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OMICS Group has organized 500 conferences, workshops and national symposiums across the major cities including San Francisco, Las Vegas, San Antonio, Omaha, Orlando, Raleigh, Santa Clara, Chicago, Philadelphia, Baltimore, United Kingdom, Valencia, Dubai, Beijing, Hyderabad, Bengaluru and Mumbai.

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# Dysregulation of Mitochondrial Quality Control and Diabetic Cardiomyopathy

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**College of Osteopathic Medicine**

**April 27, 2015, 5th Clinical and Experimental Cardiology Conference, Philadelphia.**

# Disclosure

- None.

# Diabetes

- **Inability to use glucose: hyperglycemia**

- **Type 1: insulin deficiency (<10%)**
- **Type 2: insulin resistance (>90%)**

- **In US: 18.8 million diabetic patients**
  **7.0 million undiagnosed**
  **79 million prediabetic (2010)**

**Cost: 2007: $174 billion**
**2012: $245 billion**

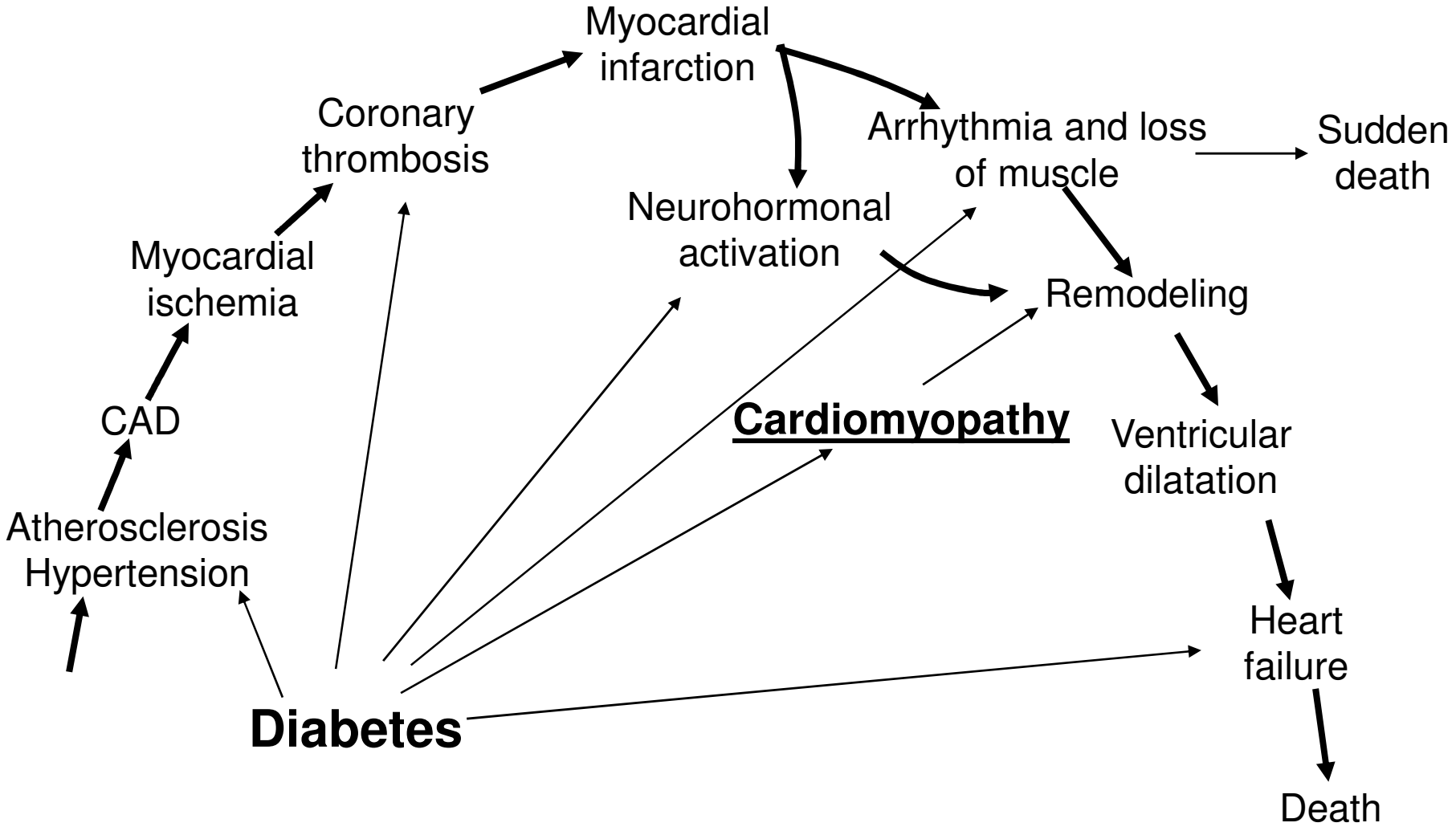
http://diabetes.niddk.nih.gov/dm/pubs/statistics/
http://www.diabetes.org/advocacy/news-events/cost-of-diabetes.html#sthash.ZZKfDbZG.dpuf

# Complications of Diabetes

- Cardiovascular disease-heart failure

  **2/3 diabetic patients die from CV complications**
- Peripheral vascular disease
- Diabetic neuropathy
- Diabetic retinopathy
- Diabetic nephropathy
- Skin problems

# Chain of Events Leading to Diabetic Heart failure

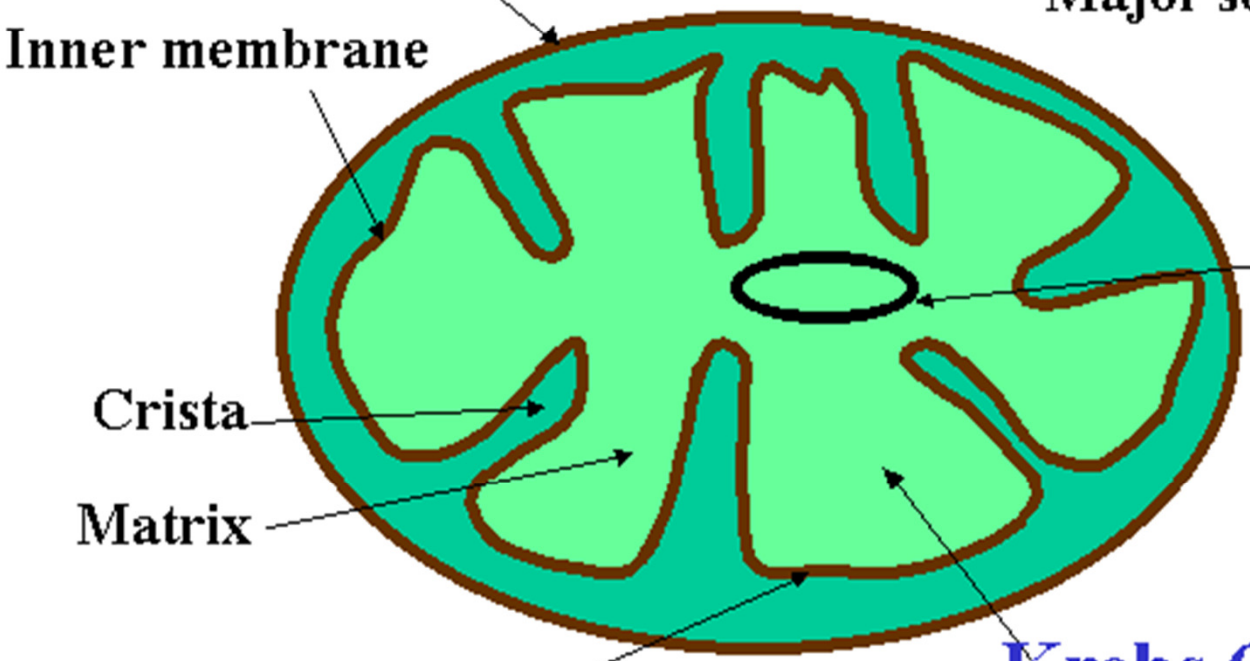



Adapted from Dzau V, Braunwald E. *Am Heart J.* 1991;121:1244-1263.

# Diabetic Cardiomyopathy

- Heart muscle specific disease
- Independent of vascular pathology
- Manifestations:
  - Cardiac hypertrophy
  - Fibrosis
  - Cardiac dysfunction (diastolic and systolic)
  - Progress to heart failure
- Underlying mechanisms not very clear

# Mitochondria




**Function:**
**Synthesis of ATP**
**Major source of energy**

**Krebs Cycle**

Sucrose + 6 $O_2$ + 38 ADP+ 38 Pi

↓

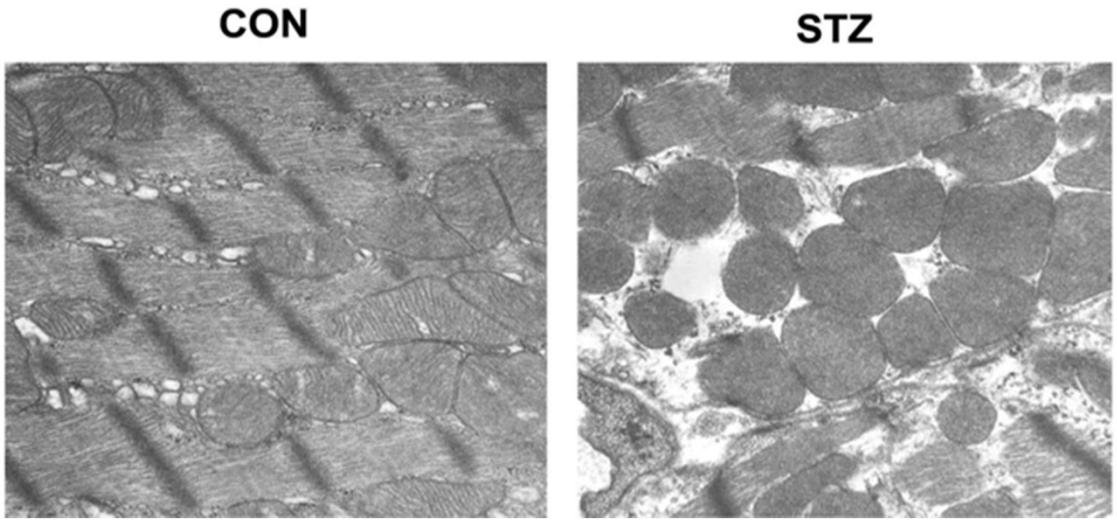
6 $CO_2$ + 6 $H_2O$ + 38 ATP

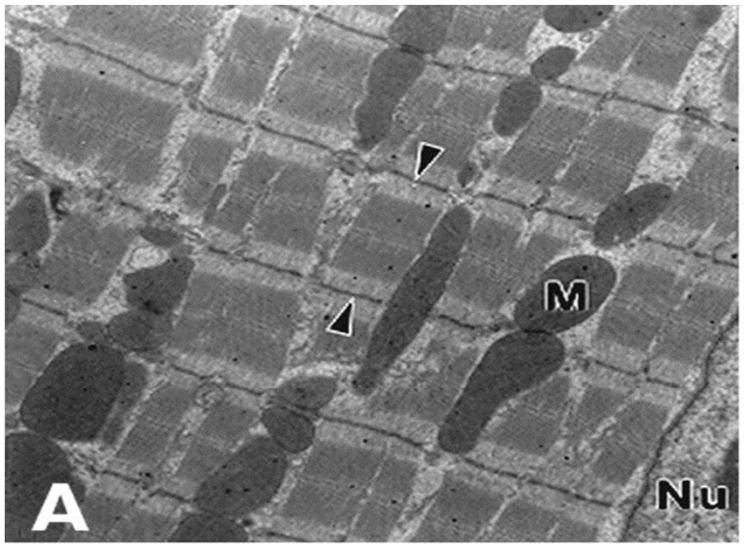
# Mitochondria & Functions

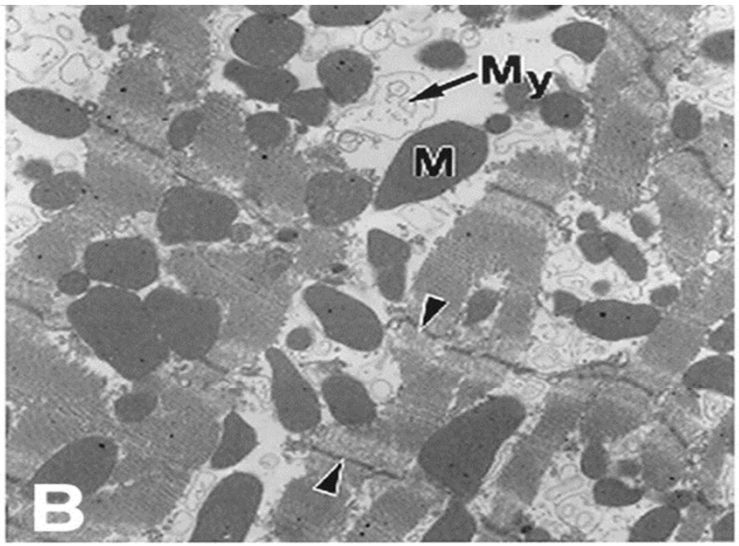
- Produce ATP.
- Generate reactive oxygen species (ROS).
- Triggers inflammation.
- Cause apoptosis and necrosis.
- Maintain calcium homeostasis.
- Regulate membrane potential, cell proliferation and metabolism.
- Form blood components and hormones.
- Detoxify ammonia in the liver.
- Produce heat.
- Synthesize heme and steroids.

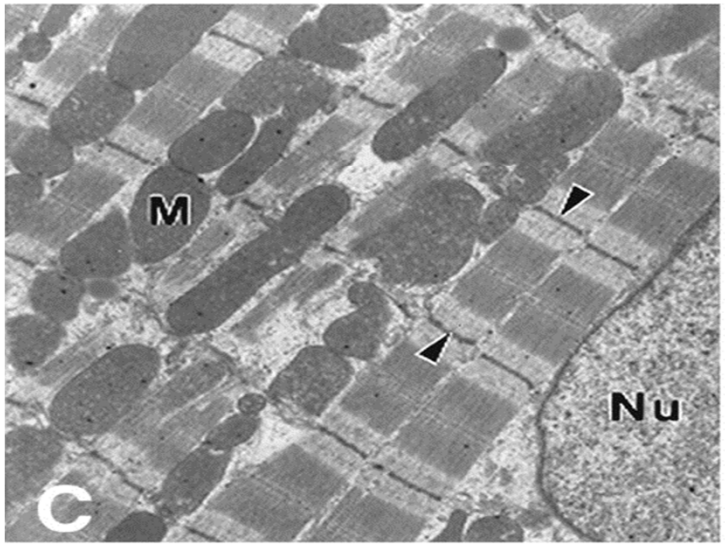
# Mitochondria-produced ROS and the diabetic heart

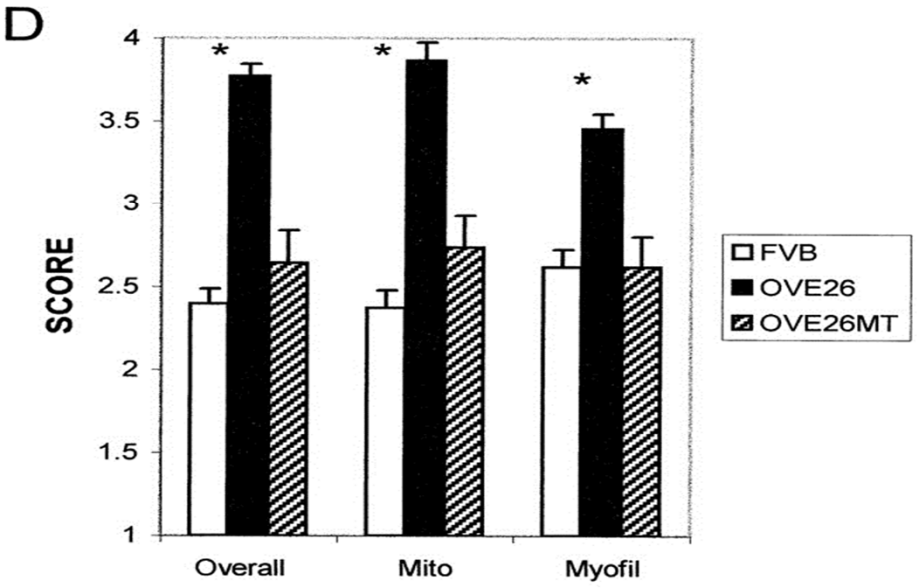
- **Mitochondria are a major source of intracellular ROS in diabetes**
- **Mitochondria are themselves a primary target of damage in diabetes**
- **Damaged mitochondria can further increase ROS production through ROS-induced ROS release**
  - A vicious cycle






**Liang Q, Diabetes. 2002 Jan;51(1):174-81.**

# ROS theory for diabetic cardiac injury

- Various antioxidants are able to reduce diabetic heart injury in animal studies

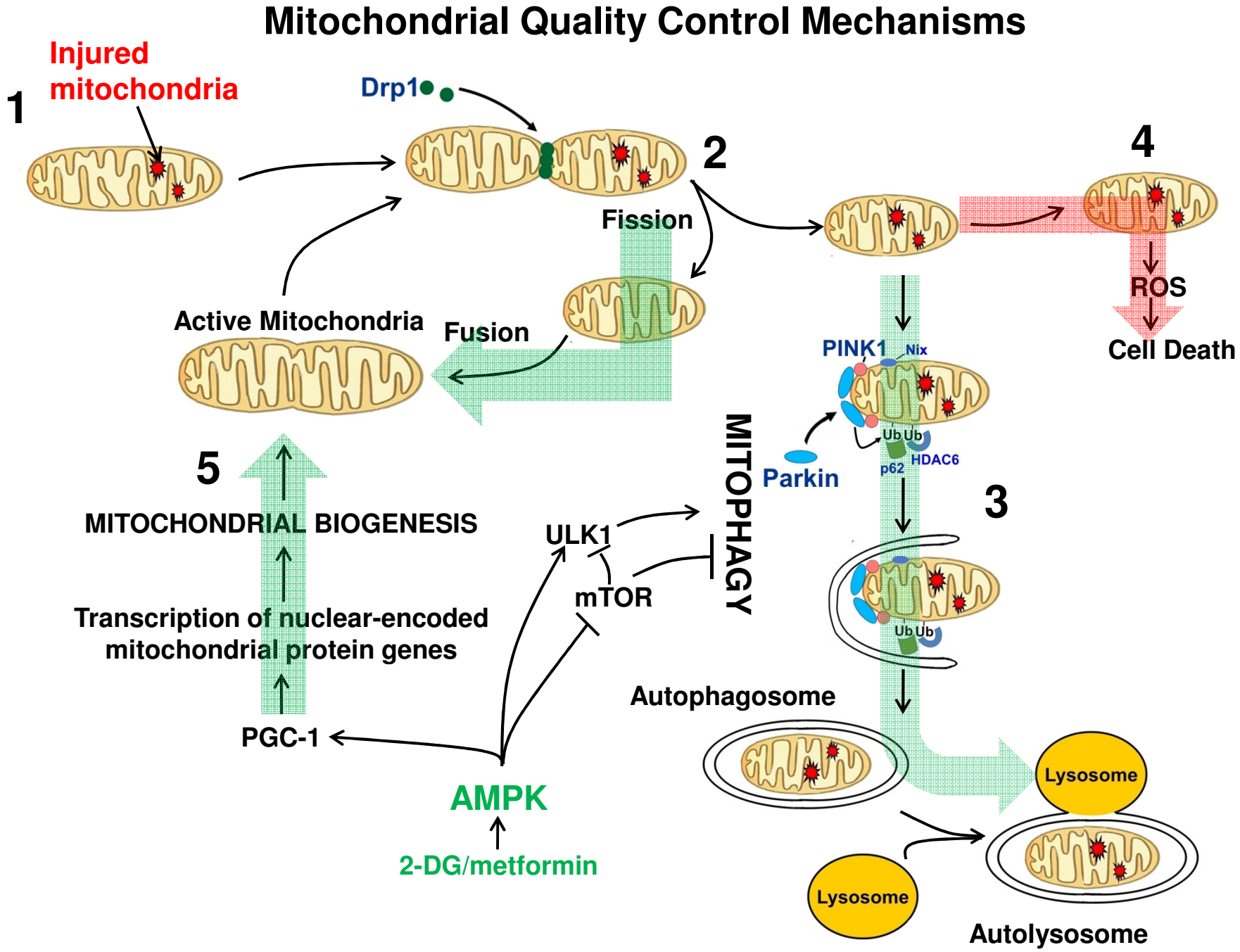
- However, clinical trials have shown **very limited effect of antioxidant therapy on cardiovascular outcomes** in diabetic patients, suggesting:

  – Antioxidants can only scavenge or antagonize existing ROS, but they can not stop ROS generation from injured mitochondria.

  – To repair or remove damaged mitochondria may be a more effective strategy to protect diabetic heart: How?

# Mechanisms of Mitochondrial Quality control

- Mitochondrial protein quality control
  - Intra-mitochondrial chaperones & proteases
  - UPS-mediated proteolysis of the outer membrane proteins
- Mitochondria fusion
- Mitochondria fission
- Degradation of mitochondria by autophagy: mitophagy
- Mitochondrial biogenesis


Mitochondrial Quality Control Mechanisms
Injured mitochondria
1
Drp1
2
Fission
Fusion
Active Mitochondria
4
ROS
Cell Death
PINK1
Nix
Ub Ub
HDAC6
p62
Parkin
3
MITOPHAGY
5
MITOCHONDRIAL BIOGENESIS
ULK1
mTOR
Transcription of nuclear-encoded mitochondrial protein genes
PGC-1
AMPK
2-DG/metformin
Autophagosome
Lysosome
Lysosome
Autolysosome

# The functional role of autophagy in type 1 diabetic heart

**J Biol Chem. 2013;288(25):18077**

**Observations:**

- Cardiac autophagy is inhibited in both STZ and OVE26 diabetic mice
- Overexpression of BCN1 restores autophagic activity and exacerbates diabetic cardiac injury in a dose-dependent manner.
- Reduced BCN1 or ATG16L1 attenuates diabetic cardiac injury.

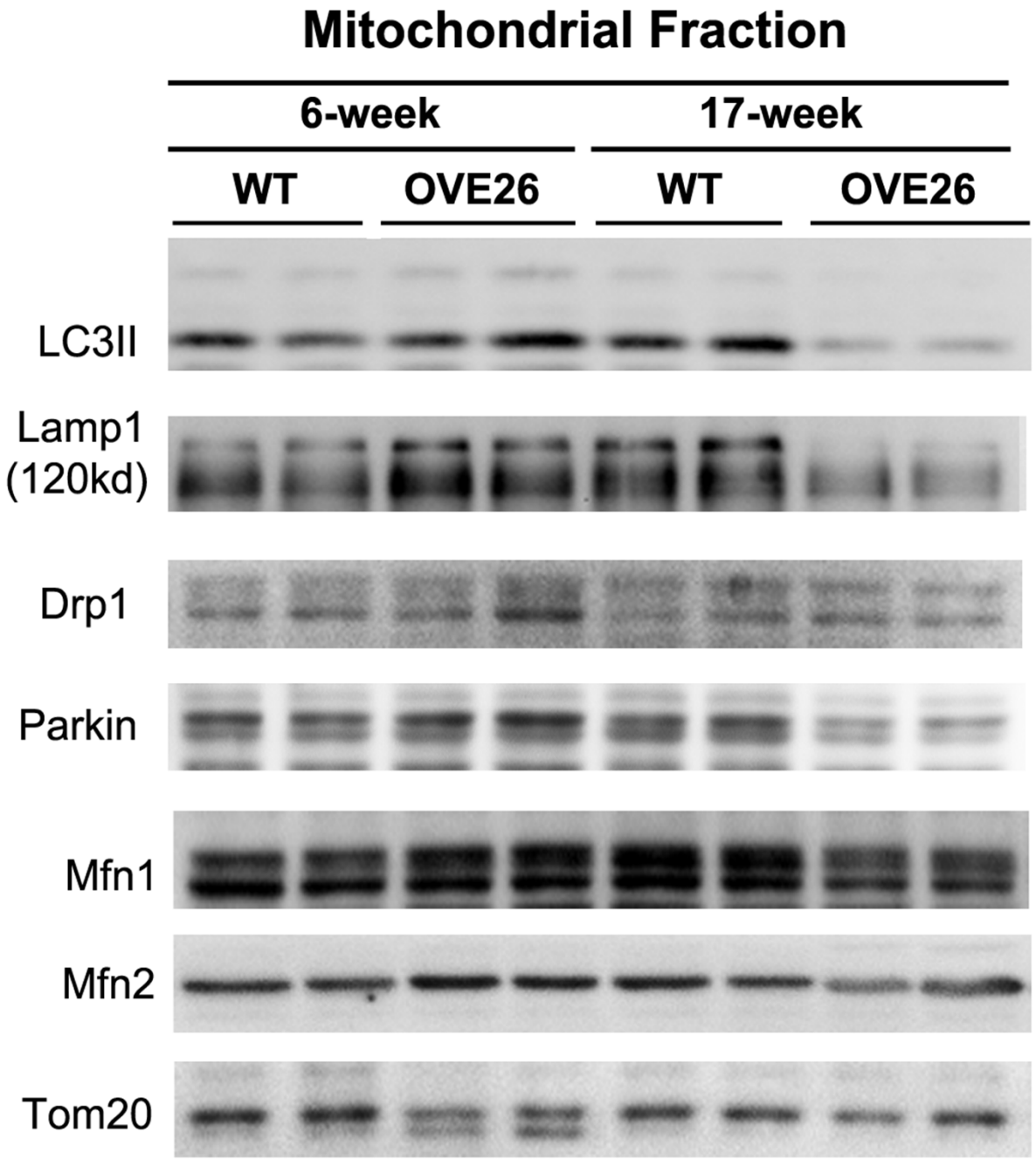
**Conclusion**: Diabetes-induced inhibition of autophagy is an adaptive response that limits cardiac injury in type 1 diabetes.

**<u>Remaining Question</u>**: What happens to mitochondrial degradation in the diabetic heart?

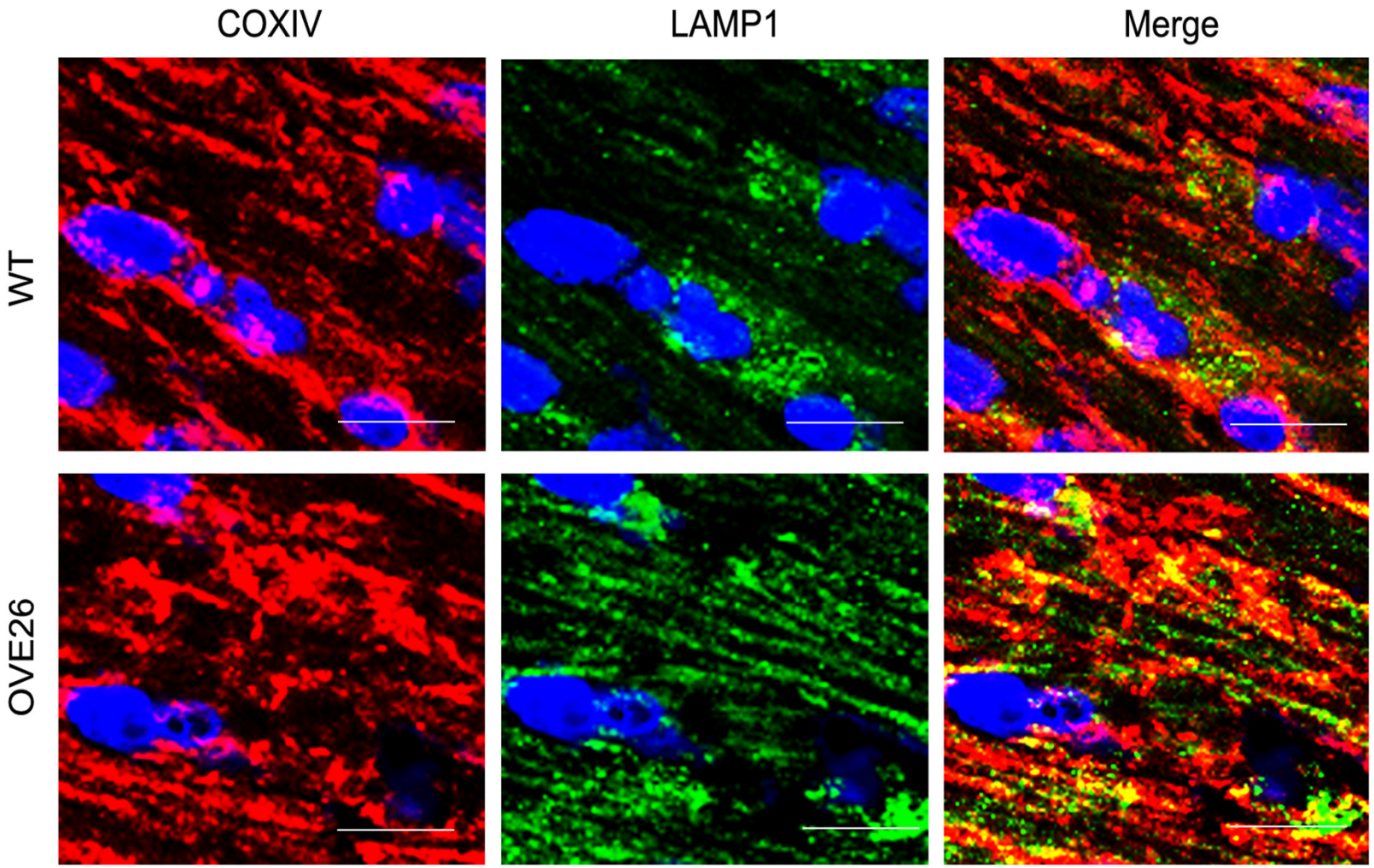
- **Changes in general autophagy does not necessarily reflect mitophagic activity**
  - Starvation induces general autophagy, but it inhibits mitophagy (Gomes L. 2011,Nat Cell Biol, 13:589-98)

- **Mitophagy can occur independently of conventional autophagy**
  - Atg5/7 independent but Rab9 dependent alternative autophagy (2009, Nature 461, 654-658)

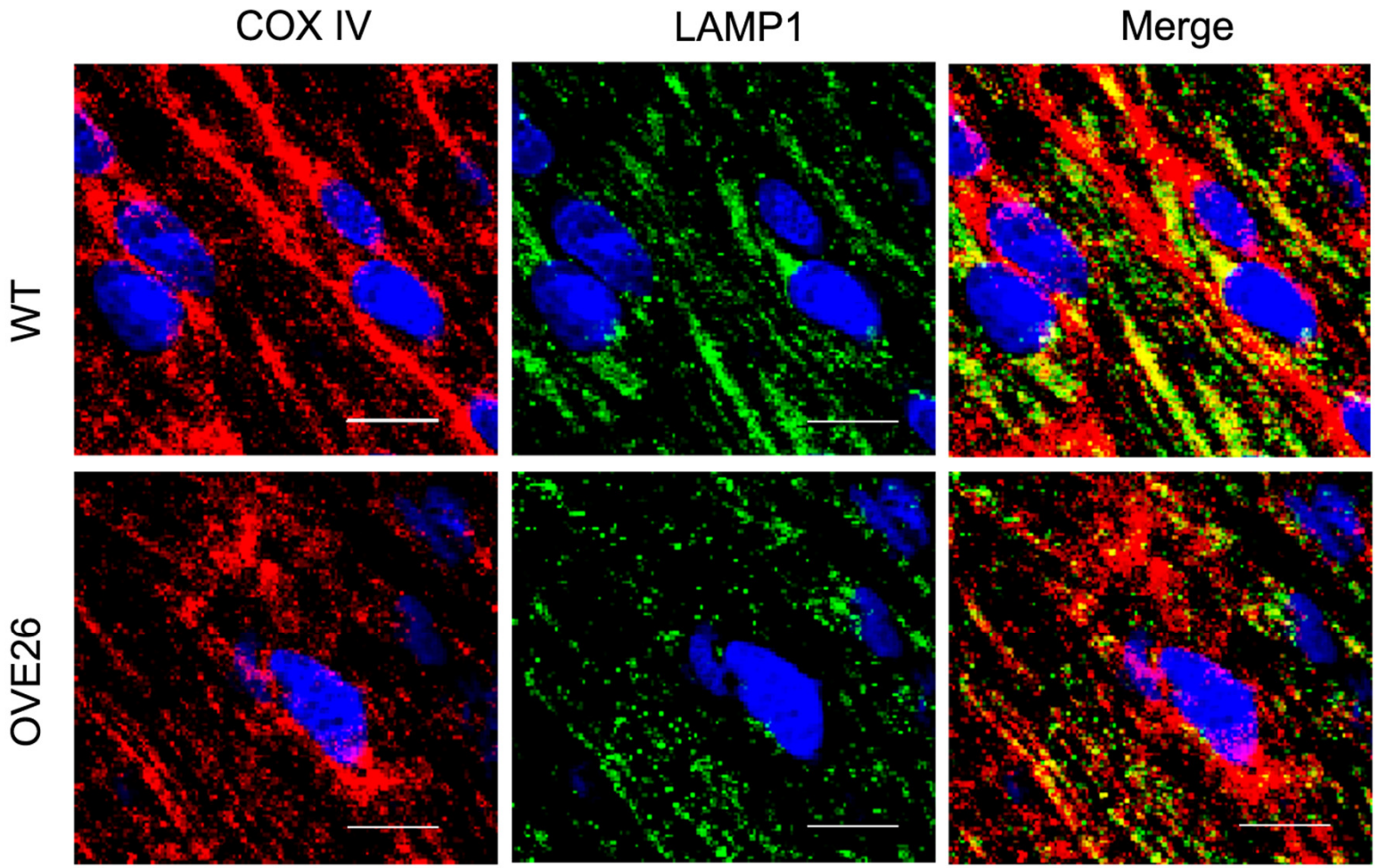
Mitophagy markers are altered in the diabetic heart



# Increased colocalization of LAMP1 with COX-IV in the diabetic mouse heart at 6-week

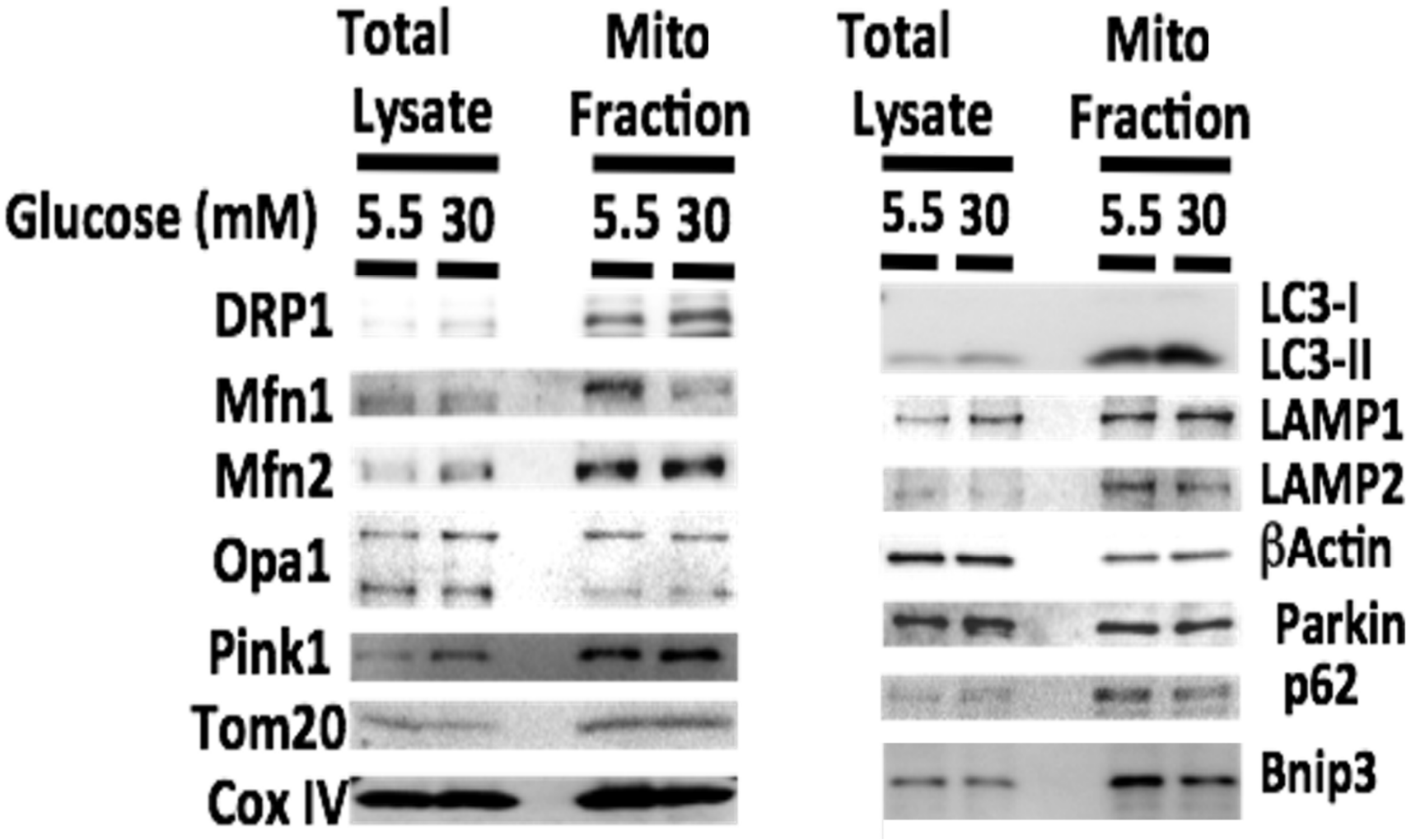


# Reduced colocalization of LAMP1 with COX-IV in the diabetic mouse heart at 17-week

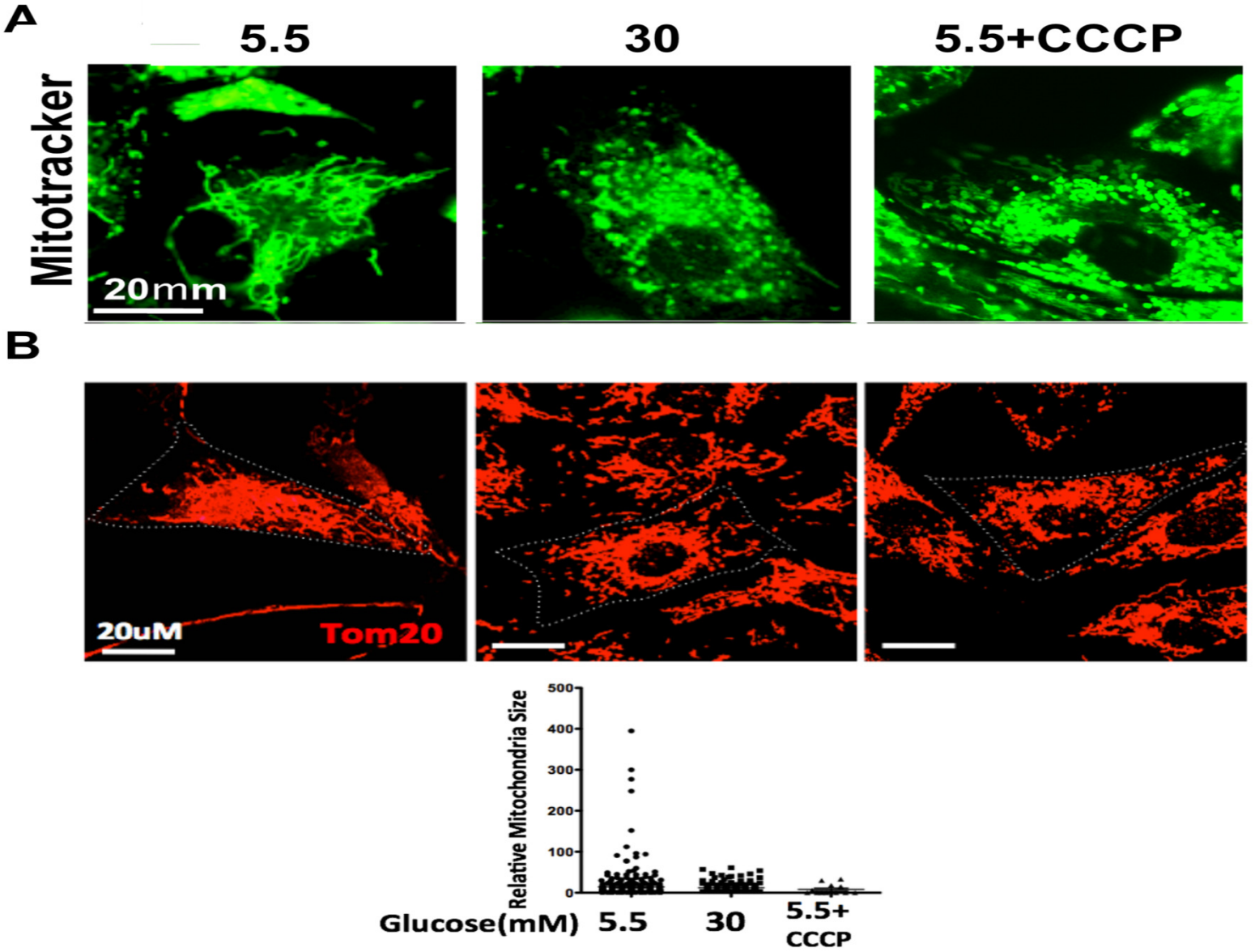



scale bar: 15μm

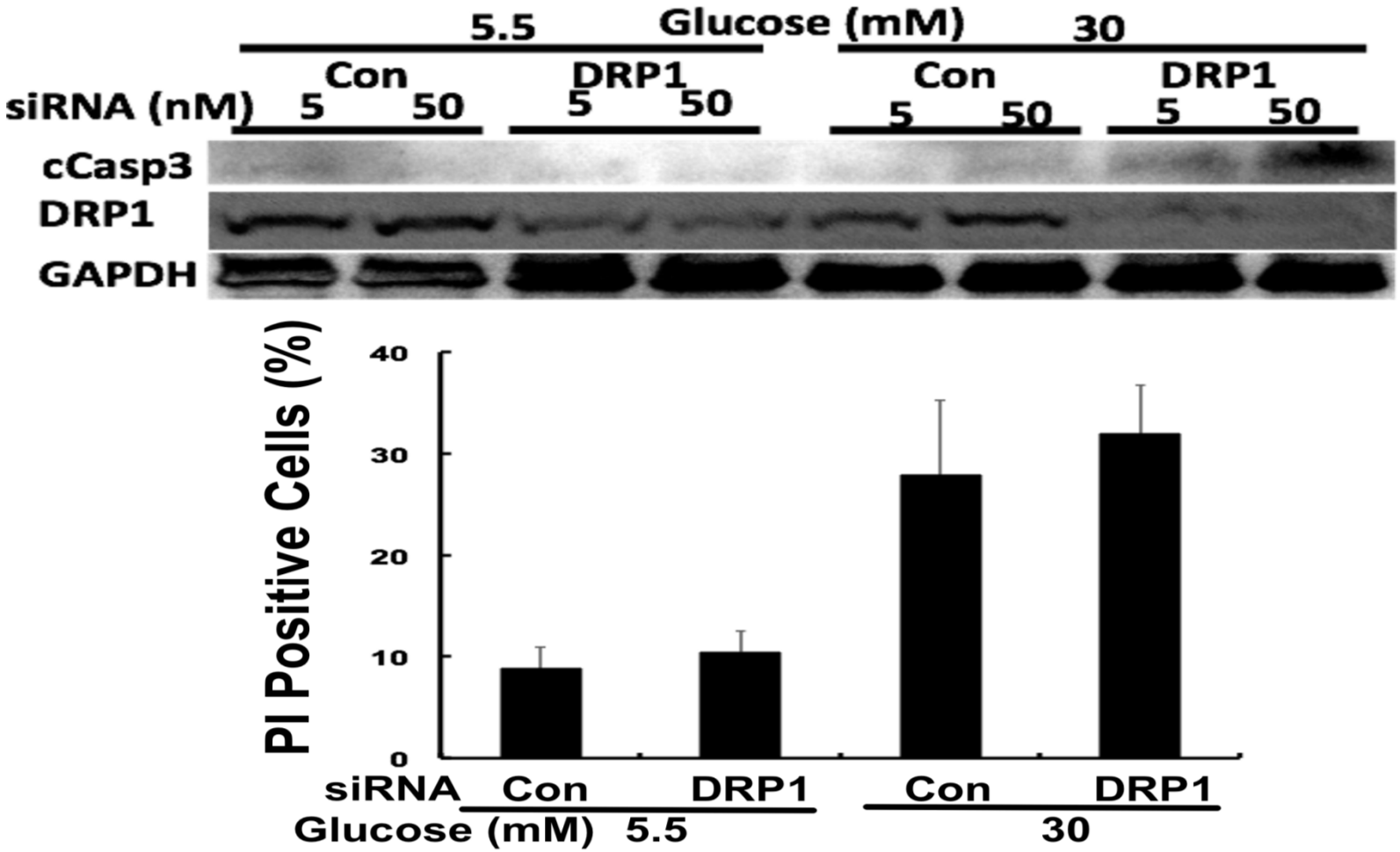
# High glucose (HG) affected the regulators of fusion, fission and mitophagy



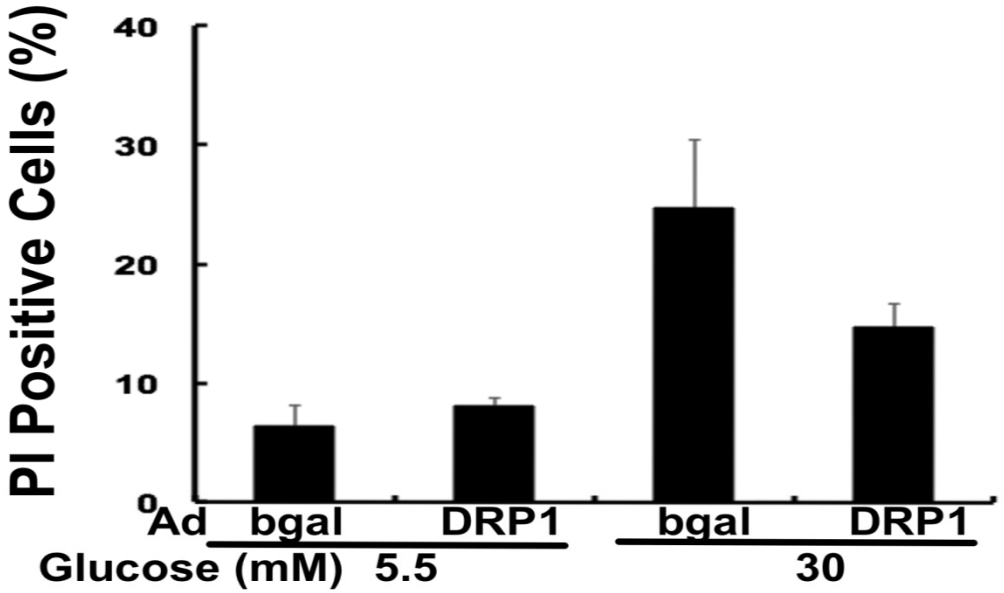
# High glucose (HG) induced mitochondrial fragmentation in cardiomyocytes

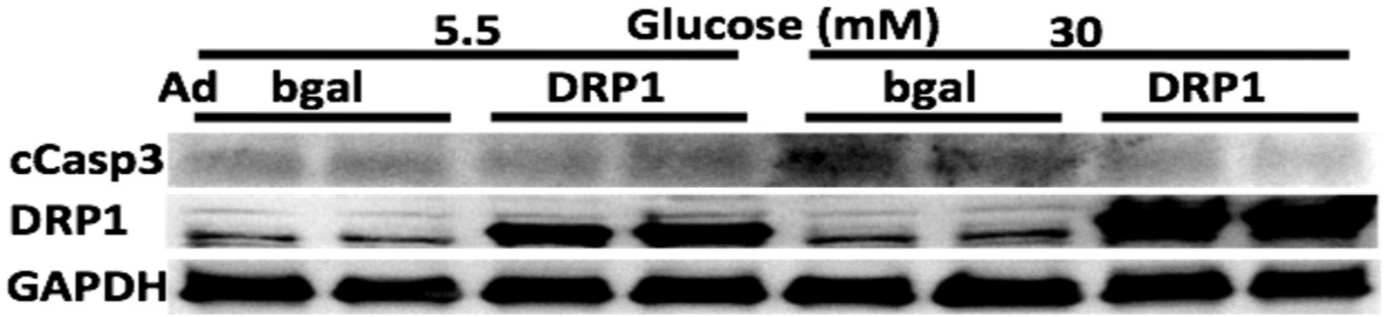


# Drp1 Knockdown increased HG-induced cardiomyocyte death

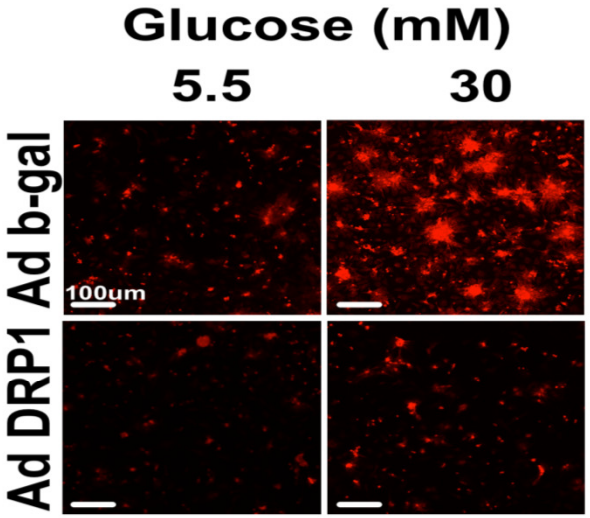


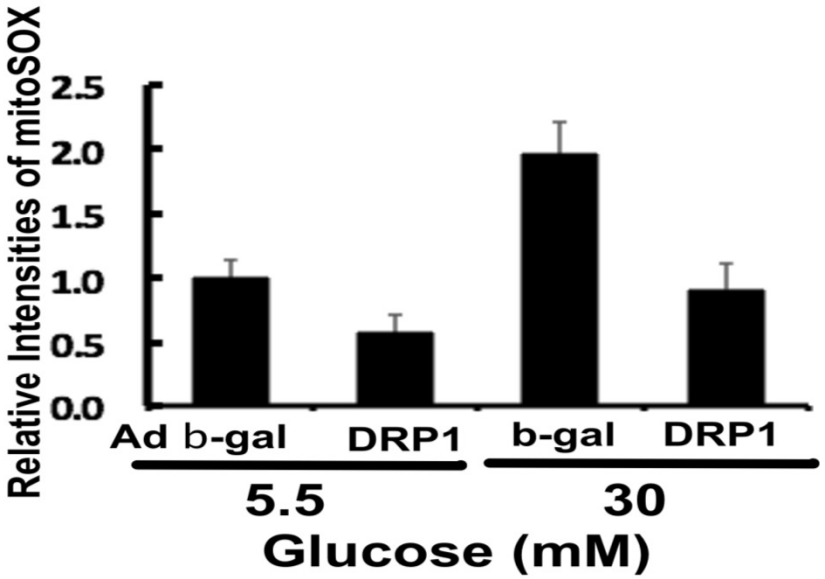
# Drp1 overexpression reduced HG-induced cardiomyocyte death

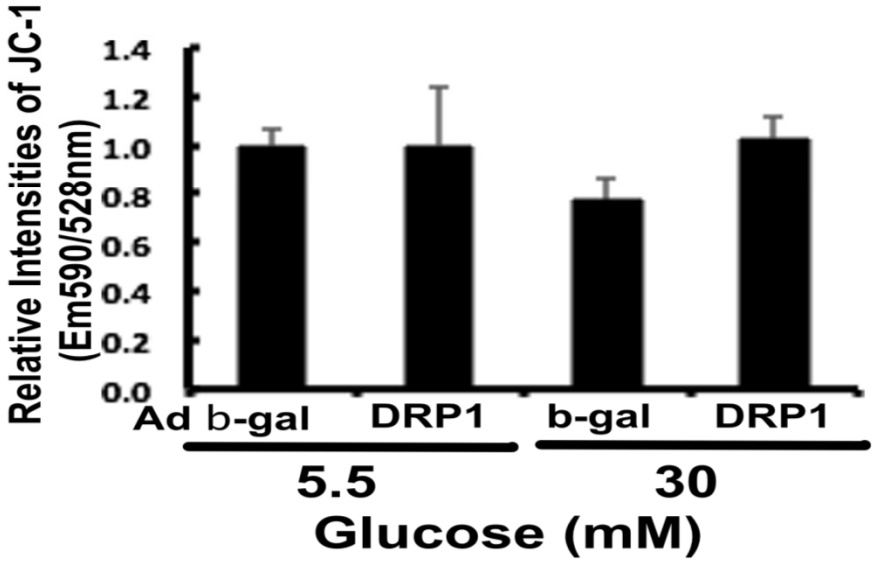


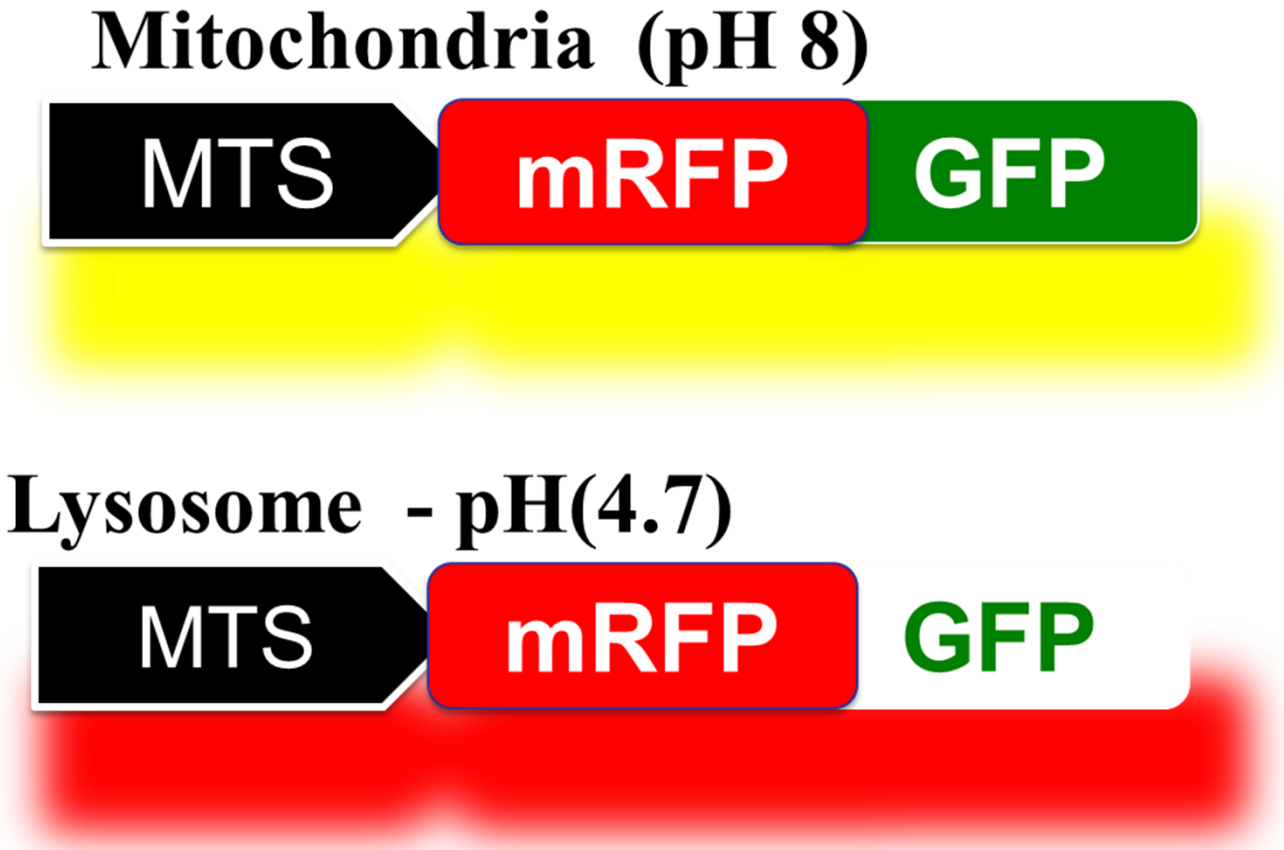
# Drp1 overexpression reduced HG-induced superoxide generation



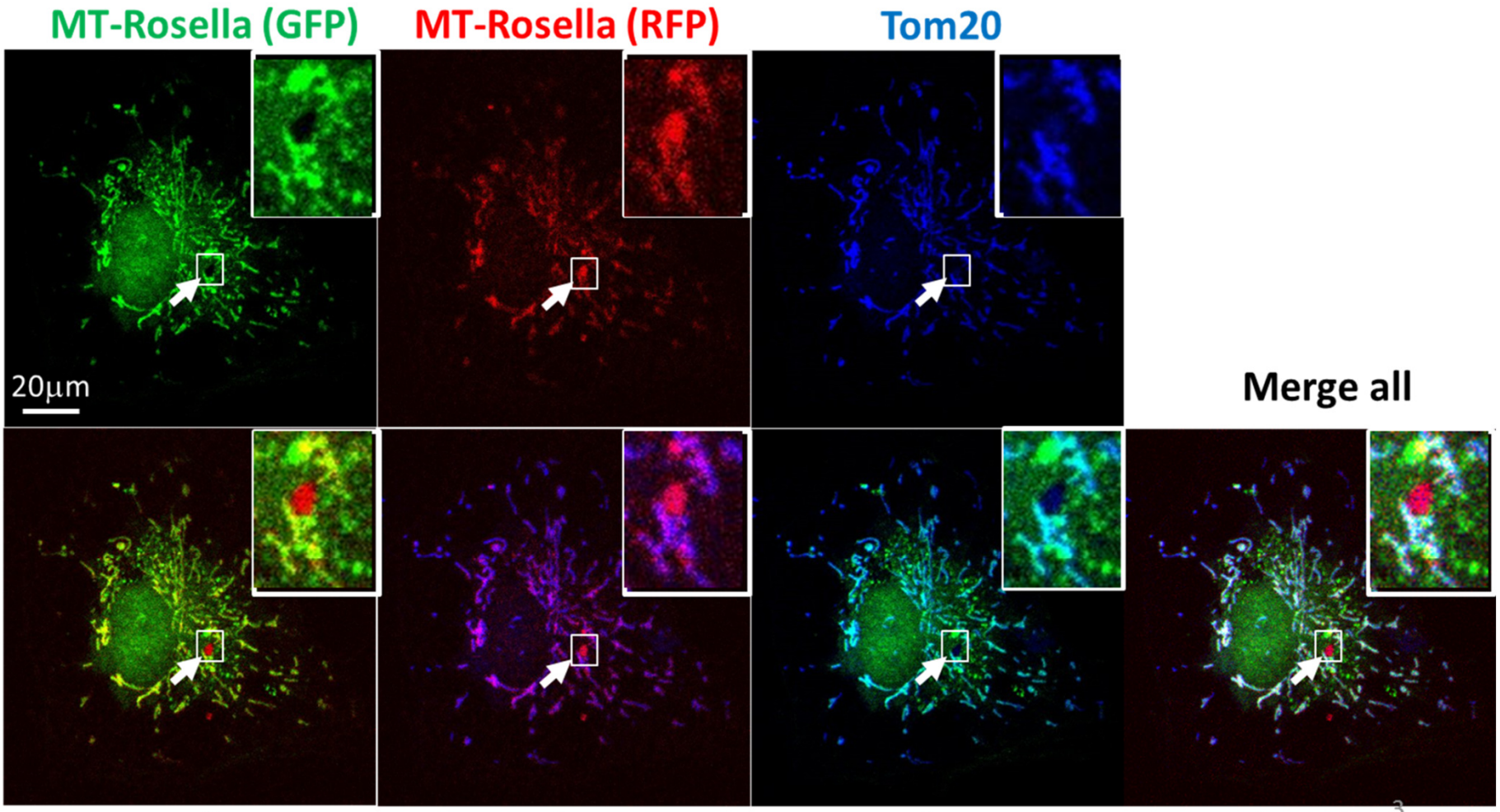



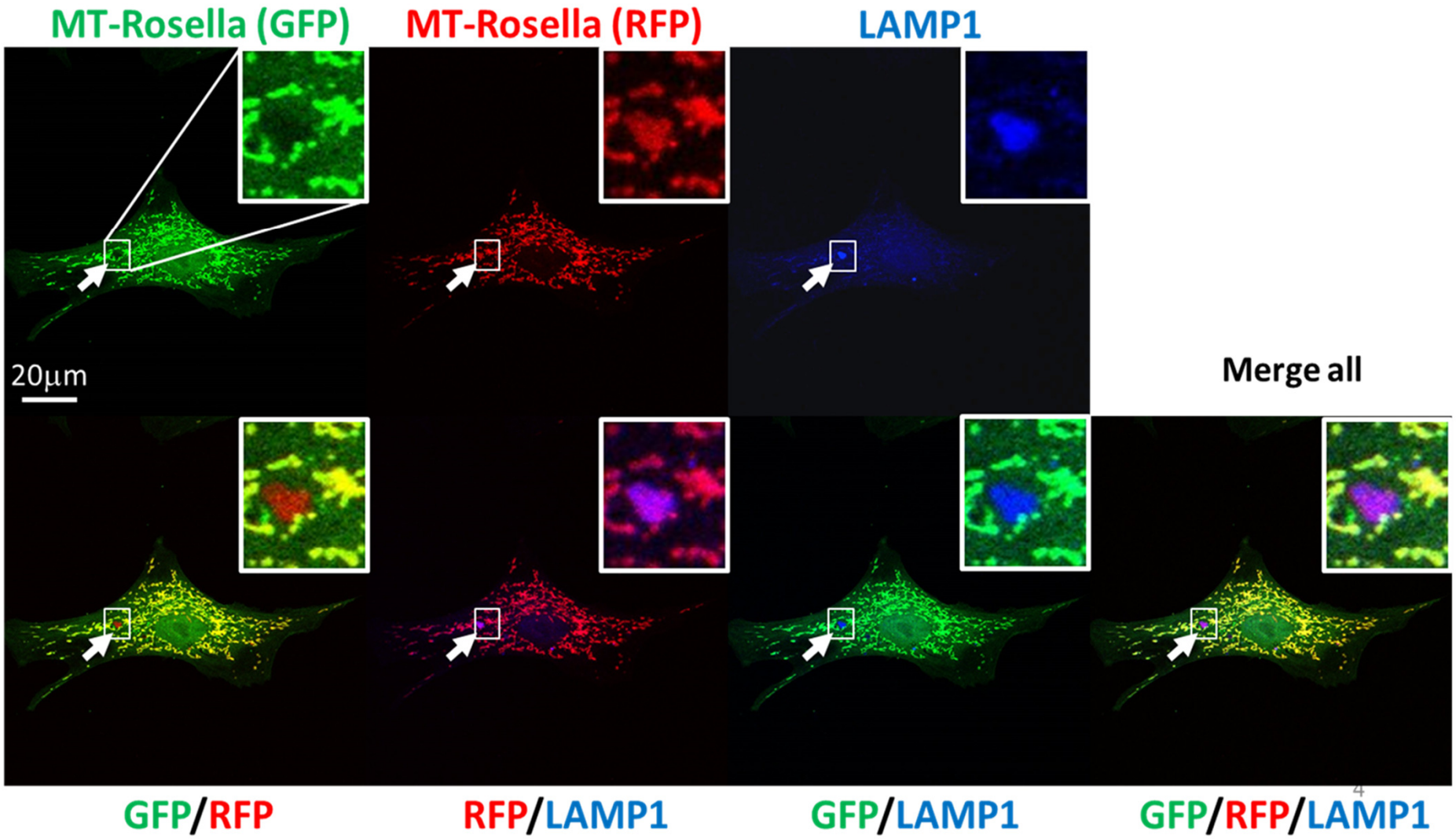
# A novel mitophagy reporter-MT-Rosella



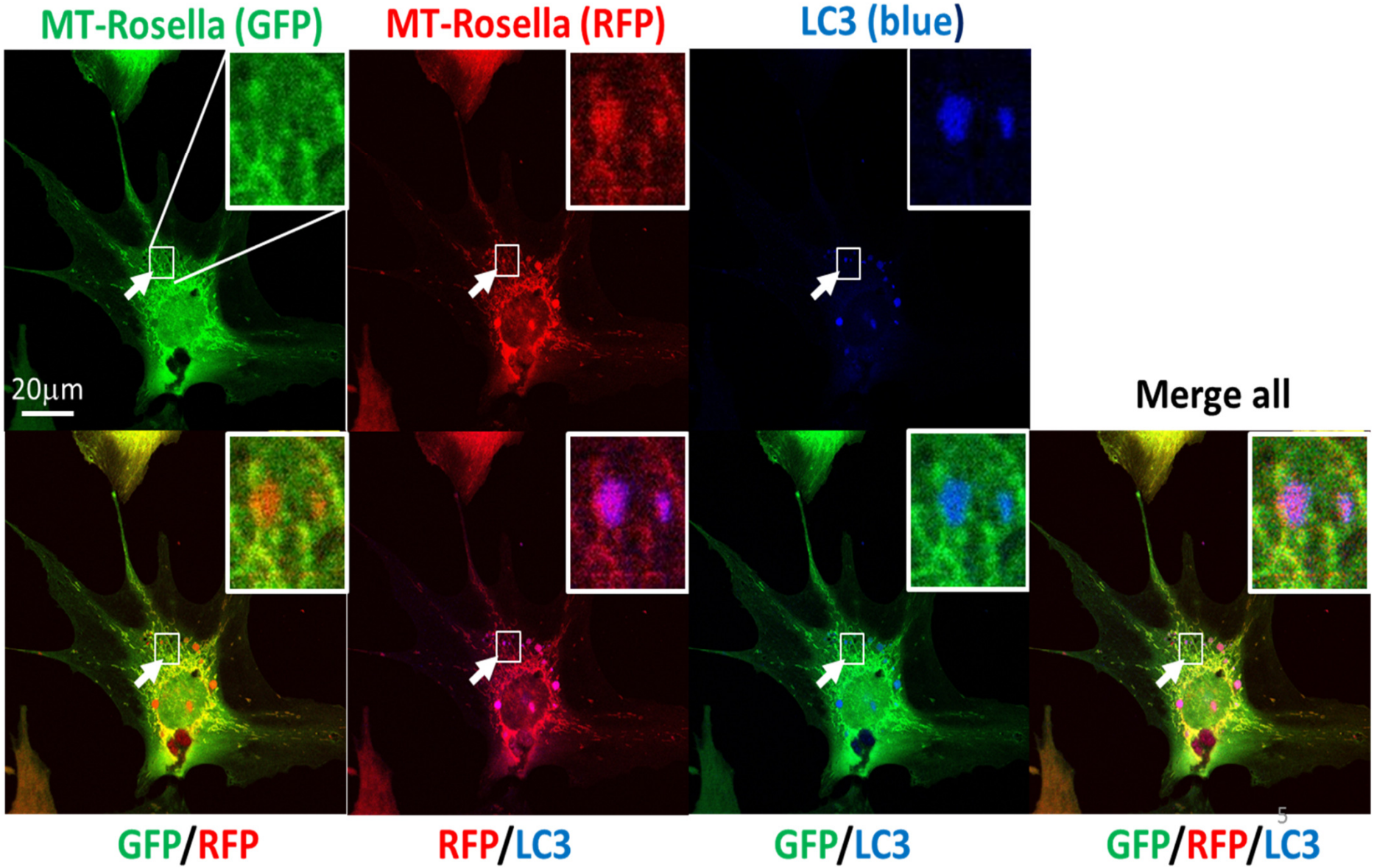
# MT-Rosella colocalize with Tom20



# Red puncta colocalize with LAMP1 on merged images

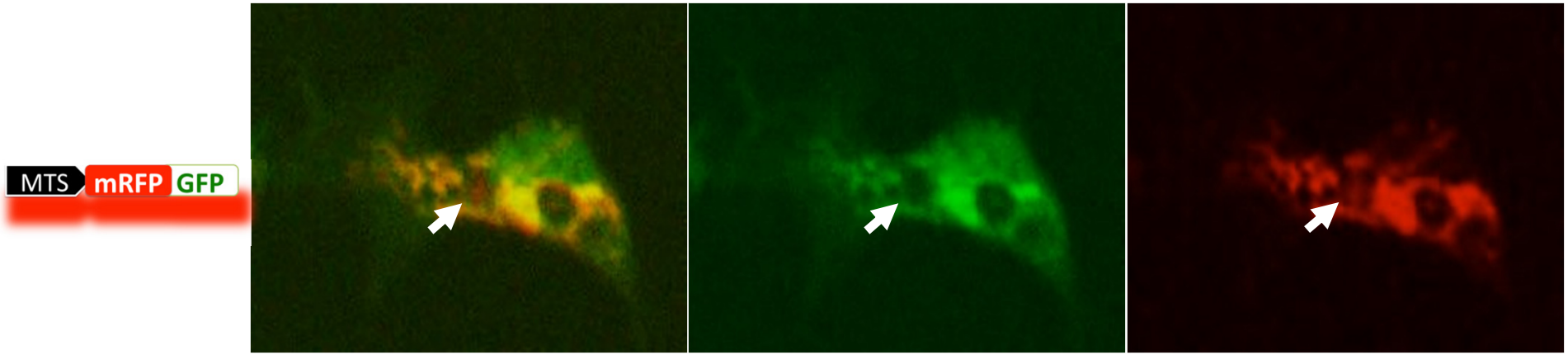


# Red puncta colocalize with LC3 on merged images

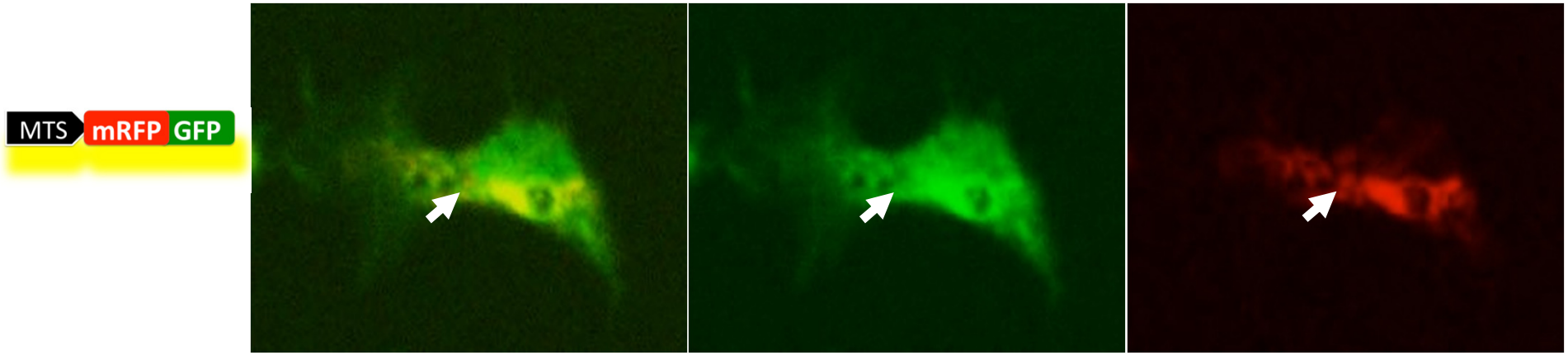


# Increased pH made GFP re-fluoresce

Pre NH4Cl

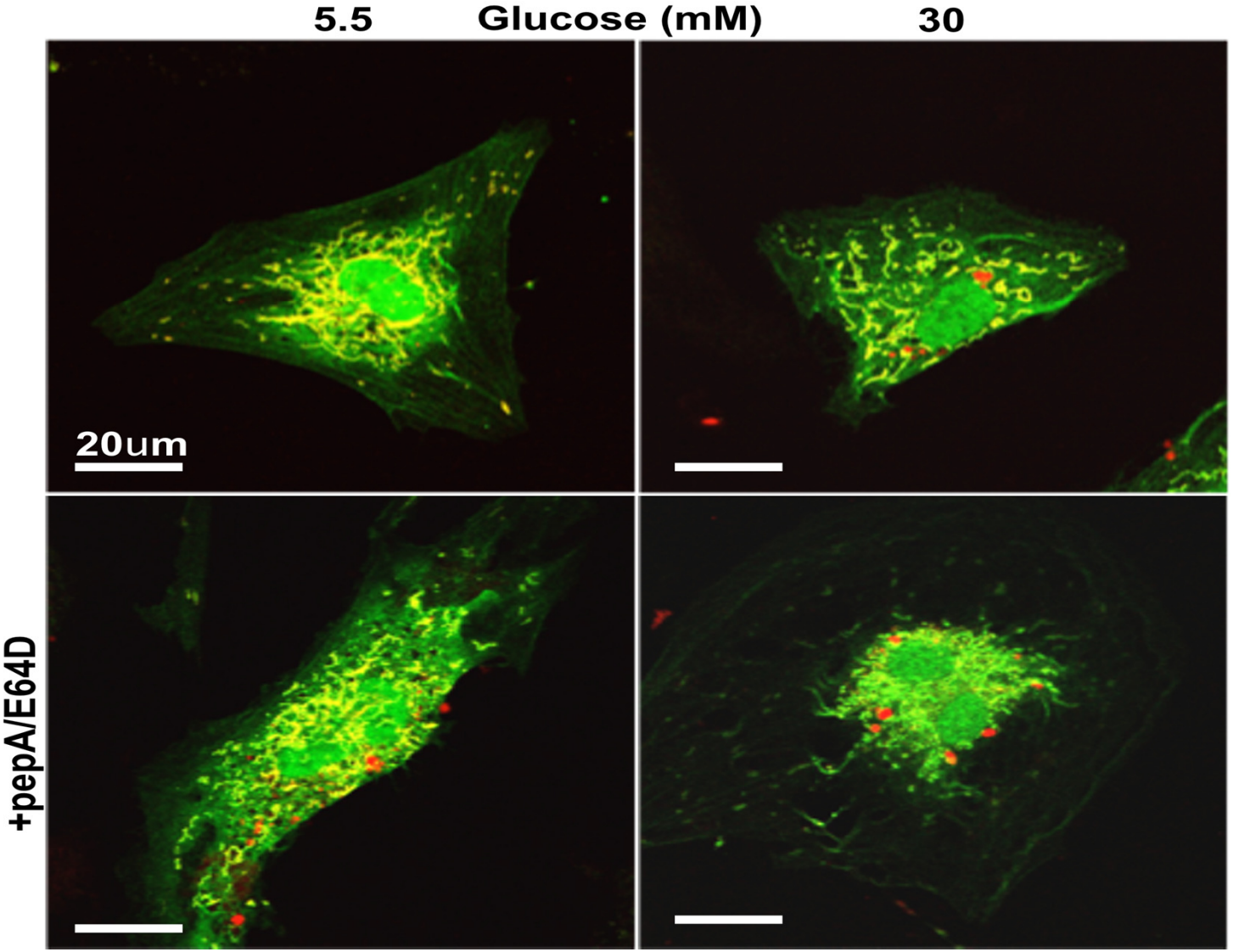



NH4Cl 1min

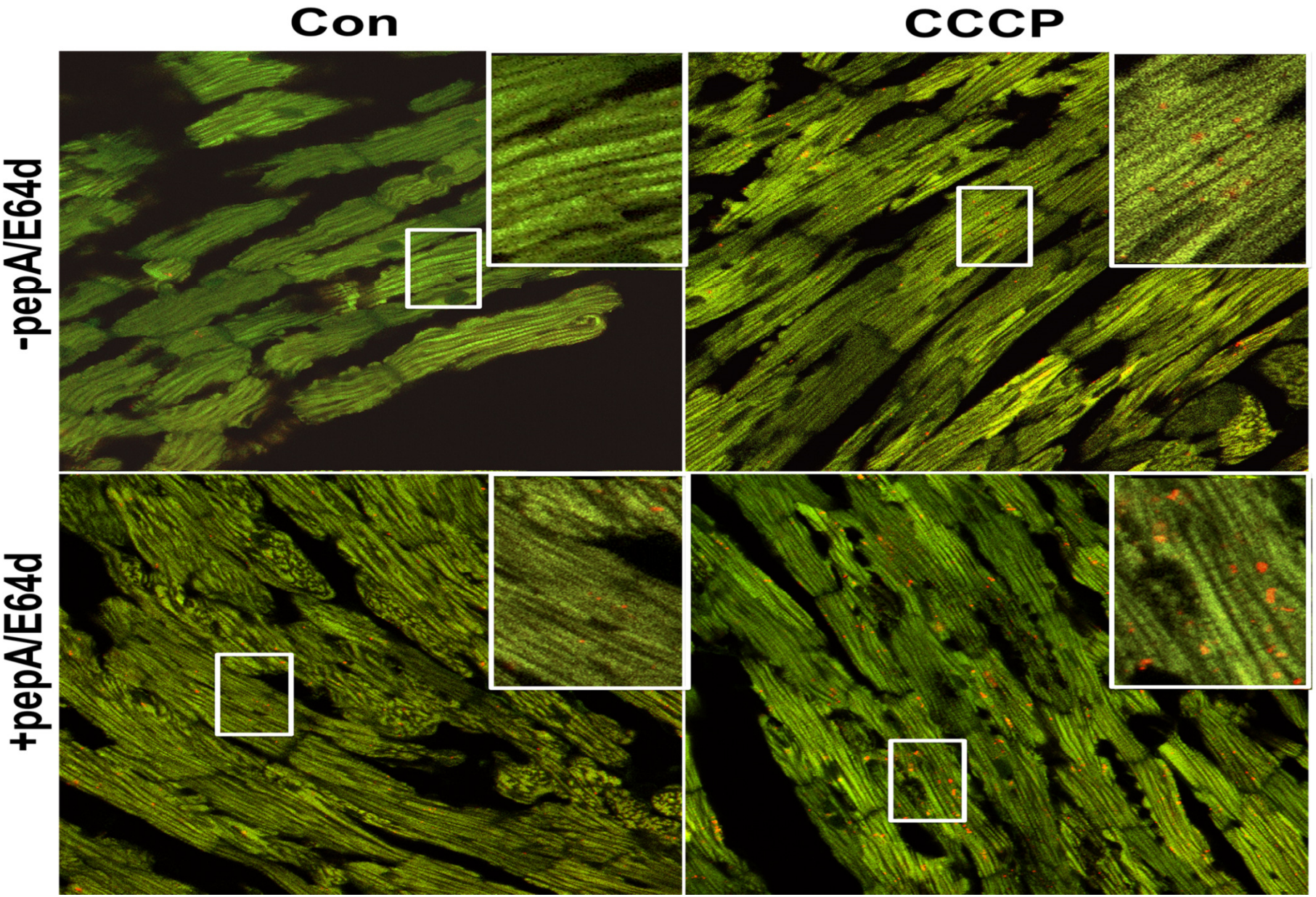



**Alkalization by Ammonium chloride de-quenched GFP**

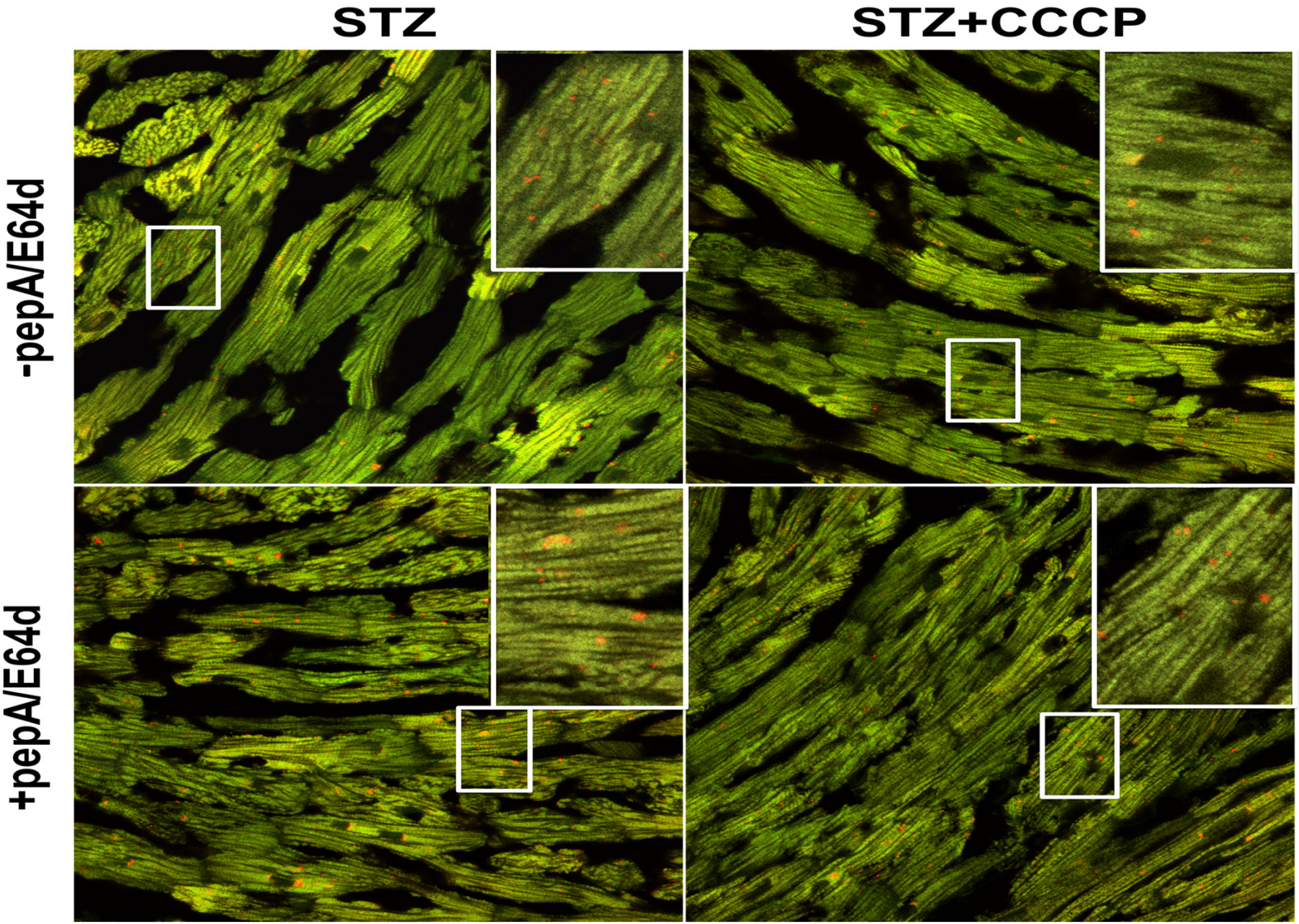
# HG reduced mitophagy flux in cardiomyocytes



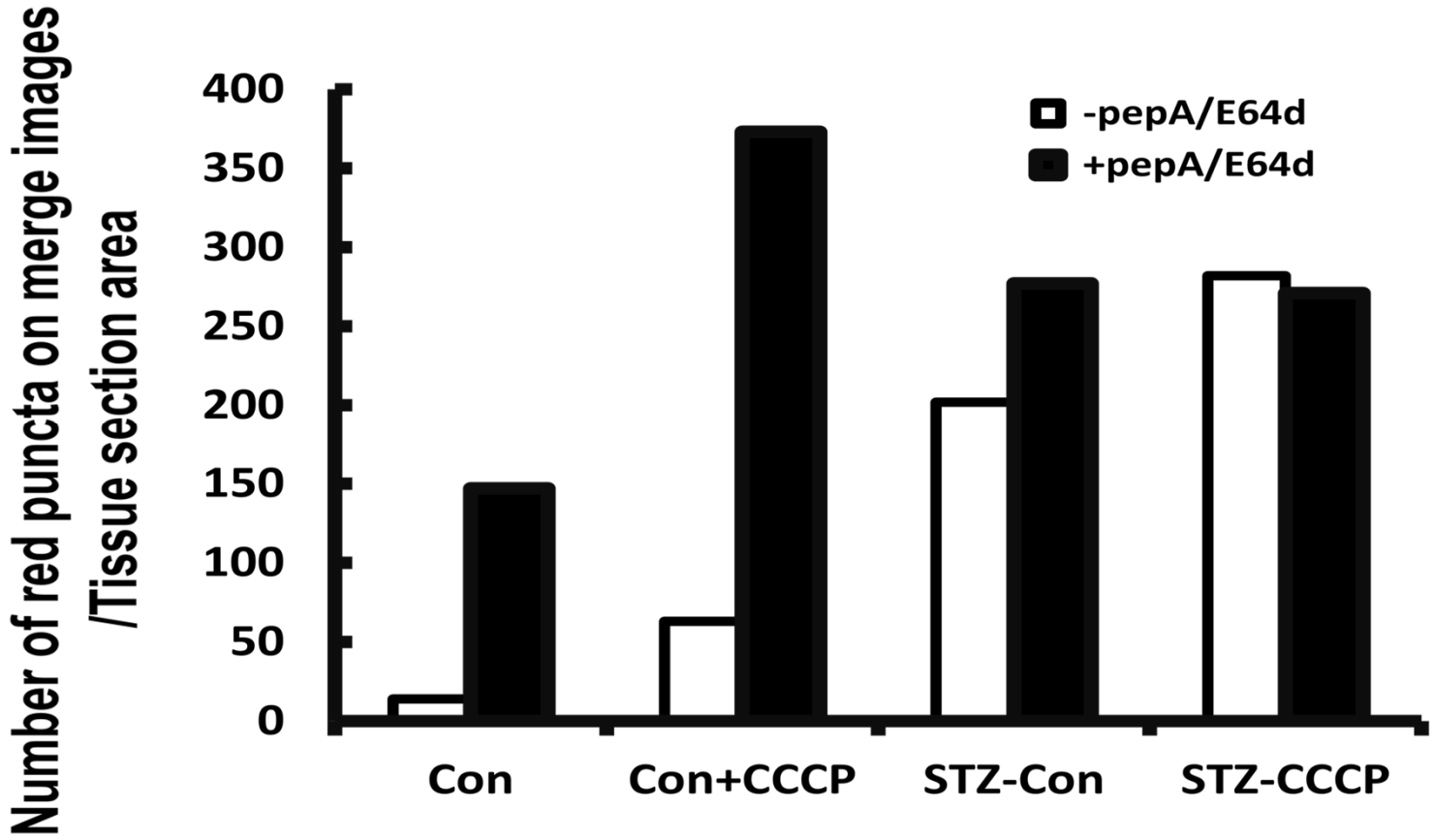
# CCCP induced mitophagy in mouse heart



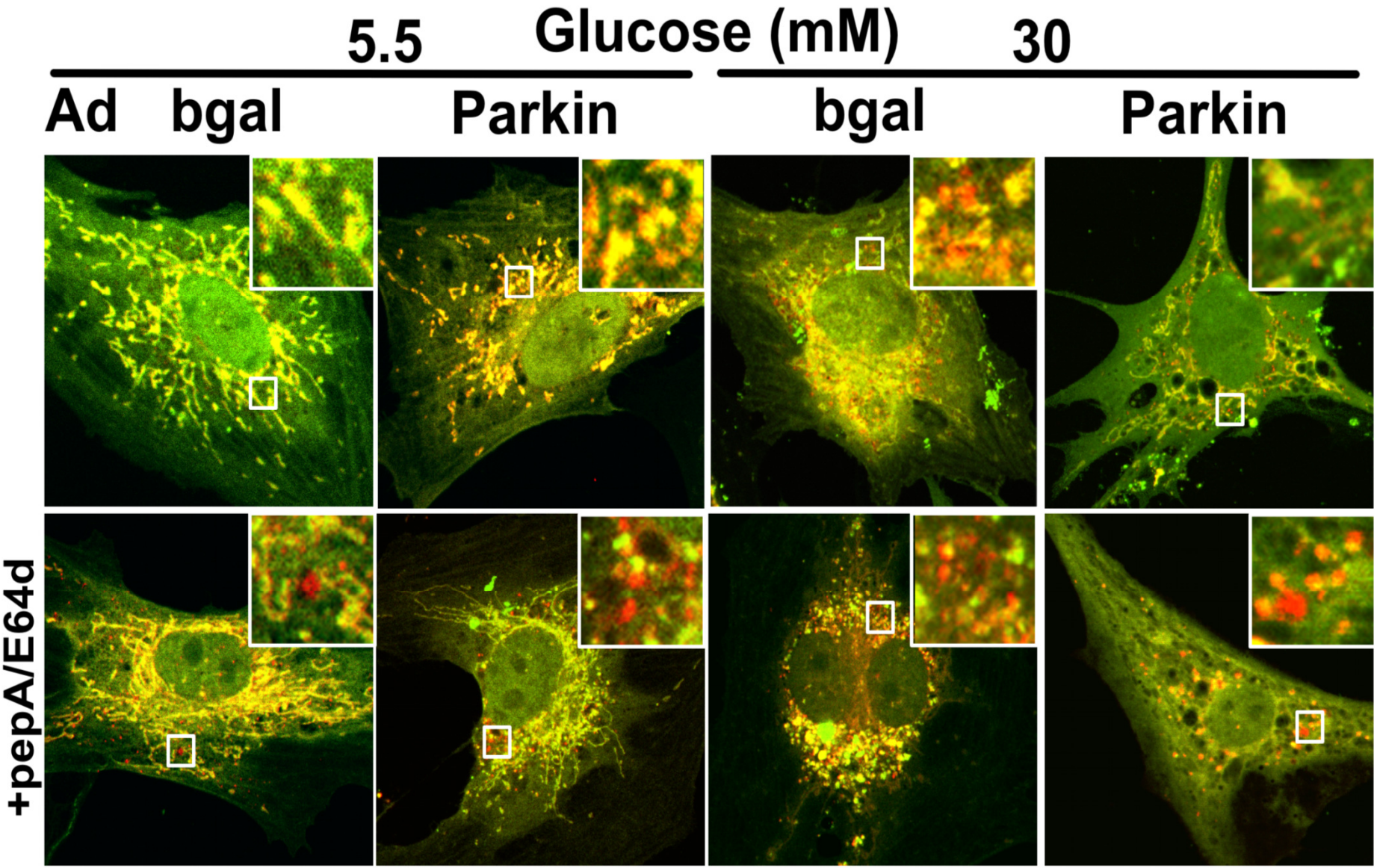
# Mitophagy flux was reduced in STZ diabetic heart



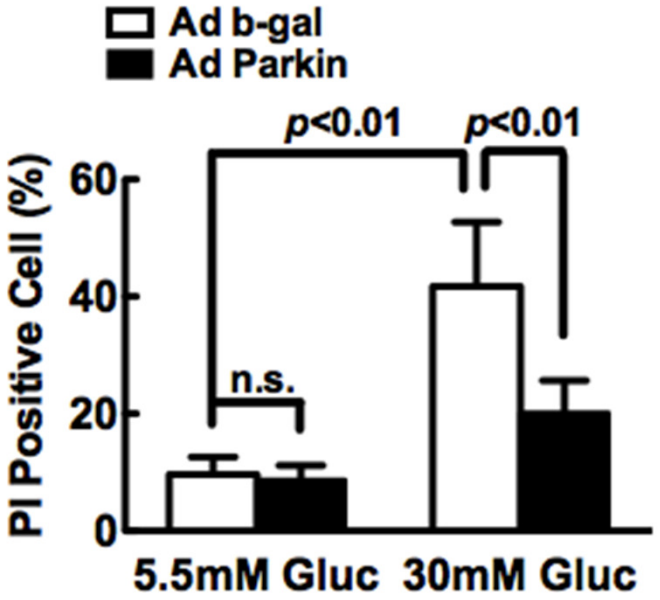
# Mitophagy flux was reduced in STZ diabetic heart

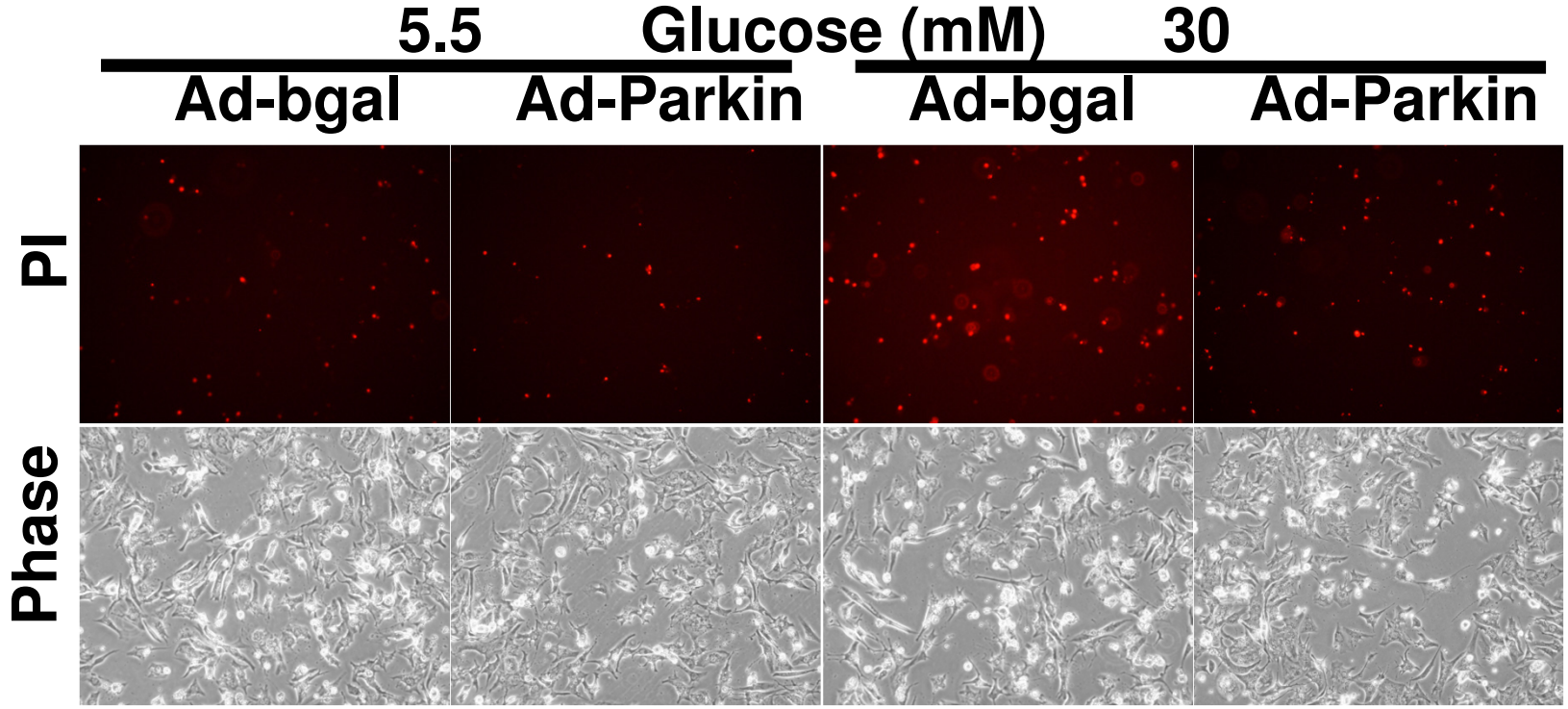


# Parkin overexpression induced mitophagy

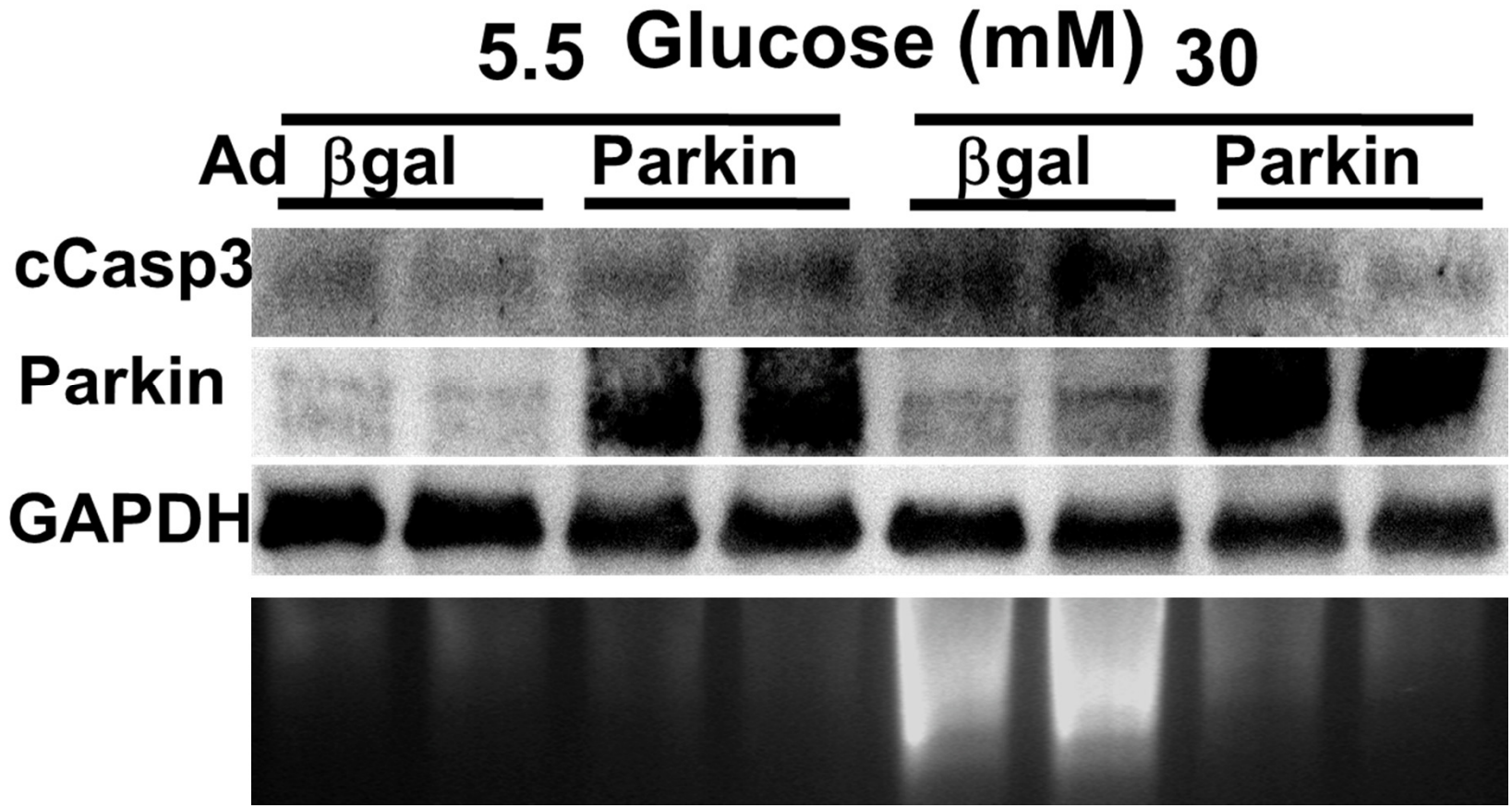


# Parkin over-expression attenuated high glucose-induced cardiomyocyte death

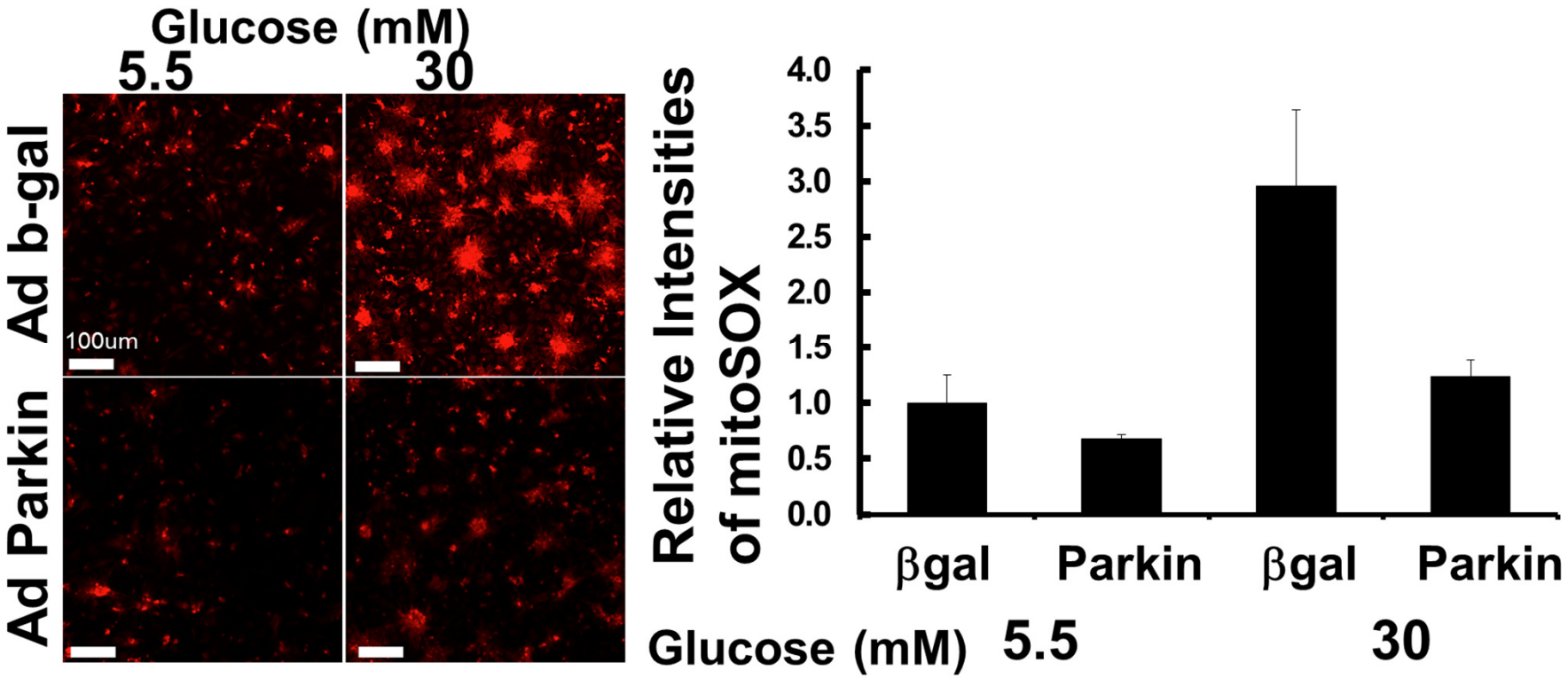


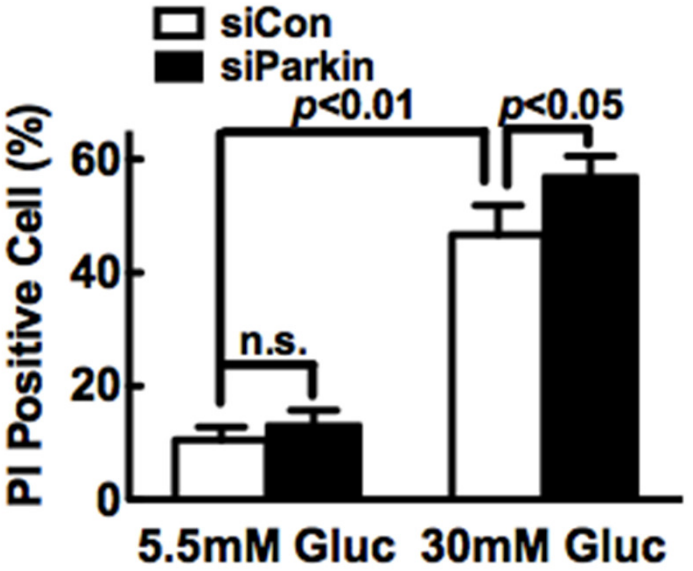
# Parkin overexpression decreased high glucose-induced apoptosis

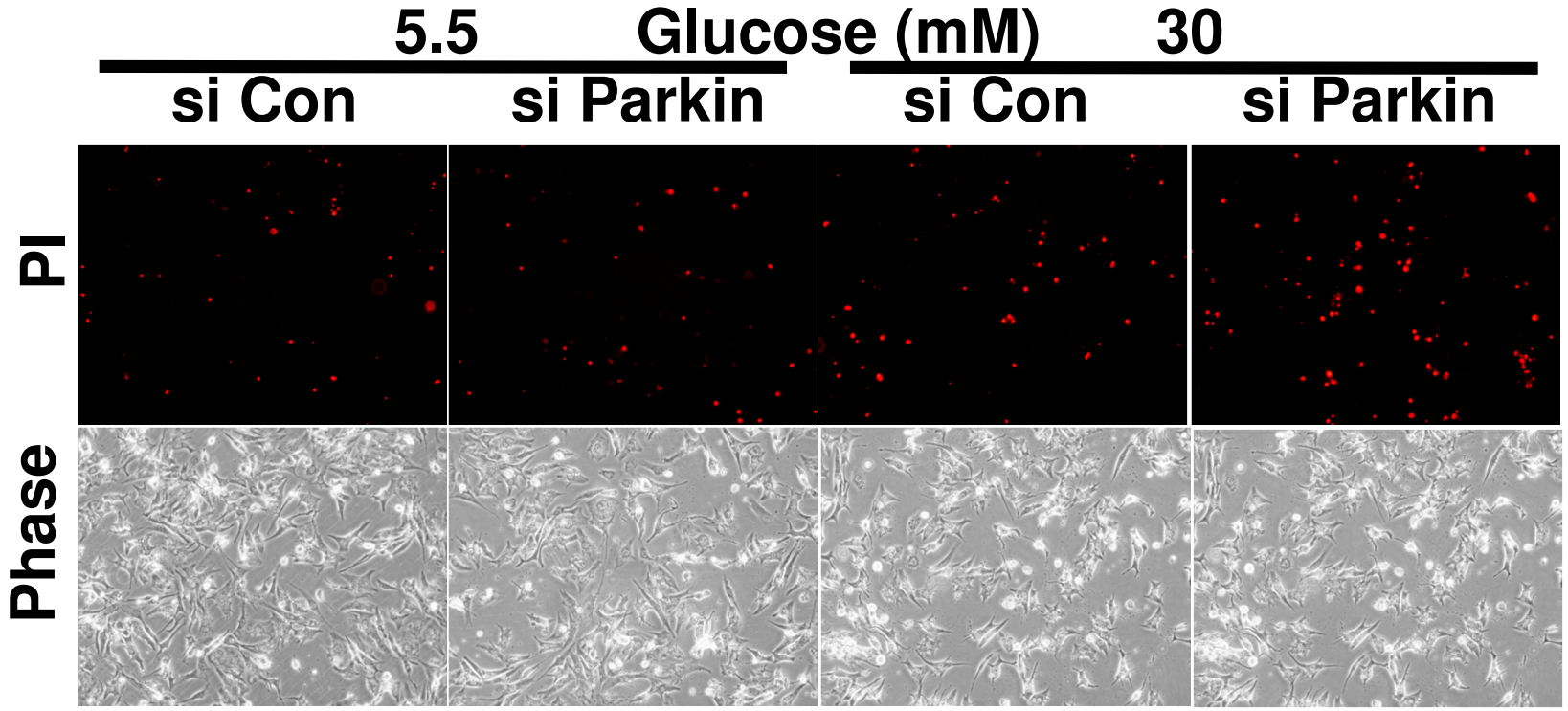


# Parkin overexpression attenuated high glucose-induced ROS generation

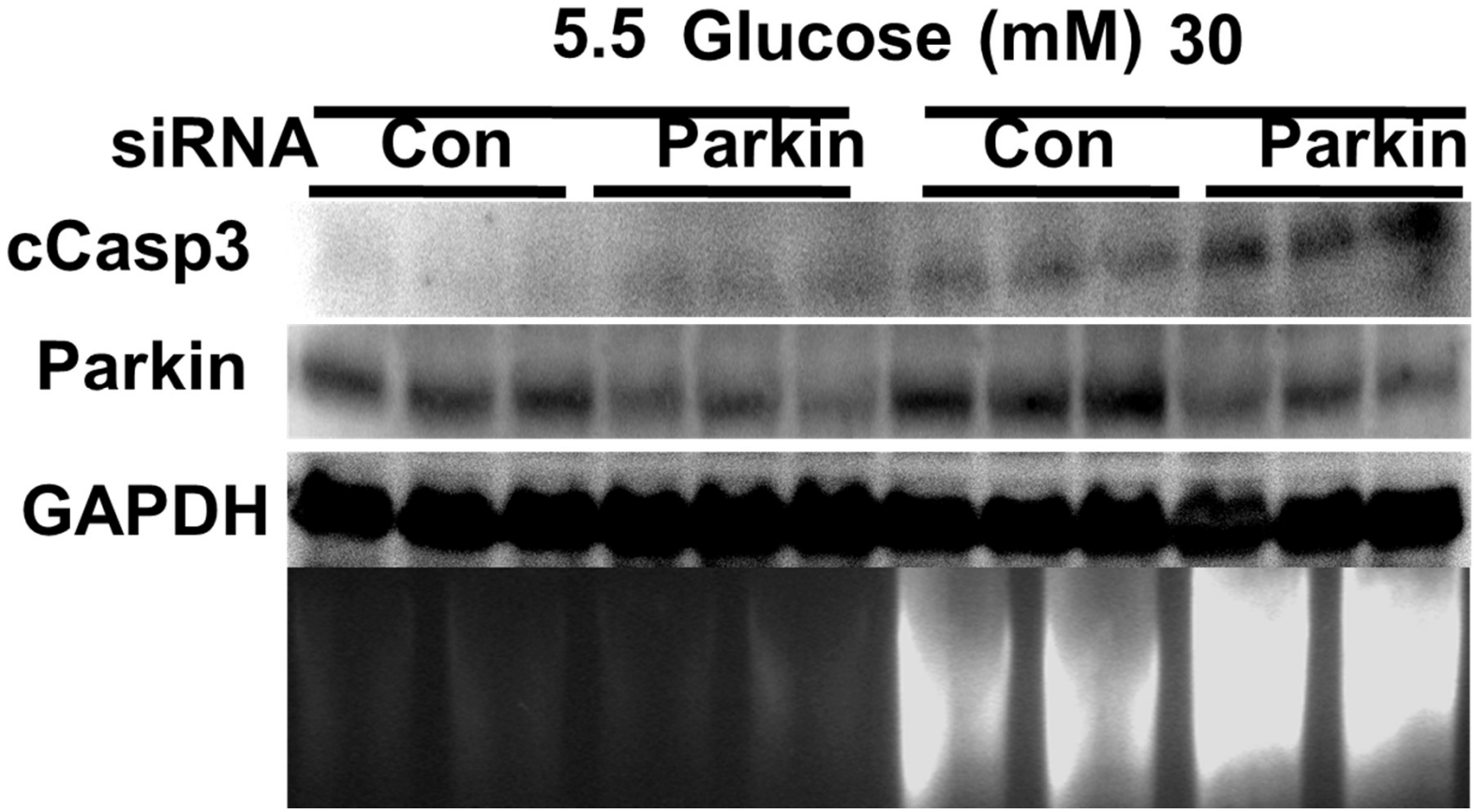


# Parkin knockdown exacerbated high glucose-induced cardiomyocyte death



# Parkin Knockdown exacerbated high glucose-induced apoptosis



# Summary

- Mitochondria damage is critical in the pathogenesis of diabetic cardiomyopathy.
- Mitochondrial quality control is impaired in the diabetic heart.
- We have constructed a novel dual fluorescent mitophagy reporter (adenovirus and transgenic mouse).
- High glucose induces mitochondrial fission and inhibits mitophagy flux.
- Mitophagy flux is inhibited in STZ diabetic heart.
- Mitochondrial fission and mitophagy protect against HG-induced cardiomyocyte injury.

# Acknowledgements

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**Washington University: Dr. Herbert W. Virgin**
**Cincinnati Children's Hospital: Dr. Jeff Robbins**

**NIH**
**American Diabetes Association**
**Juvenile Diabetes Research Foundation (JDRF)**

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