Clusterin and PGC1α coordinately activates mitophagy and mitochondrial biogenesis to inhibit apoptosis in oral cancer

Prakash P. Praharaj, Sujit K. Bhutia

Cancer and Cell Death Laboratory, Department of Life Science, National Institute of Technology Rourkela, Rourkela-769008, Odisha, India.

E-mail: sujitb@nitrkl.ac.in

Abstract

Mitophagy involves the selective elimination of defective mitochondria during chemotherapeutic stress to maintain mitochondrial homeostasis and sustain cancer growth. Here, we showed that CLU (clusterin) is localized to mitochondria to induce mitophagy controlling mitochondrial damage in oral cancer cells. Moreover, overexpression and knockdown of CLU establish its mitophagy-specific role, where CLU coordinately interacts with BAX and LC3 forming a tri-complex to clear damaged mitochondria in response to cisplatin treatment. Interestingly, CLU triggers class III phosphatidylinositol 3-kinase (PtdIns3K) activity around damaged mitochondria, and inhibition of mitophagic flux causes the accumulation of excessive mitophagosomes causing reactive oxygen species (ROS)-dependent apoptosis during cisplatin treatment in oral cancer cells. In parallel, we determined that PPARGC1A/PGC1α (PPARG coactivator 1 alpha) activates mitochondrial biogenesis during CLU-induced mitophagy to maintain the mitochondrial pool. Intriguingly, PPARGC1A inhibition through small interfering RNA (si*PPARGC1A*) and pharmacological inhibitor (SR-18292) treatment counteracts CLU-dependent cytoprotection leading to mitophagy-associated cell death. Furthermore, co-treatment of SR-18292 with cisplatin synergistically suppresses tumor growth in oral cancer xenograft models. In conclusion, CLU and PPARGC1A are essential for sustained cancer cell growth by activating mitophagy and mitochondrial biogenesis, respectively, and their inhibition could provide better therapeutic benefits against oral cancer.

Keywords: Clusterin; mitochondrial biogenesis; mitophagy; mitophagy-associated cell death; PPARGC1A/PGC1α

CLU (clusterin) and PPARGC1A/PGC1α coordinately control mitophagy and mitochondrial biogenesis for oral cancer cell survival

Presented By;

Sujit Kumar Bhutia

Associate Professor

Department of Life Science

National Institute of Technology Rourkela

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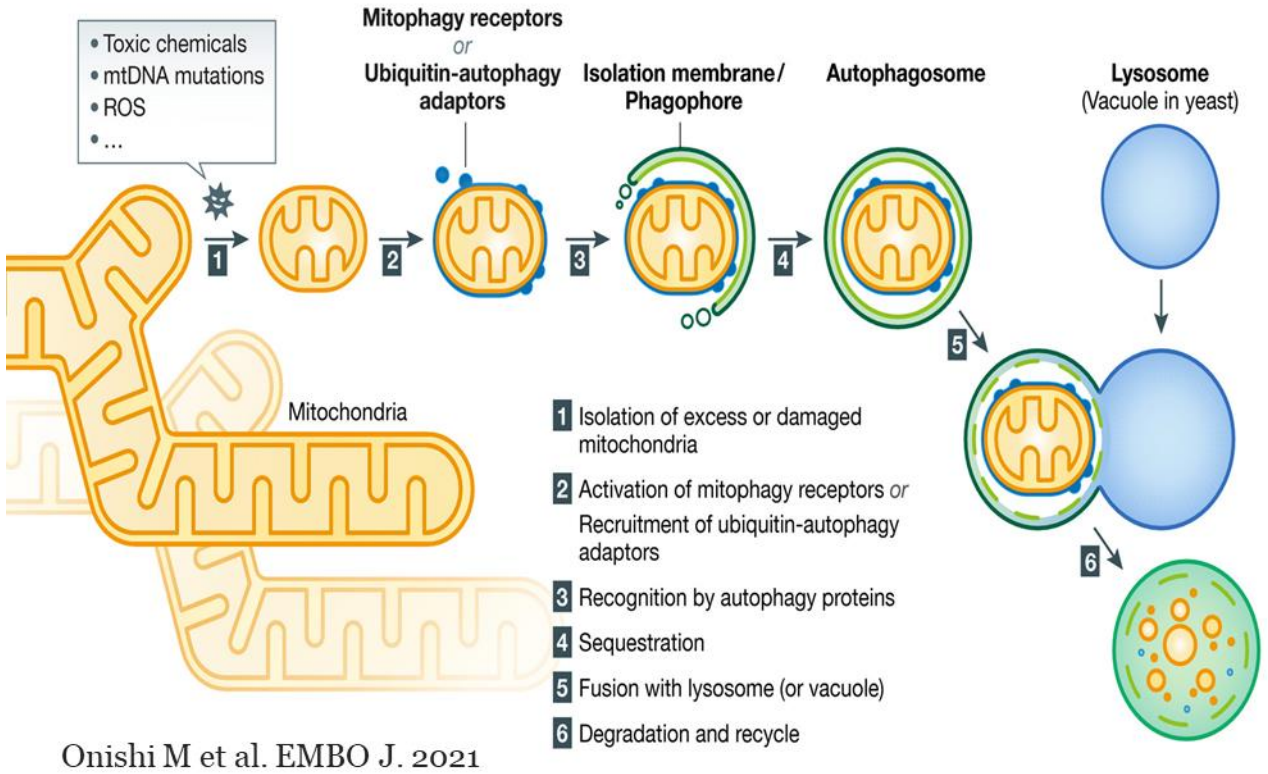
Outline

- **Introduction**
  - CLU (clusterin)
  - Mitophagy
  - Mitochondrial biogenesis
- **Results**
- **Conclusion**

Introduction

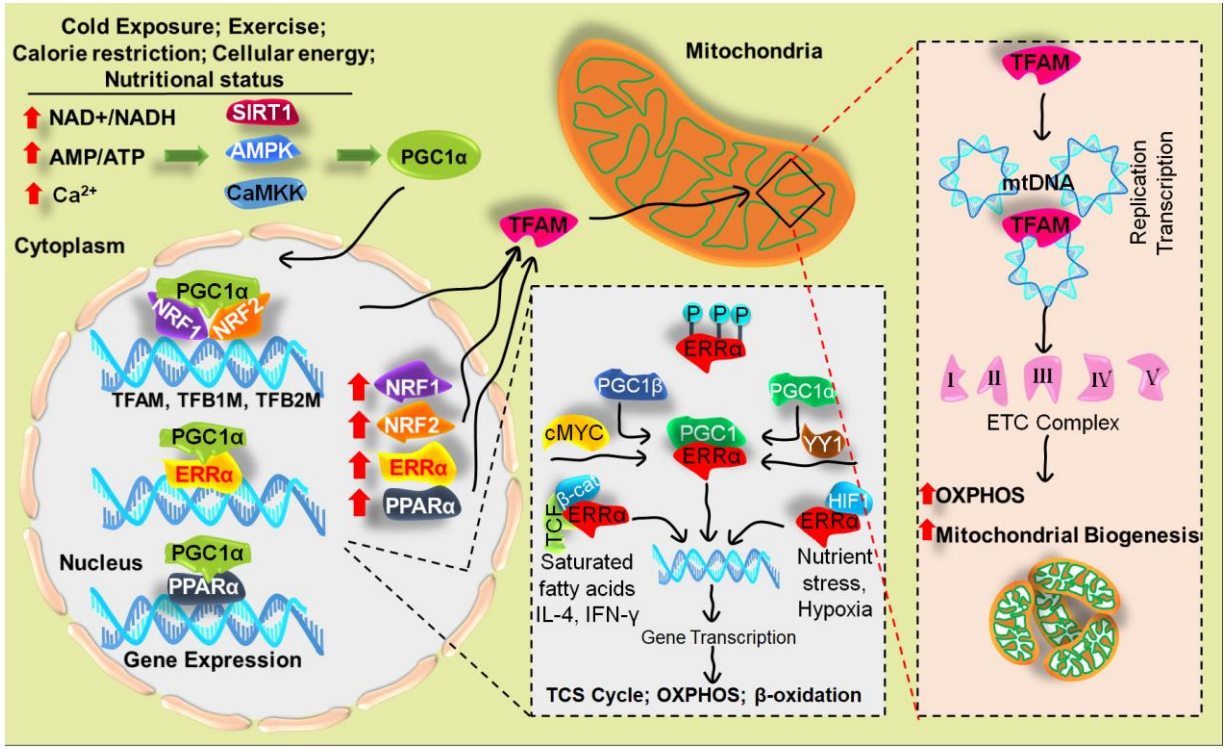
- **CLU**: a single copy gene located in Human chromosome 8, and its secretory protein form **regulates autophagy** by promoting Atg3-mediated PE-conjugation of LC3I (LC3 lipidation) to form a stable **Atg3–LC3 heterocomplex**

Mitophagy



Onishi M et al. EMBO J. 2021

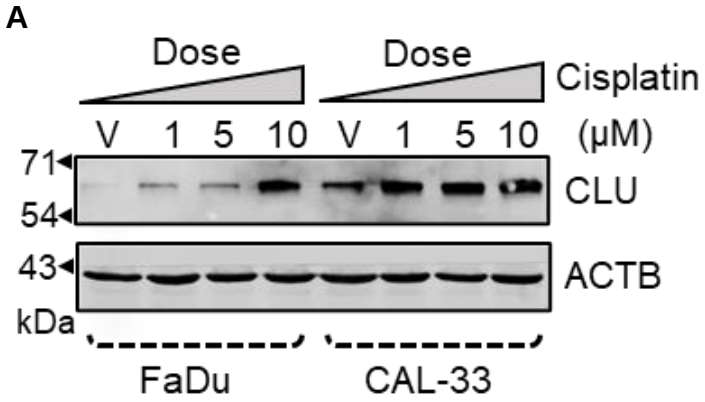
Mitochondrial biogenesis

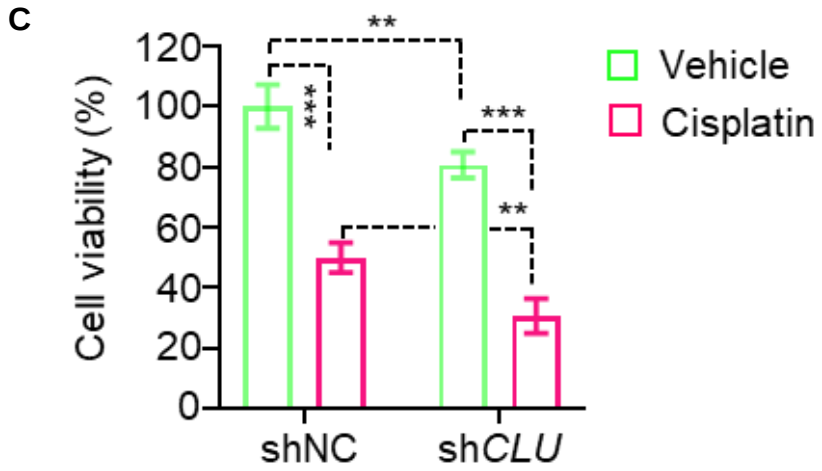


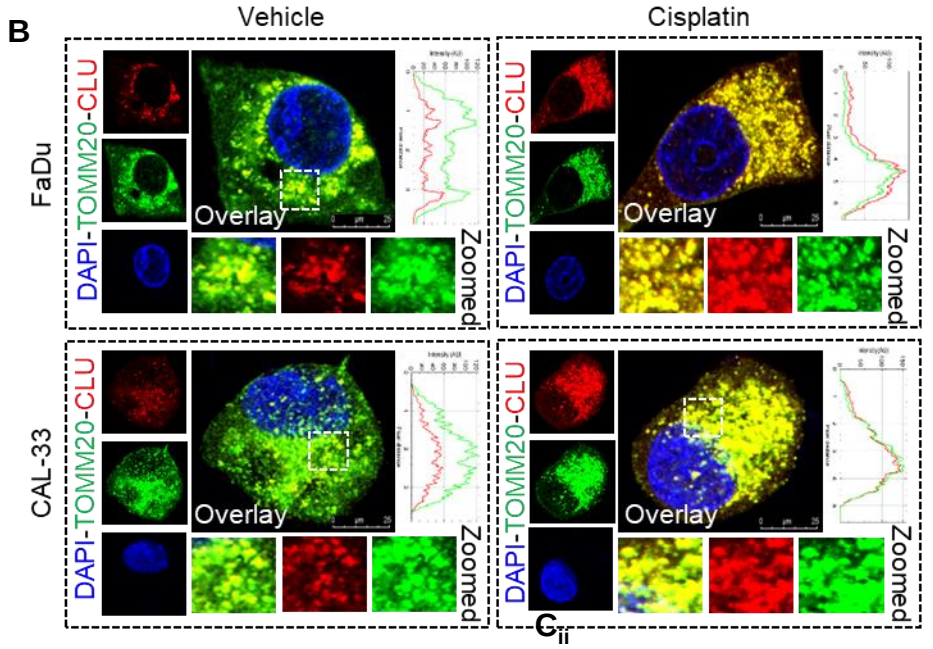
Praharaj et al. Autophagy in tumor and tumor microenvironment 2020

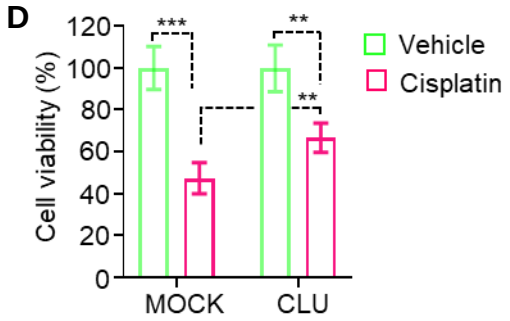
- **To address the mechanism, cancer cell adapt for stress tolerance and treatment resistance we need to understand the connection between stress-induced mitophagy and mitochondrial biogenesis in Oral squamous cell carcinoma**

CLU localizes to mitochondria and protects mitochondria from damage due to cisplatin

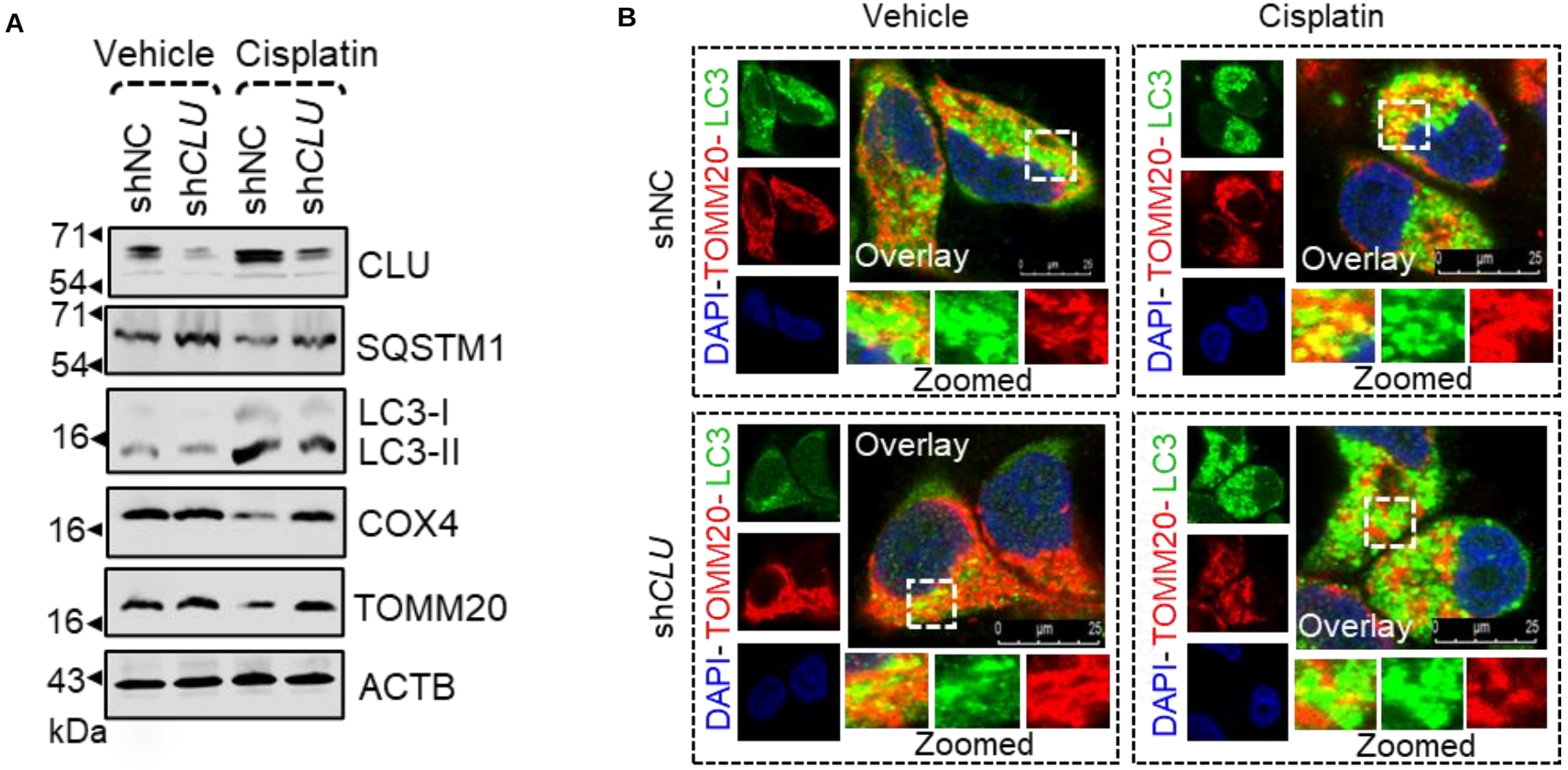




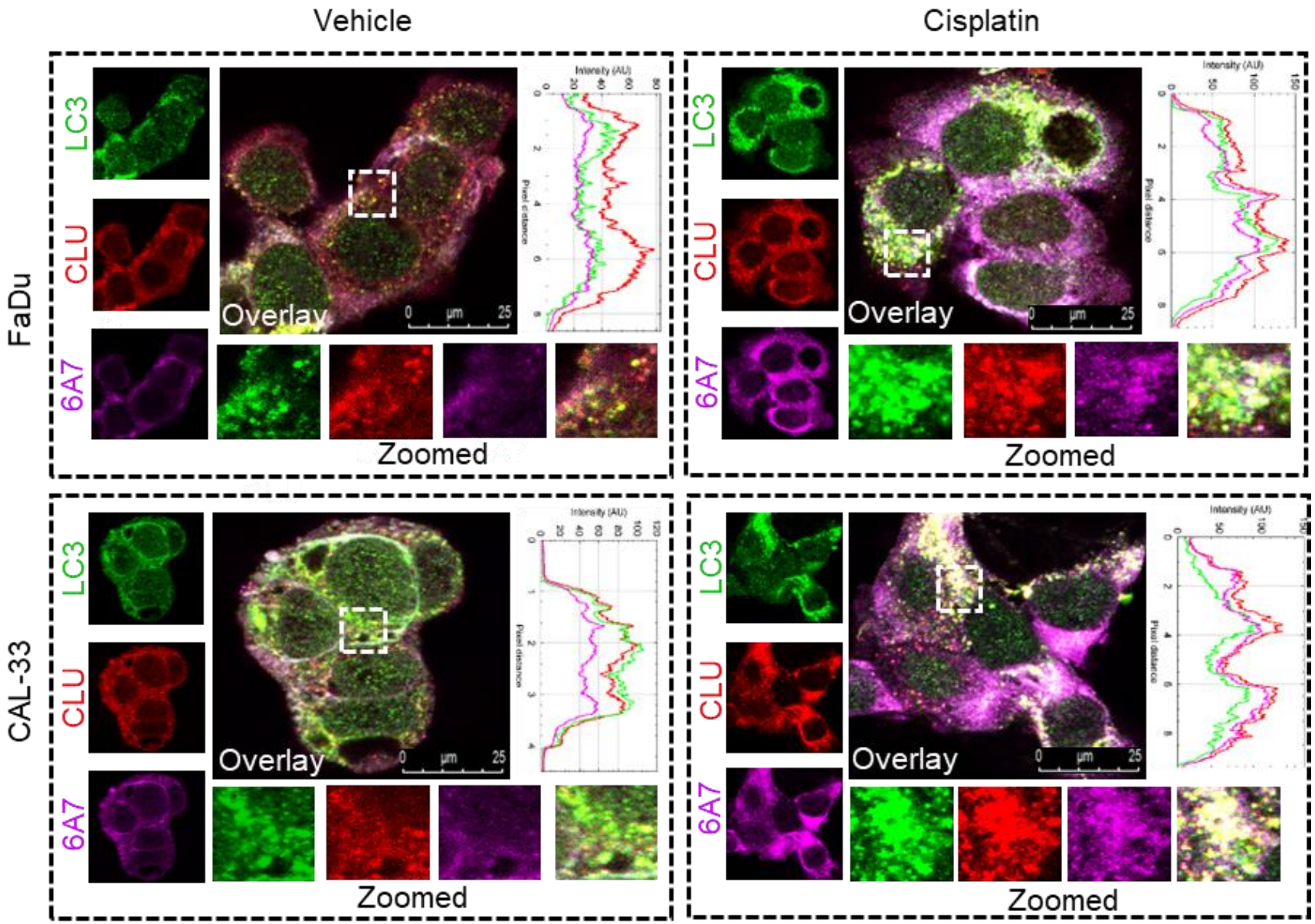




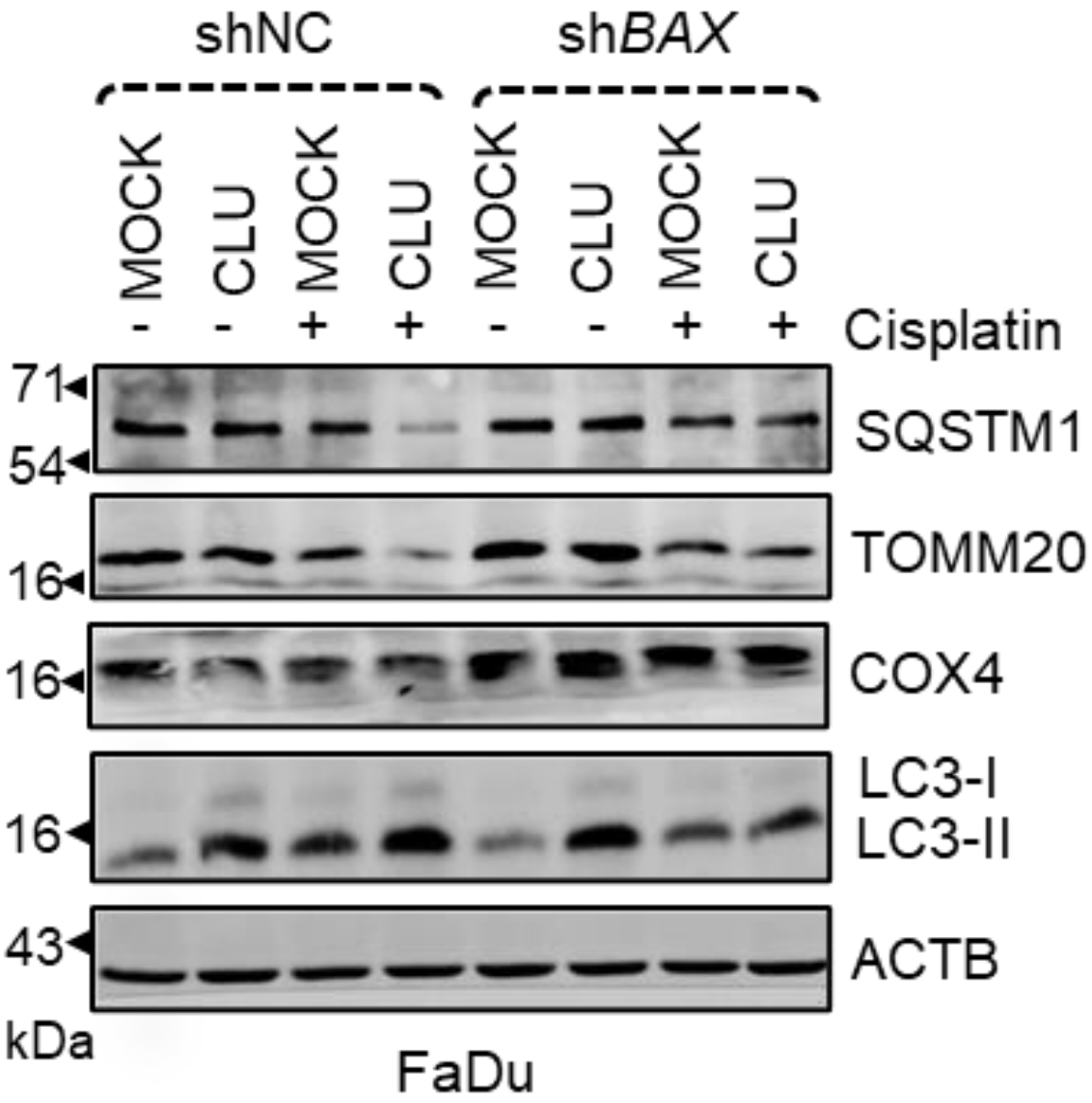
CLU deficiency attenuates cisplatin-induced mitophagy in oral cancer cells



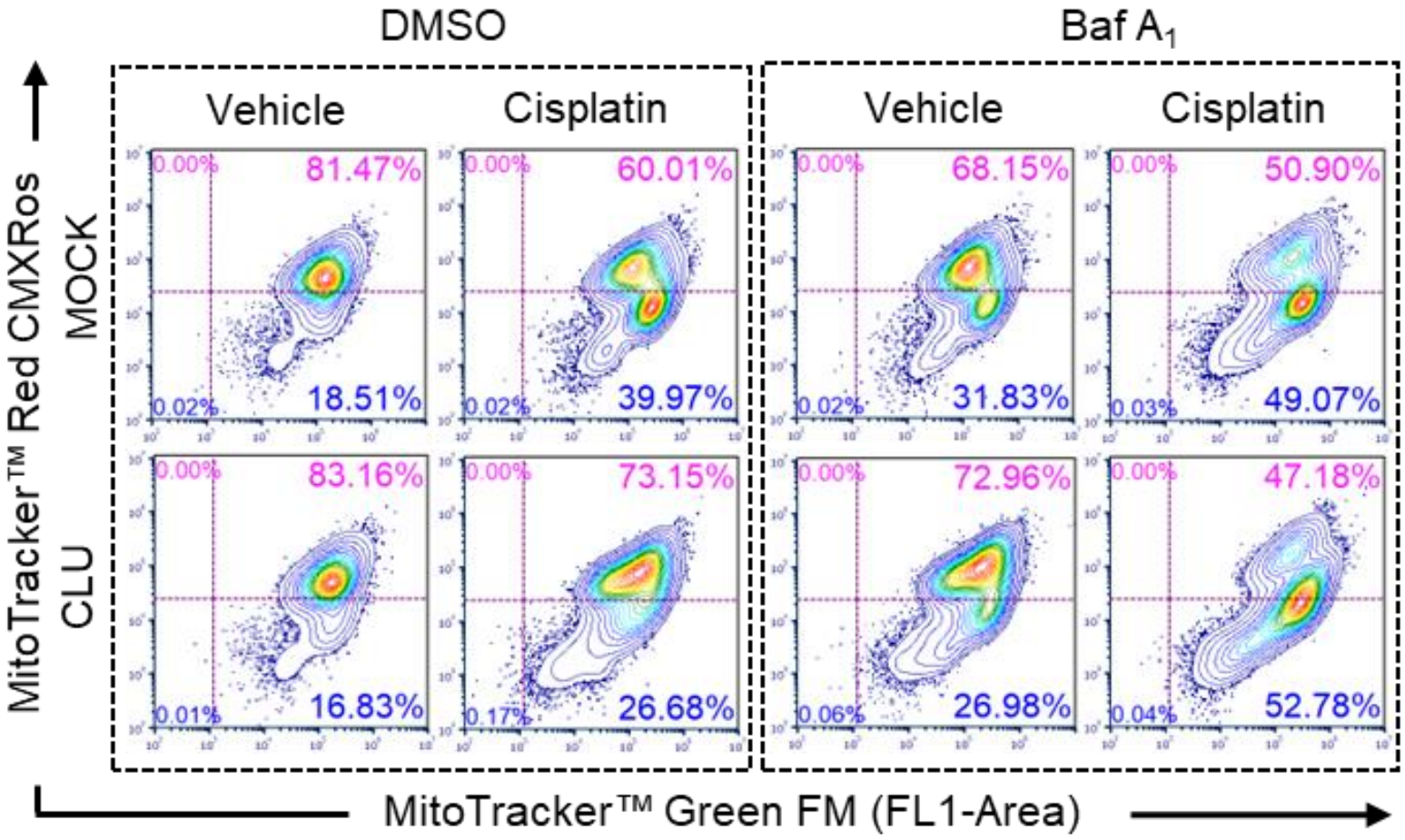
CLU interact with BAX (activated) and LC3 during cisplatin exposure in oral cancer cells

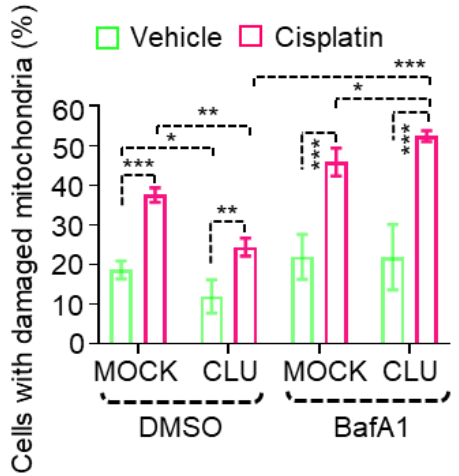


BAX is required for CLU-mediated clearance of damaged mitochondria in oral cancer cells

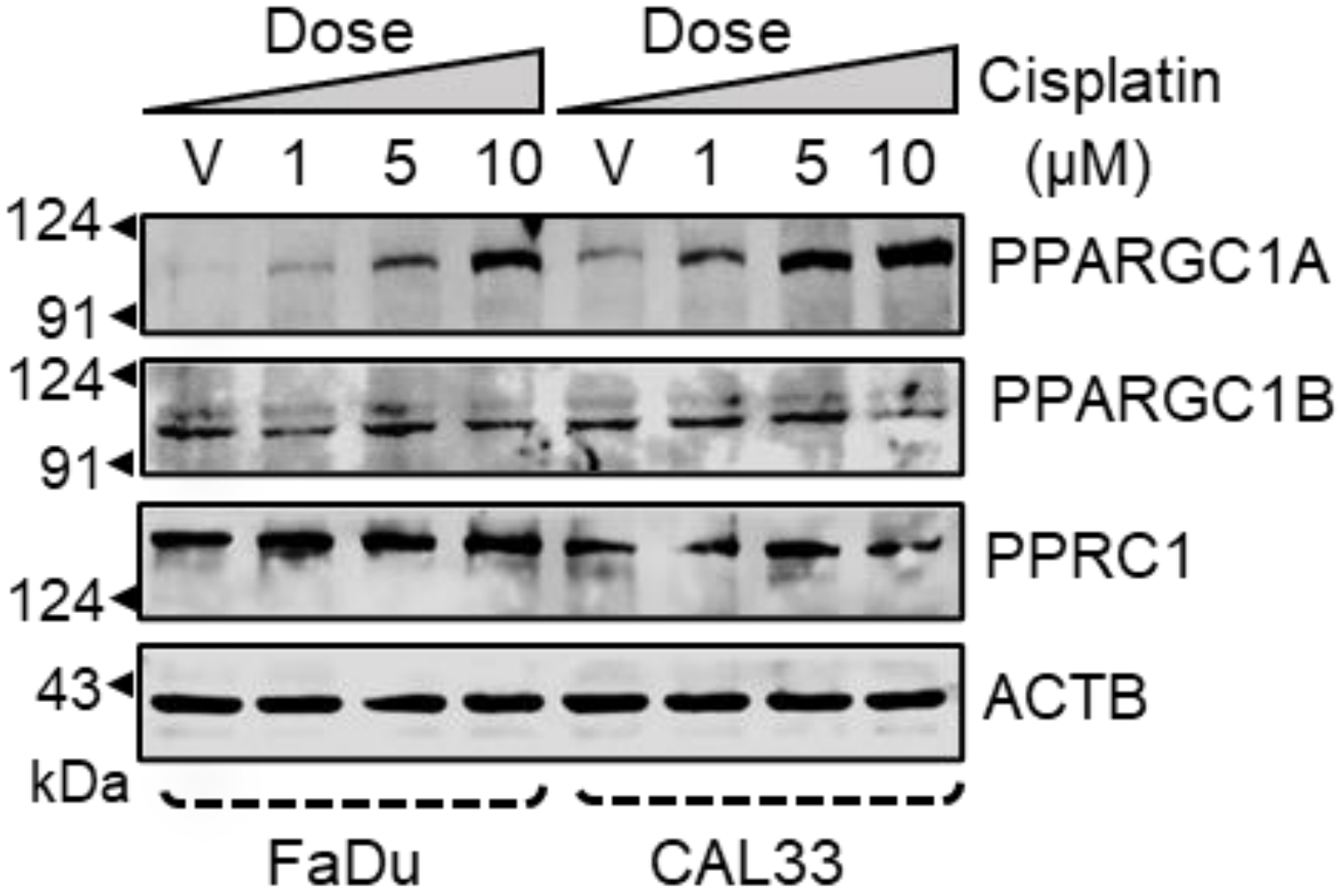


Inhibition of mitophagic flux promotes CLU-mediated mitophagosome accumulation

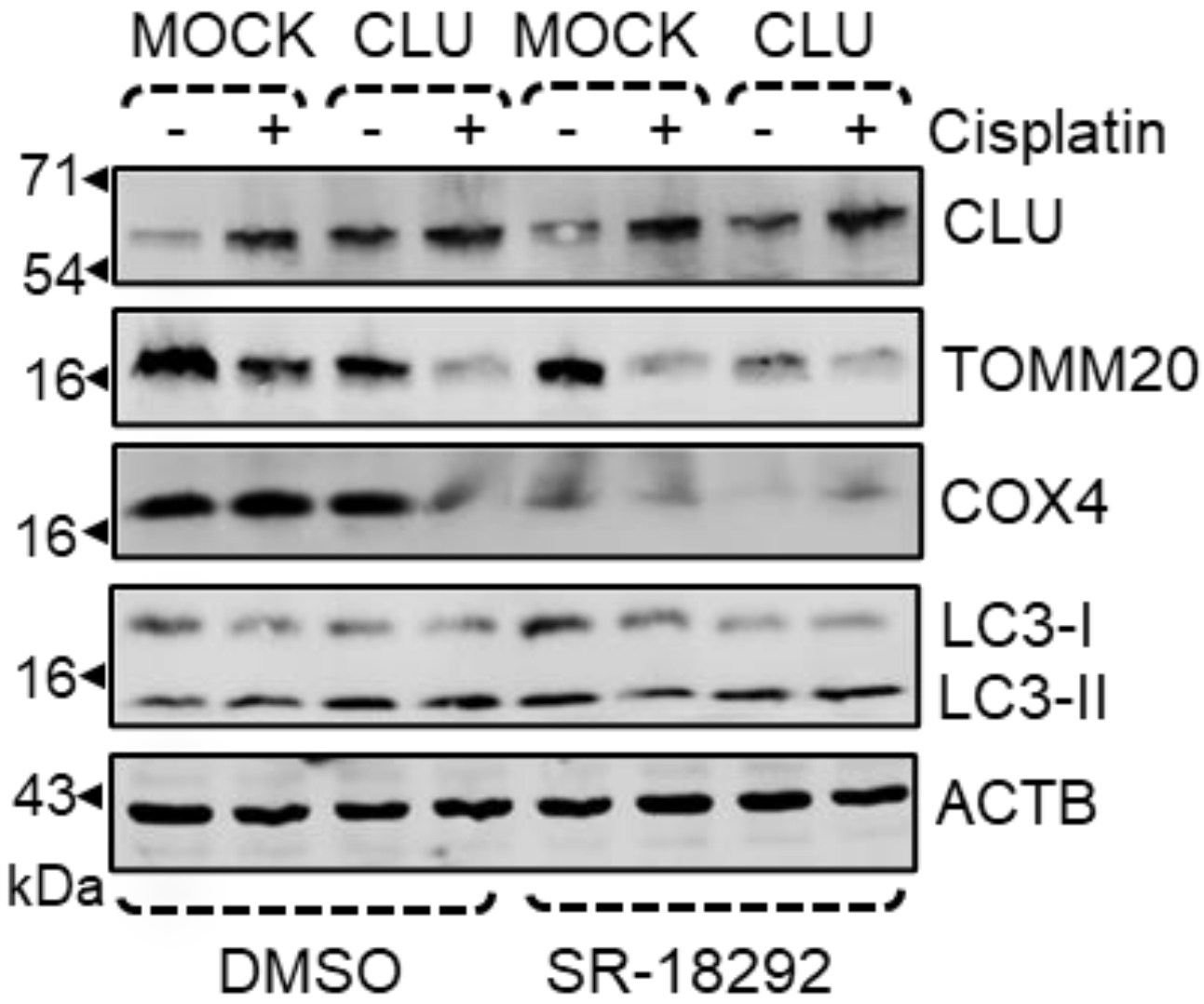




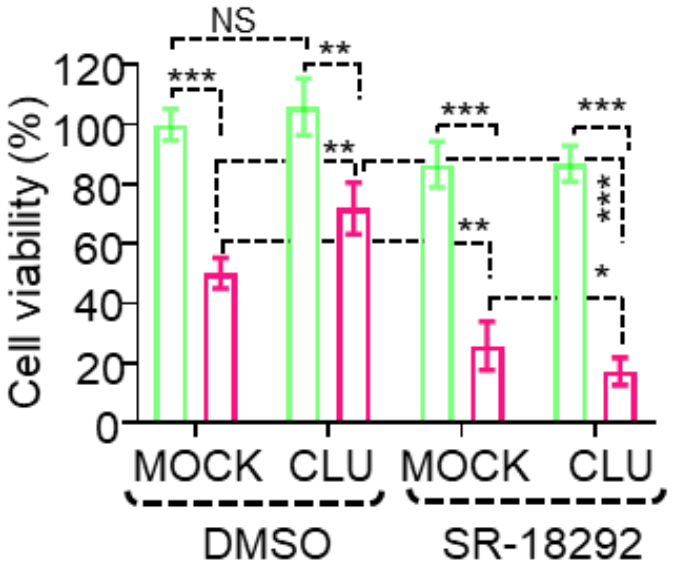
PPARGC1A maintains mitochondrial biogenesis during CLU-mediated mitophagy

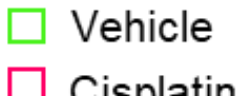


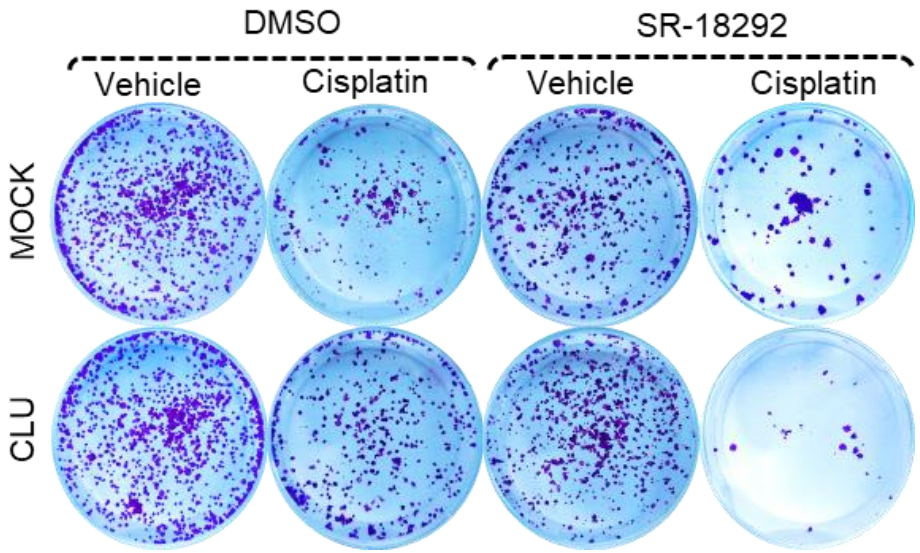
PPARGC1A inhibition promotes excessive loss of mitochondrial mass in CLU overexpressing oral cancer cells

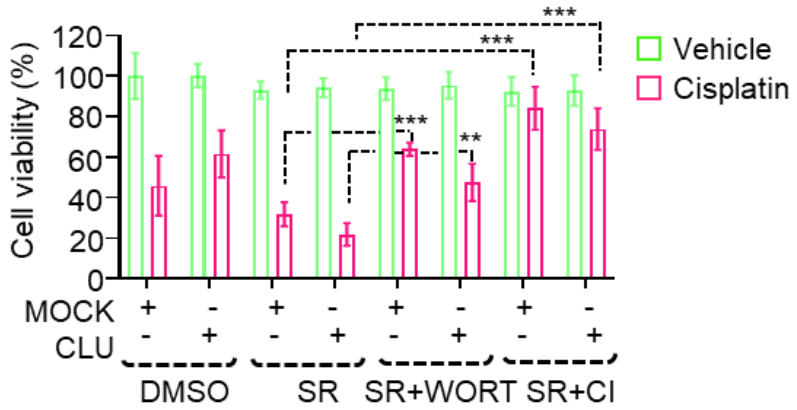


PPARGC1A inhibition triggers mitophagy-associated cell death in CLU-overexpressing cells



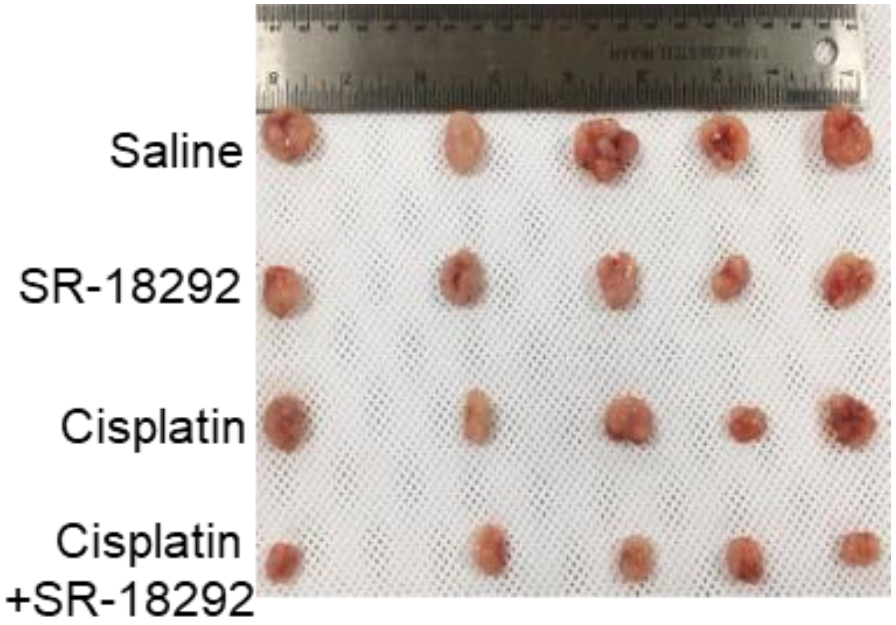






PPARGC1A inhibitor and cisplatin synergistically inhibit tumor growth in a mouse xenograft model

A



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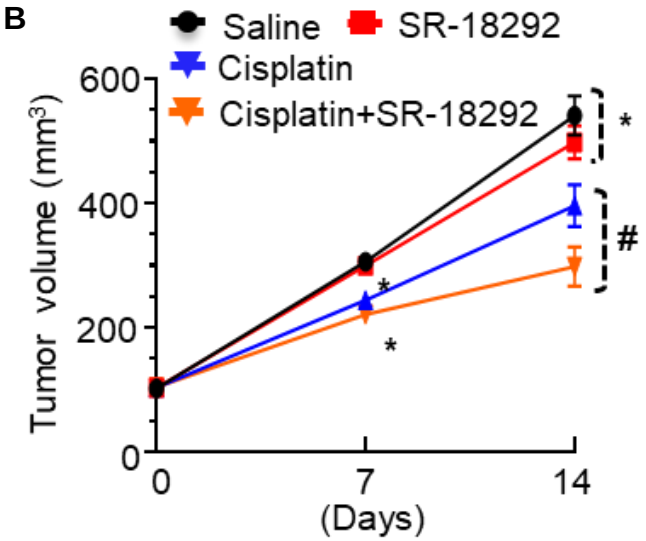

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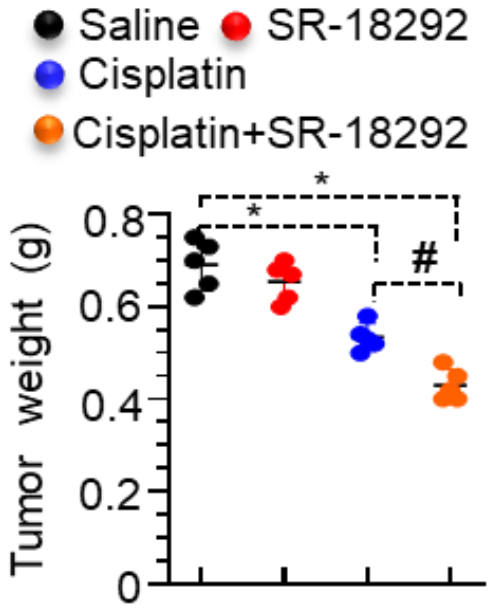
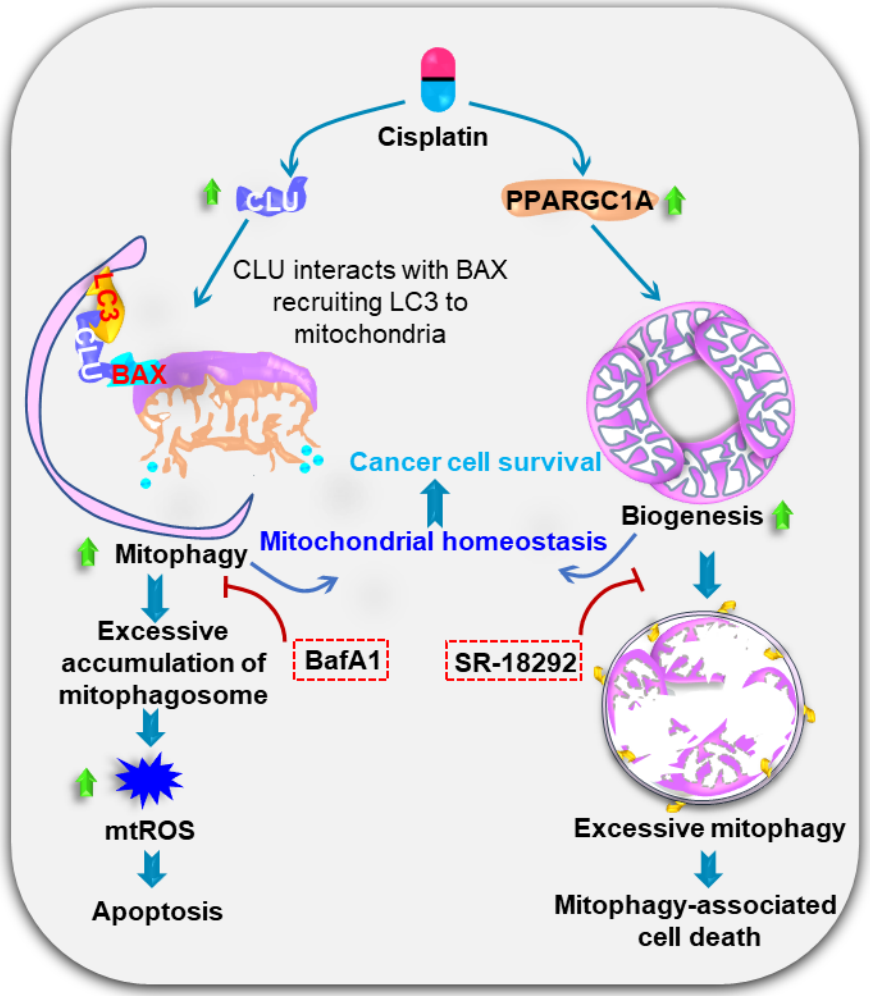


Conclusion



1. CLU forms a complex structure (BAX-CLU-LC3) to regulate cisplatin-induced mitophagy.

2. PPARGC1A activates mitochondrial biogenesis to maintain mitochondrial content during CLU-mediated mitophagy.

3. PPARGC1A inhibitor (SR-18292) synergistically improved cisplatin cytotoxicity, inhibiting tumor growth of OSCC *in vitro* and *in vivo*.

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