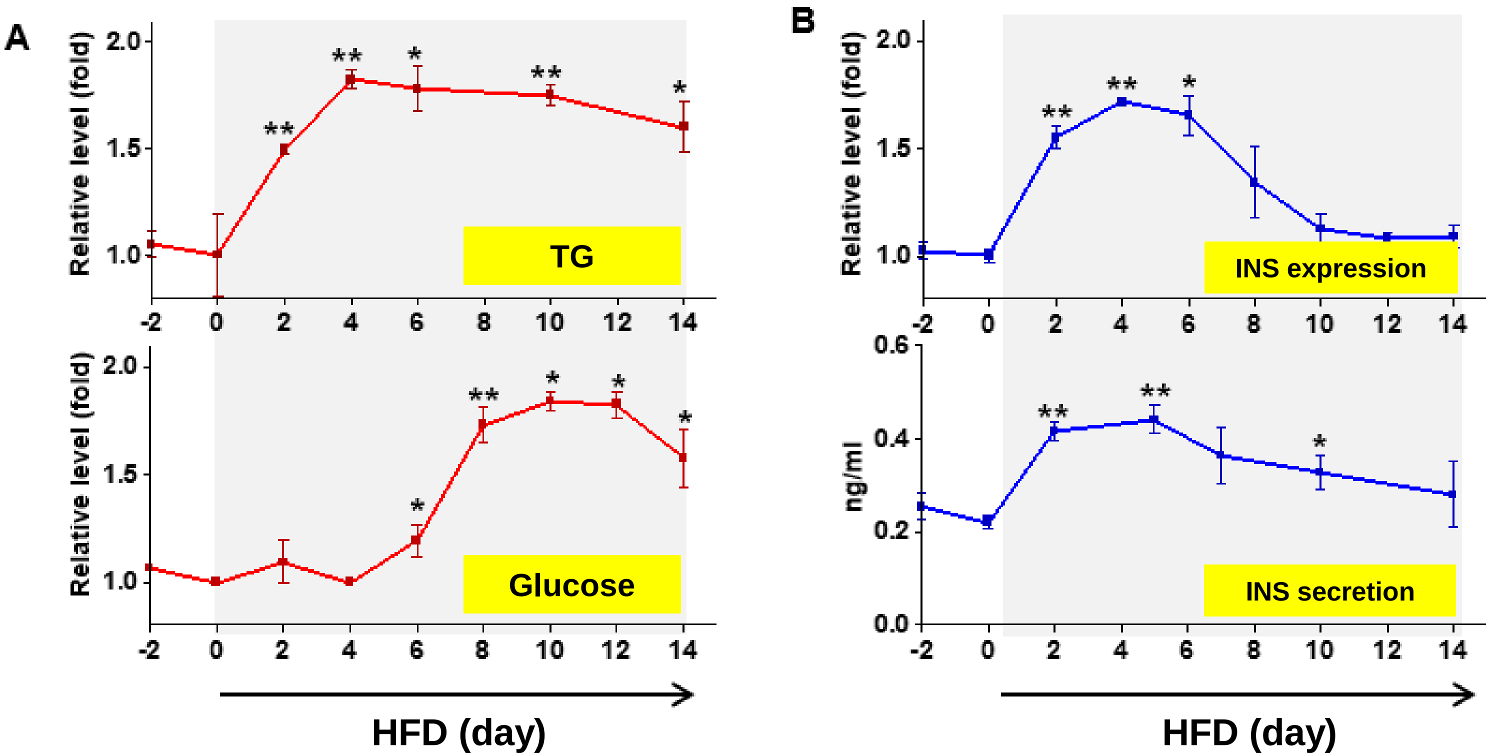
Arruda et al., 2014, Nat Med.

Drosophila model for HFD-induced metabolic disease



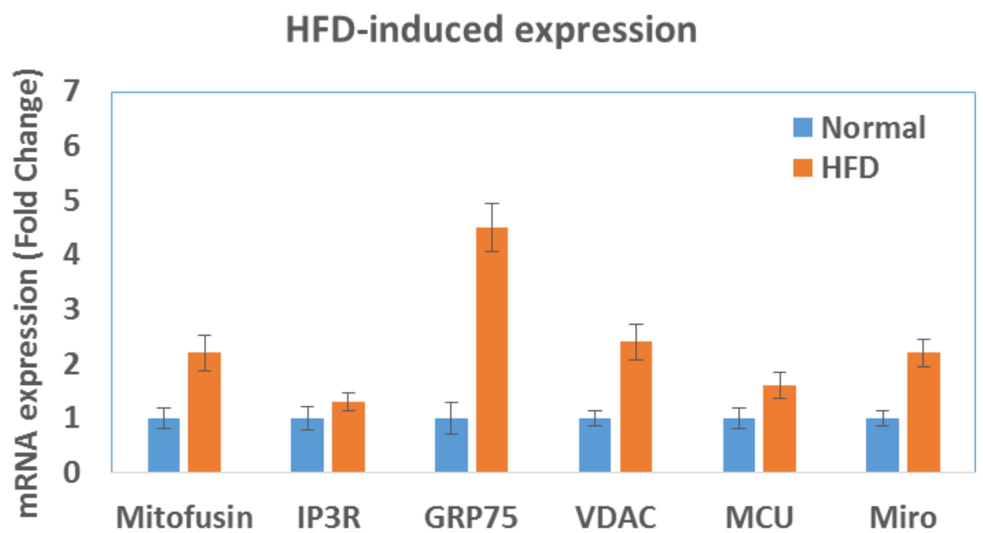
Normal diet

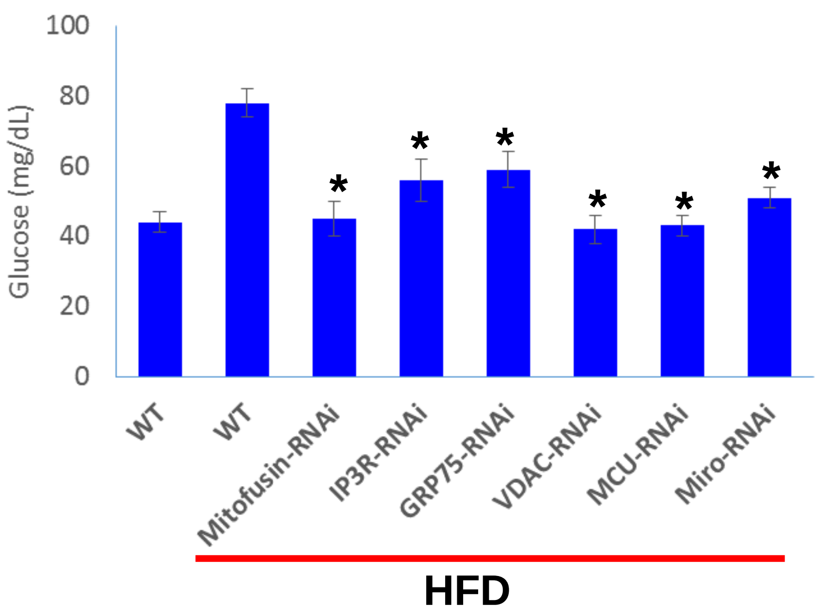
High-Fat diet

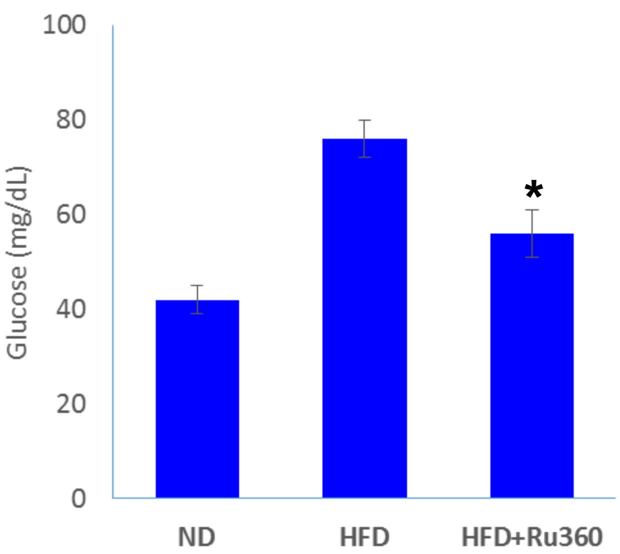


Hong et al, 2016, Sci Rep.

Inhibition of Mito[Ca^{2+}] uptake rescued HFD-phenotypes







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