

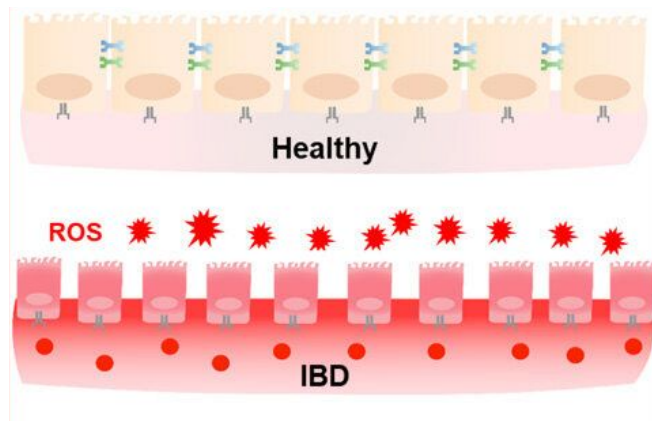
Orally cascade targeting delivery systems alleviate colitis by protecting mitochondria and regulating gut microbiota

Liyun Xing

West China School of Pharmacy
Sichuan University

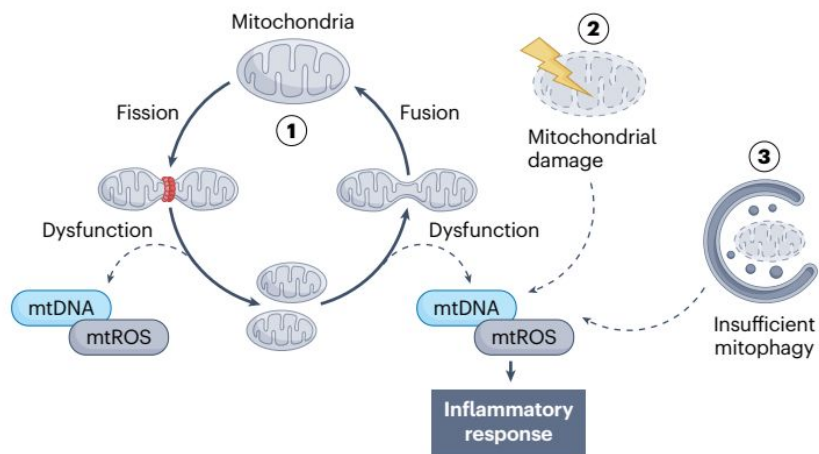


Inflammatory bowel disease (IBD)

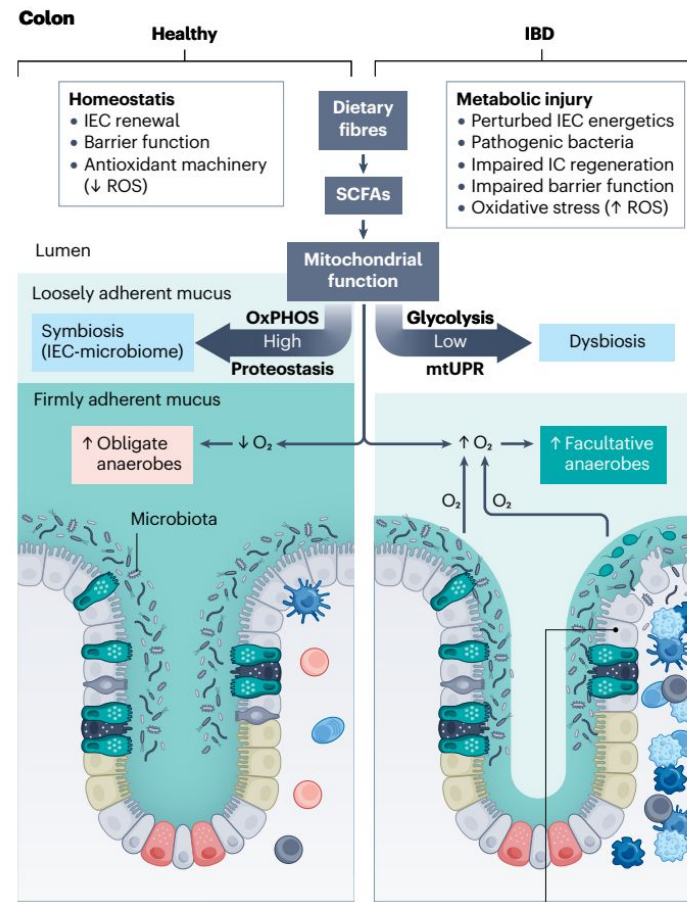


mitochondrial dysfunction drives inflammatory responses

Perturbed mitochondrial function



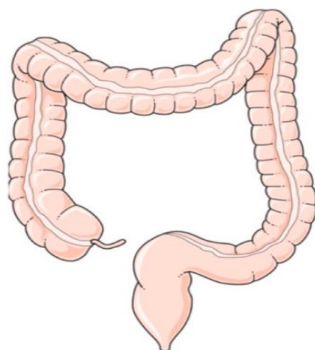
Mitochondrial dysfunction occurs in IBD



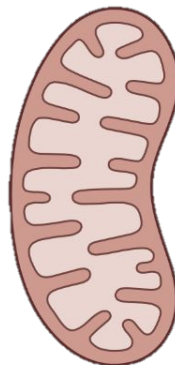
Haque, P.S., Kapur, N., Barrett, T.A. et al. Nat Rev Gastroenterol Hepatol, 2024.

- ROS
- Oxidative phosphorylation
- NLRP3 activation
- MAM
- mtUPR
- Barrier function
- Mitochondrial dynamics
- Mitophagy
- Mitochondrial biogenesis
- Mucosal repair

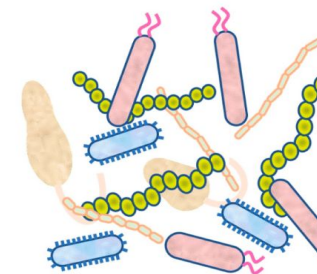
Colon mucosa



Mitochondria



Gut microbiota



- ROS
- Processing of internalized bacteria
- Butyrate and other SCFA metabolism
- Barrier function

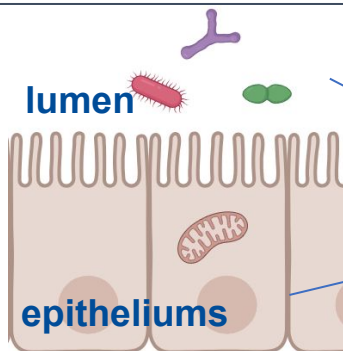
López-Gómez, C, et al. Int. J. Mol. Sci. 2023



Protect mitochondria + Regulate gut microbiota



Relieve IBD

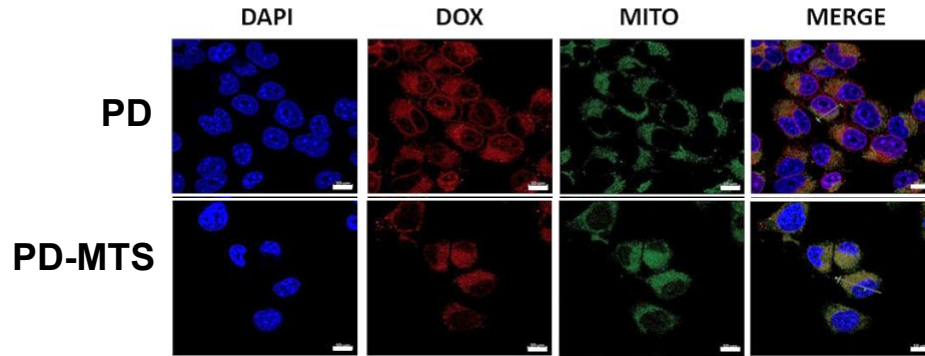


**Disparities in spatial distribution
of mitochondria and microbiota**



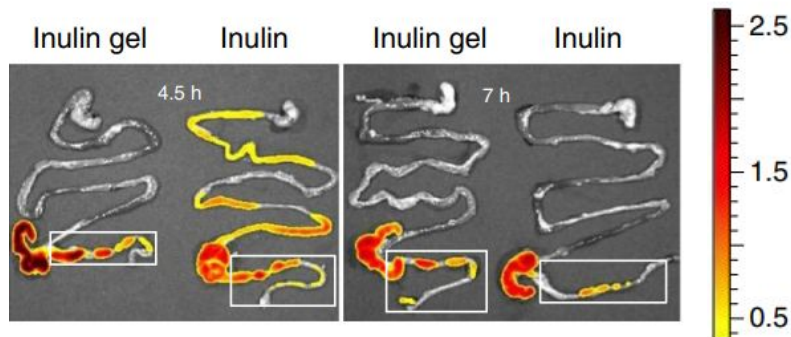
Drug delivery?

Mitochondria-Targeting Sequences (MTS)



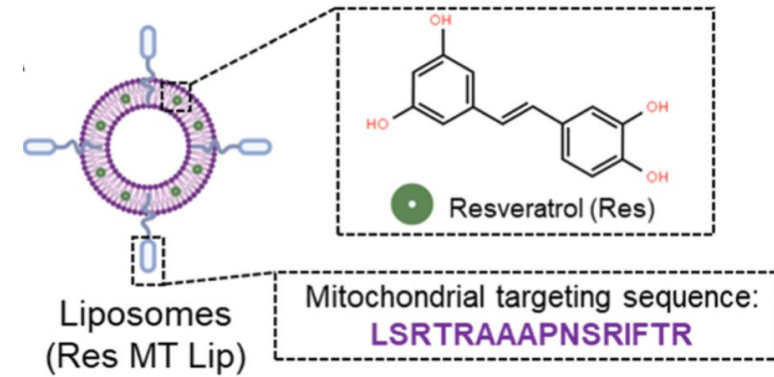
Qiuyi Li, Yuan Huang, et al. *J Control Release.*, 2020.

Polysaccharide gel prolongs colonic retention

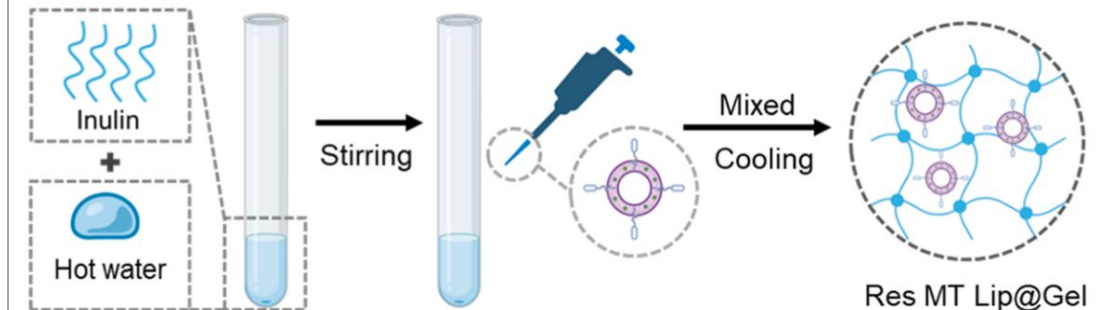


Han, K., Nam, J., Xu, J. et al. *Nat Biomed Eng.*, 2021.

MTS modified liposomes



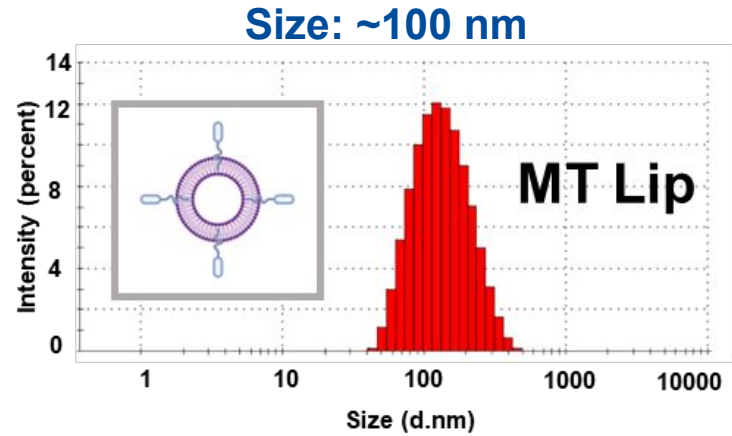
Probiotic inulin gel encapsulated liposomes



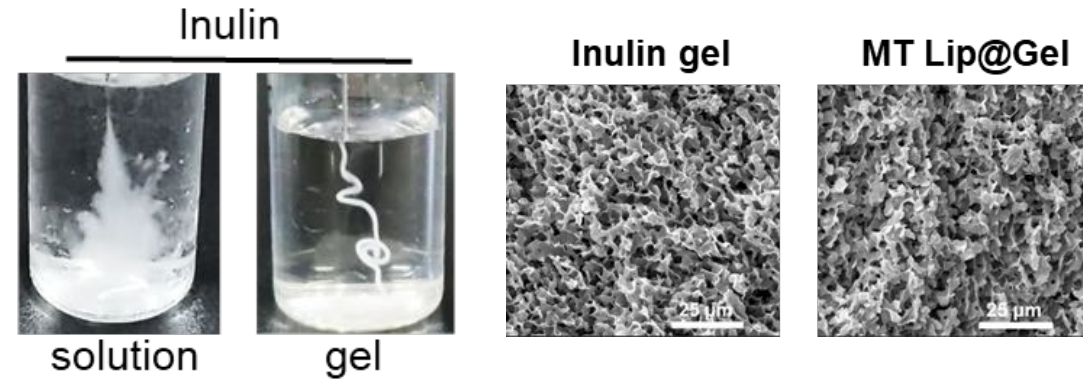
Characterization of orally delivery system



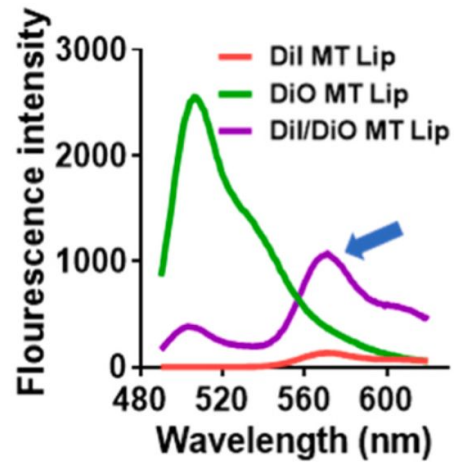
四川大学
SICHUAN UNIVERSITY



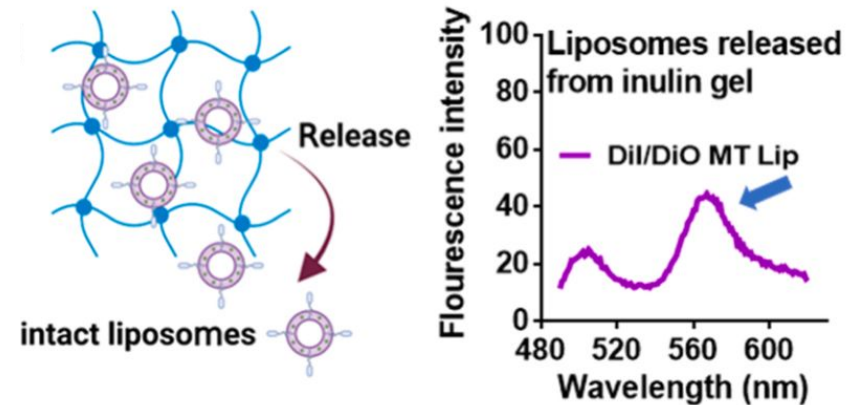
microstructure of inulin gel



FRET assay for fresh prepared liposomes

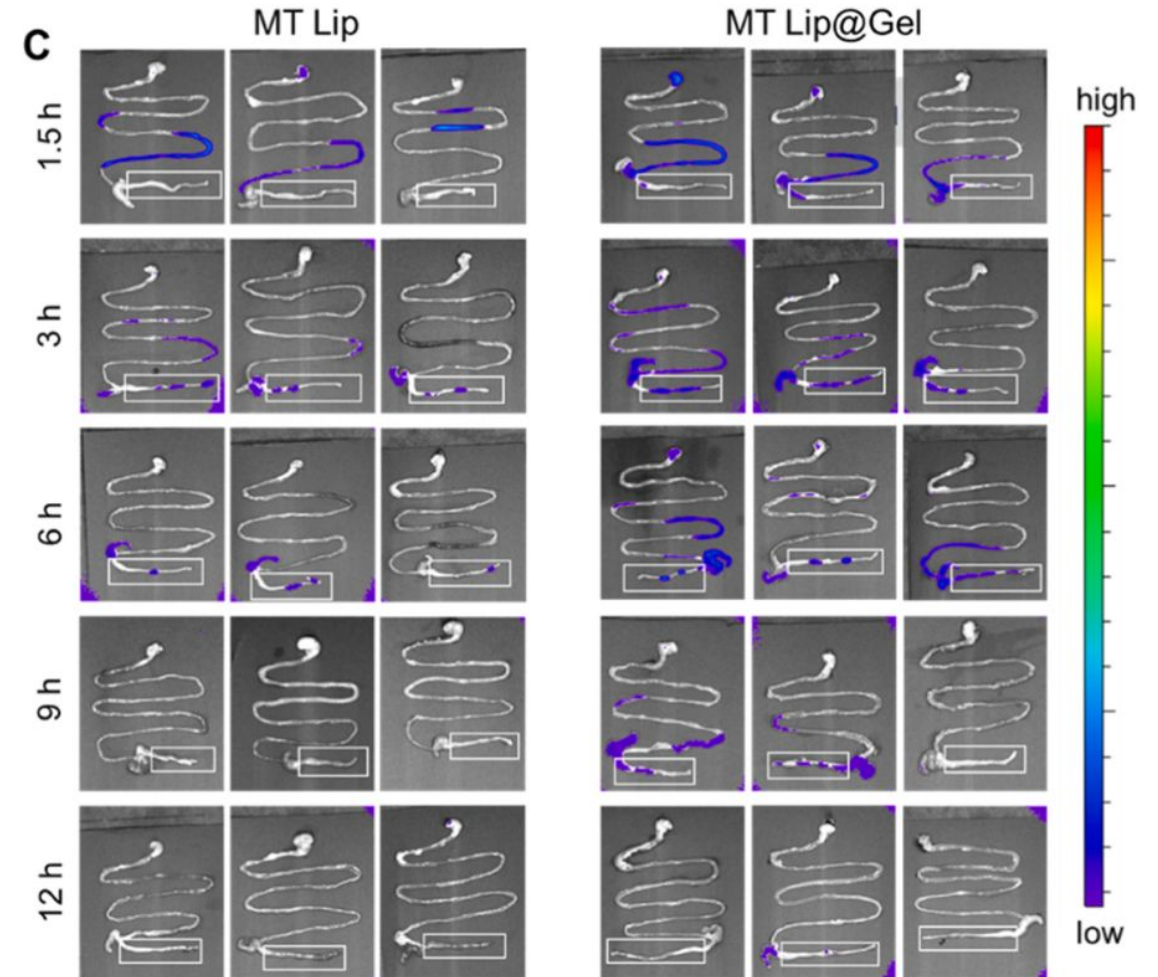
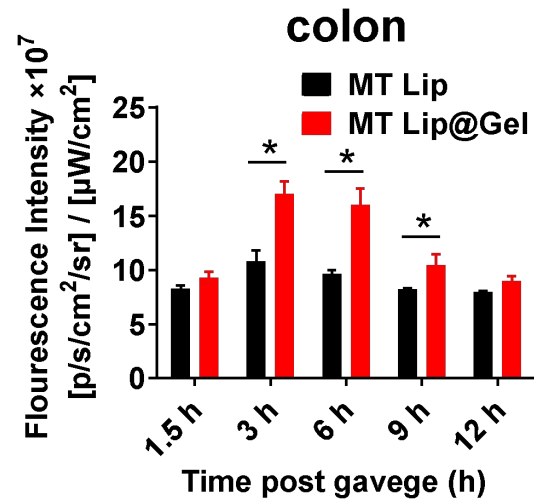
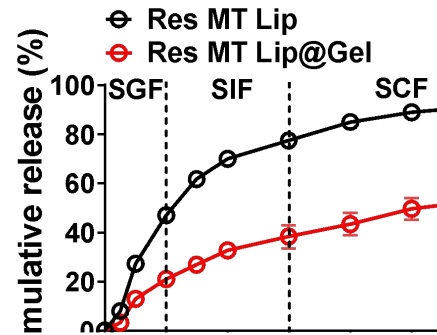
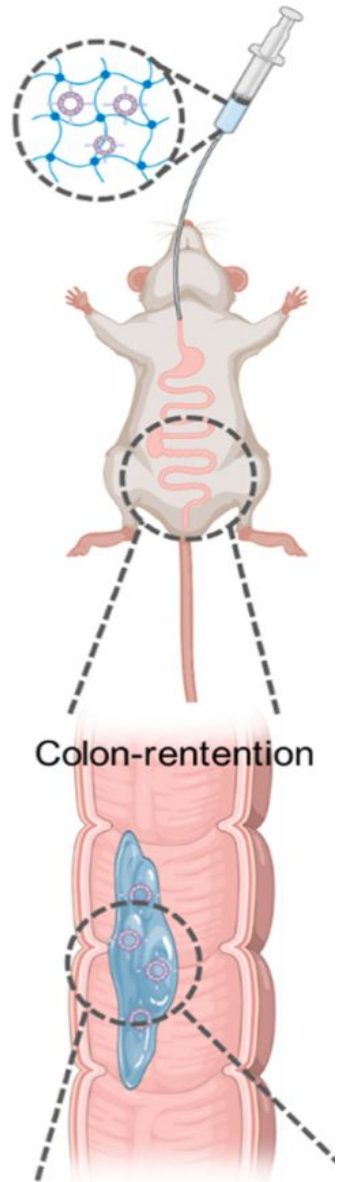


The intact liposomes released from inulin gel



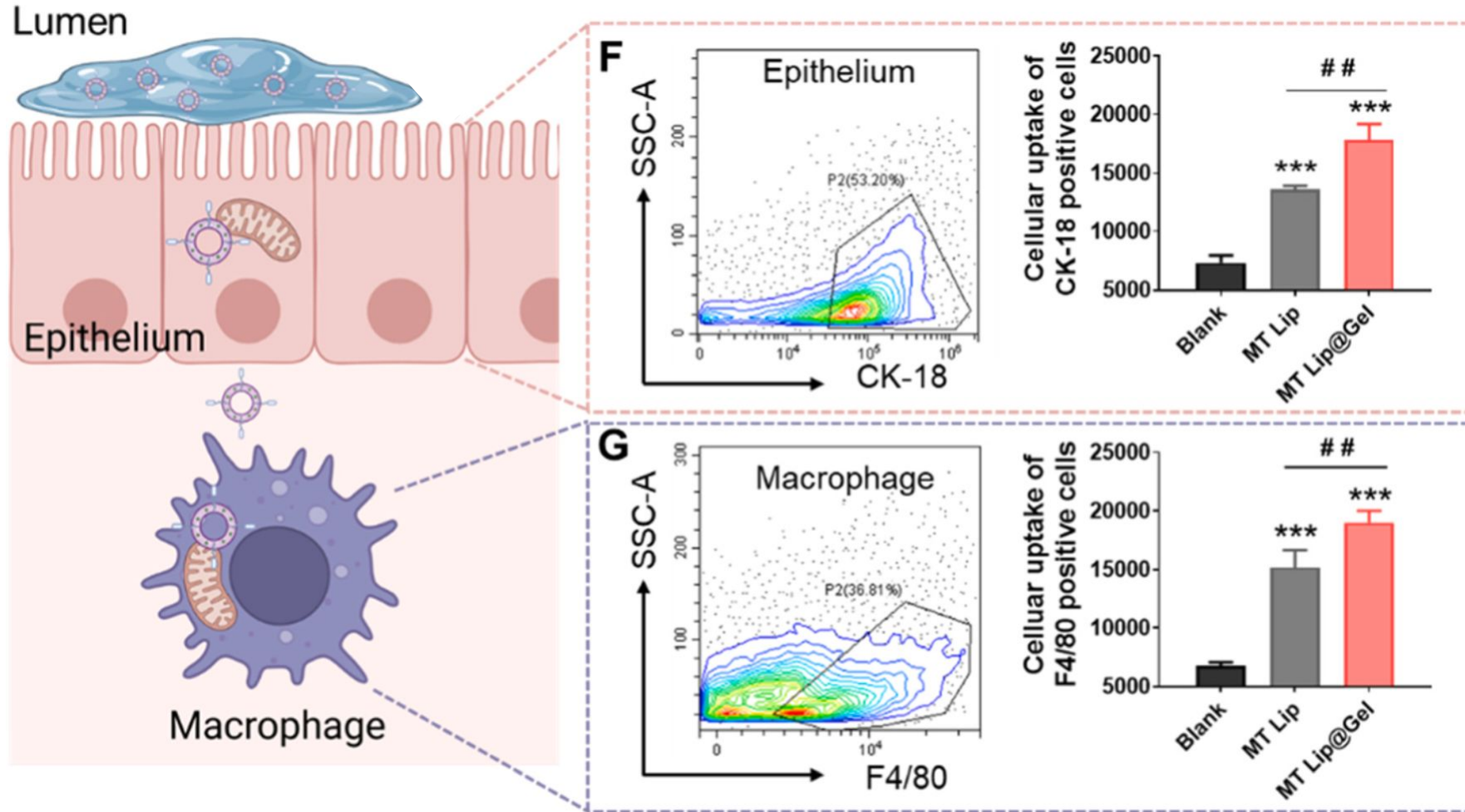
Orally cascade targeting: **colon**-cell-mitochondria

Inulin gel decrease drug leakage in stomach and small intestine



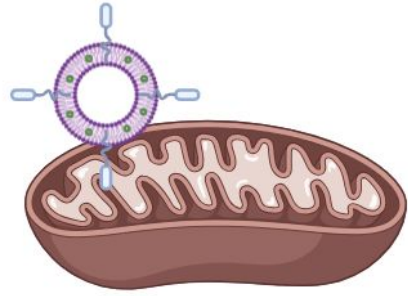
Inulin gel prolongs colonic retention

Orally cascade targeting: colon- cell -mitochondria

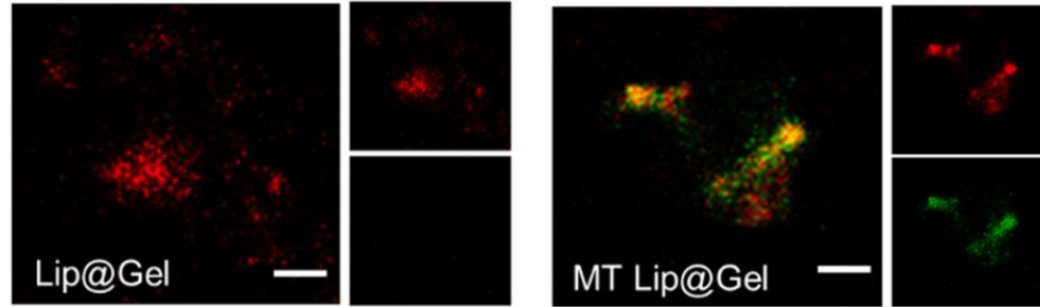


- liposomes were delivered to colonic macrophages and epitheliums
- increasing colonic retention via inulin gel could enhance the cellular uptake

Orally cascade targeting: colon-cell- mitochondria

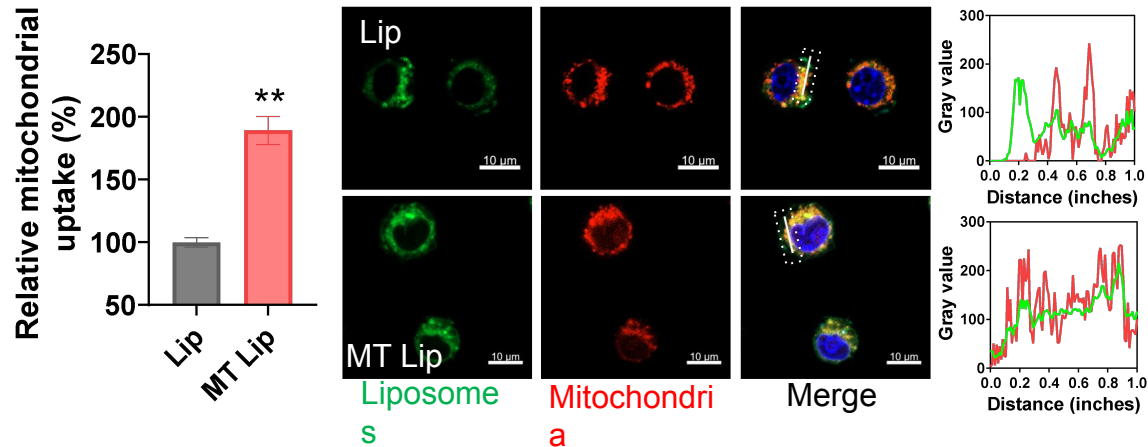


Red: Mitochondria isolated from colon tissue
Green: Preparations



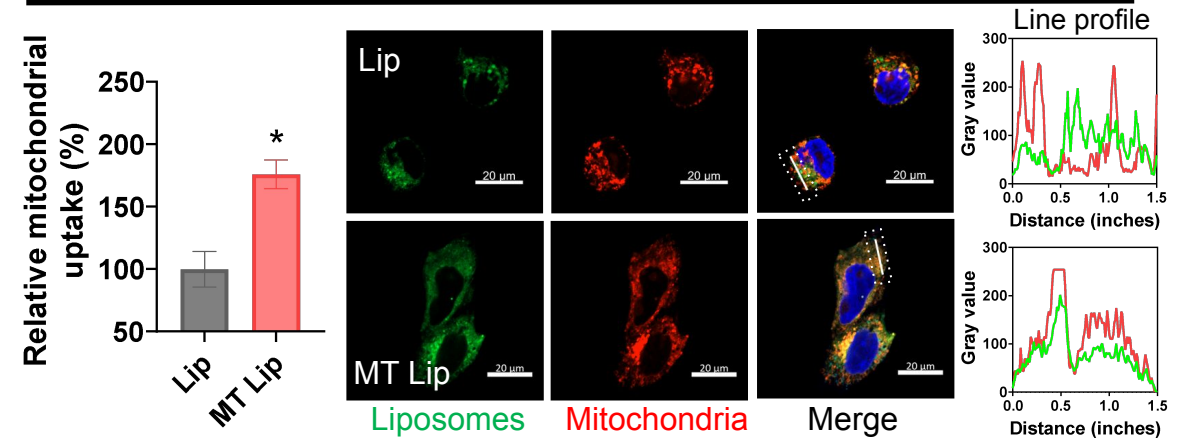
Liposomes accumulated in
colonic mitochondria

RAW264.7



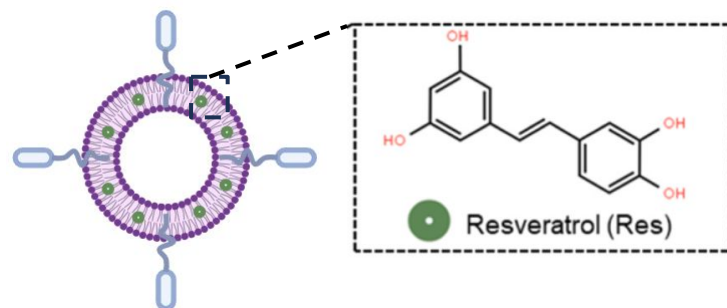
Liposomes targeted to mitochondria in macrophages

Caco-2

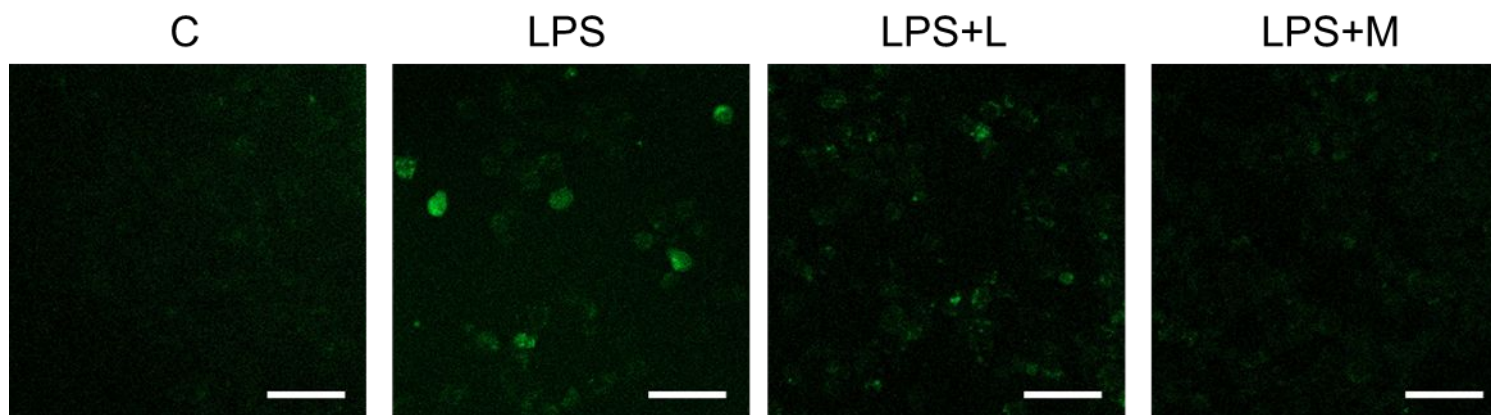
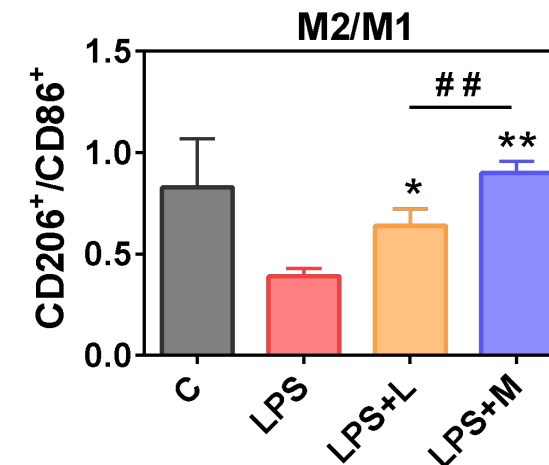
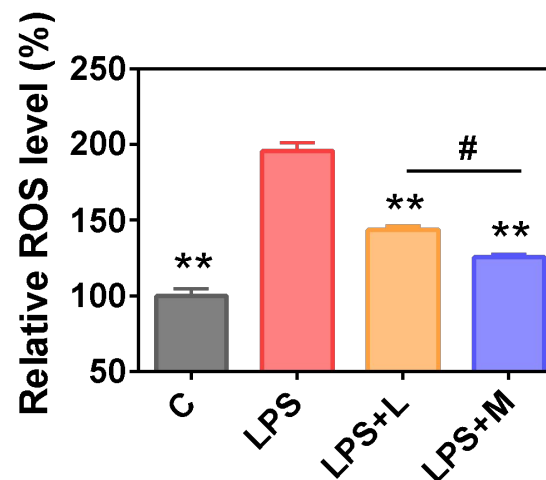


Liposomes targeted to mitochondria in epitheliums

Res MT Lip facilitated ROS-scavenging in macrophages



Resveratrol loaded mitochondrial targeting liposomes (Res MT Lip)



□ Mitochondrial-targeted Res MT Lip facilitated ROS-scavenging

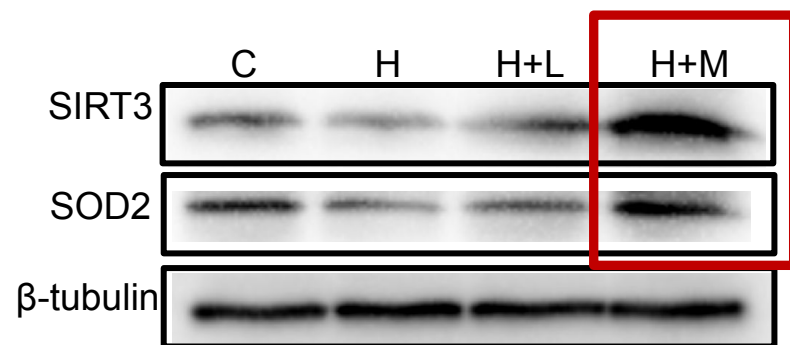
■ C: control ■ LPS ■ LPS+L: LPS+Res Lip ■ LPS+M: LPS+Res MT Lip



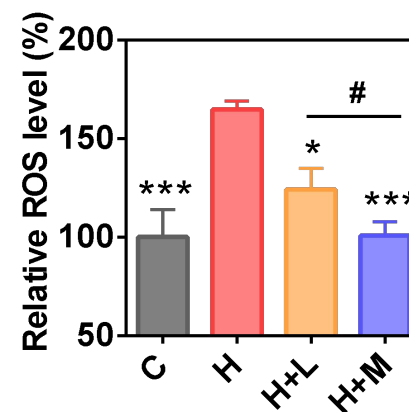
Res MT Lip facilitated wound healing in epitheliums



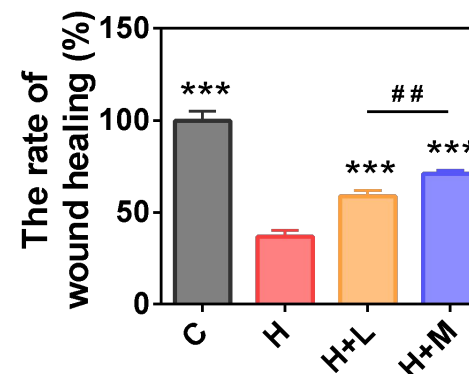
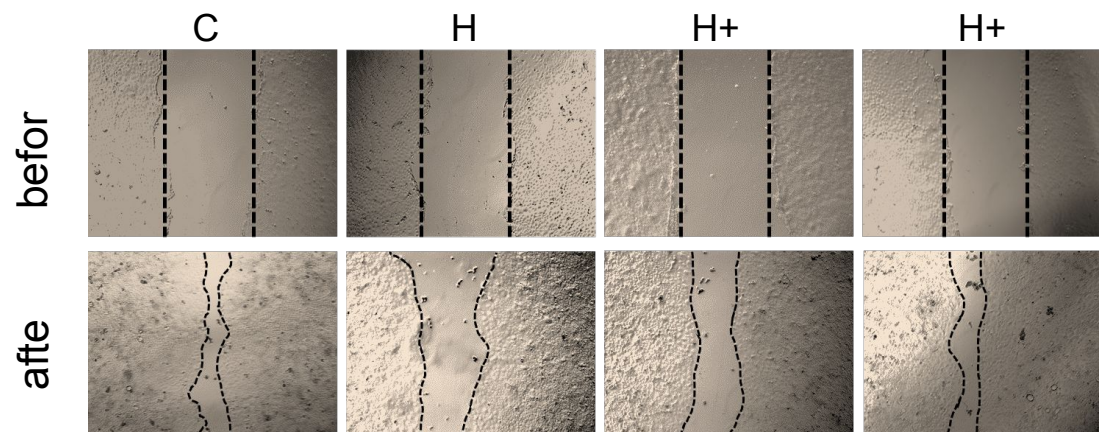
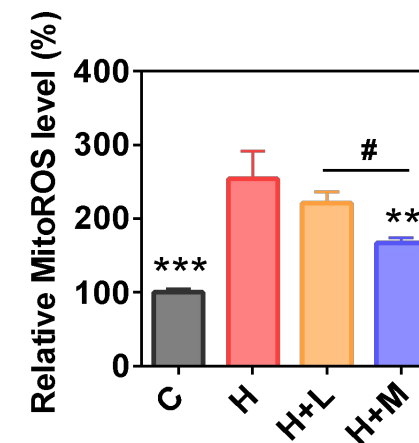
Activate SIRT3 for mitochondrial protection



ROS scavenging



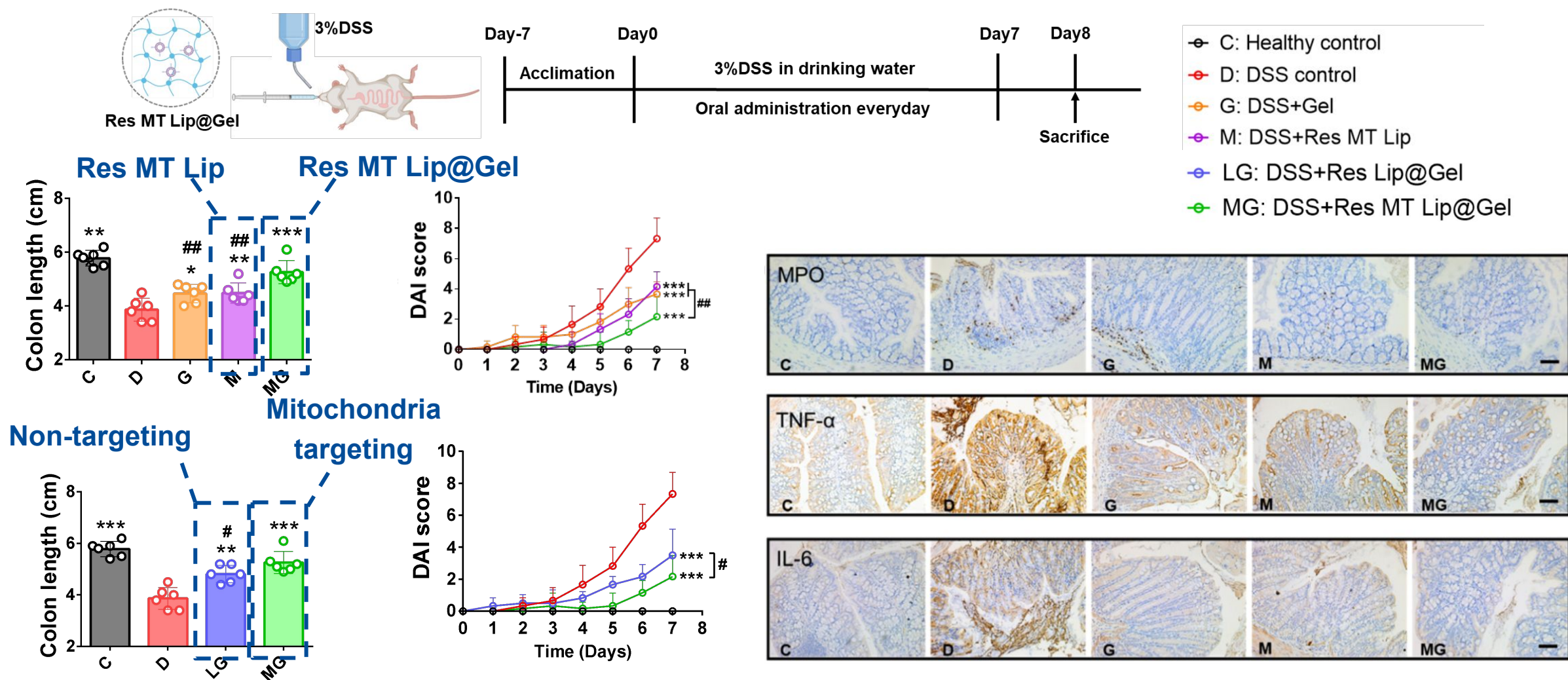
Decrease mitochondrial ROS



Protect epitheliums under oxidative damage

■ C: control ■ H: H₂O₂ ■ H+L: H₂O₂+Res Lip ■ H+M: H₂O₂+Res MT Lip

Res MT Lip@Gel relieved DSS-induced acute colitis



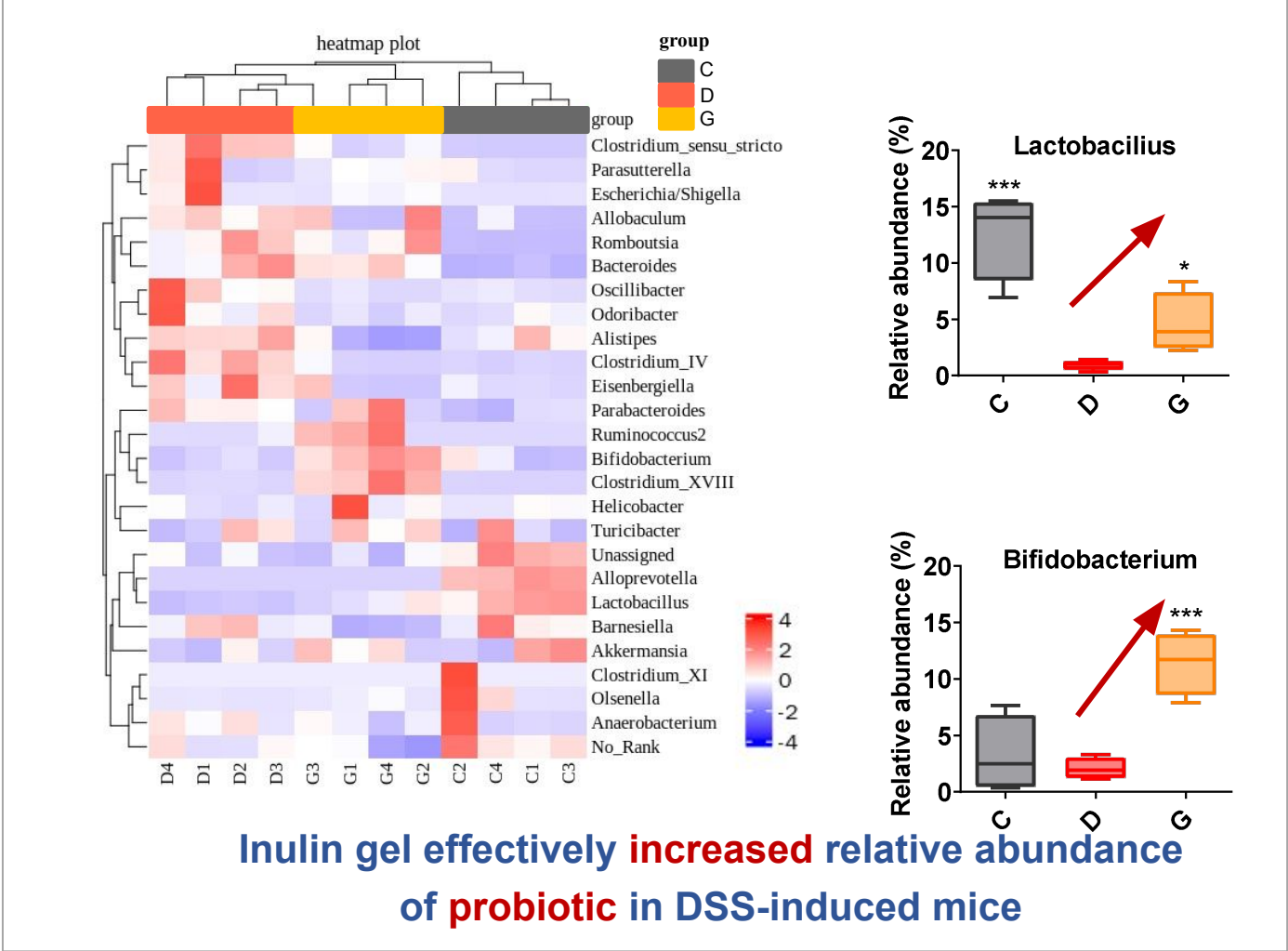
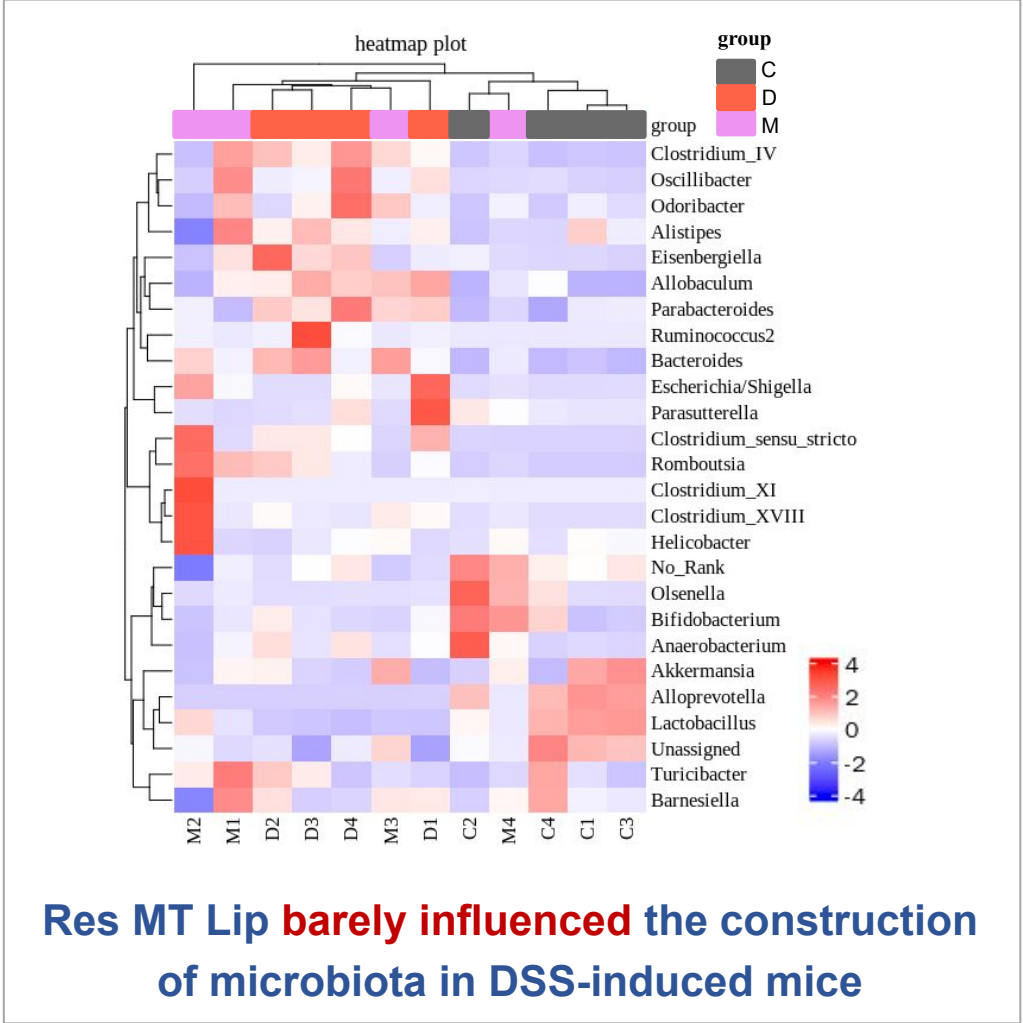
Inulin gel modulated gut microbiota

C: Healthy control

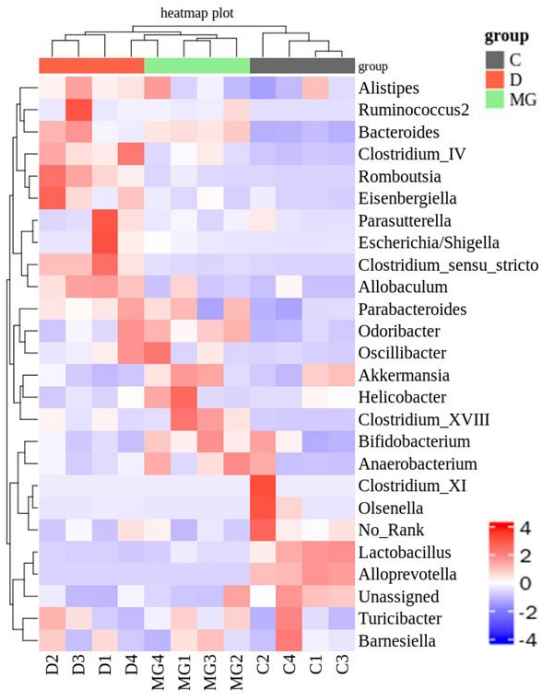
D: DSS control

M: DSS+Res MT Lip

G: DSS+Gel



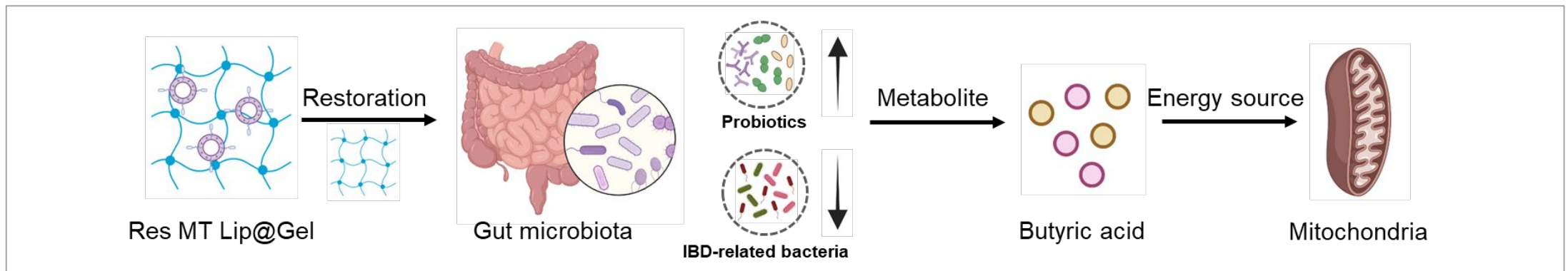
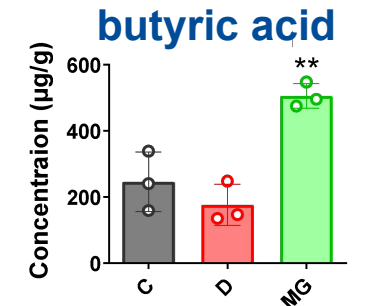
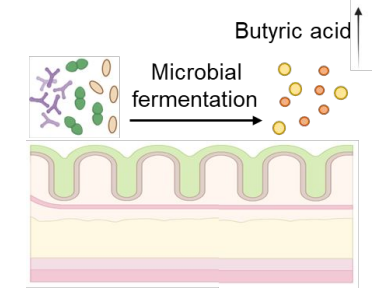
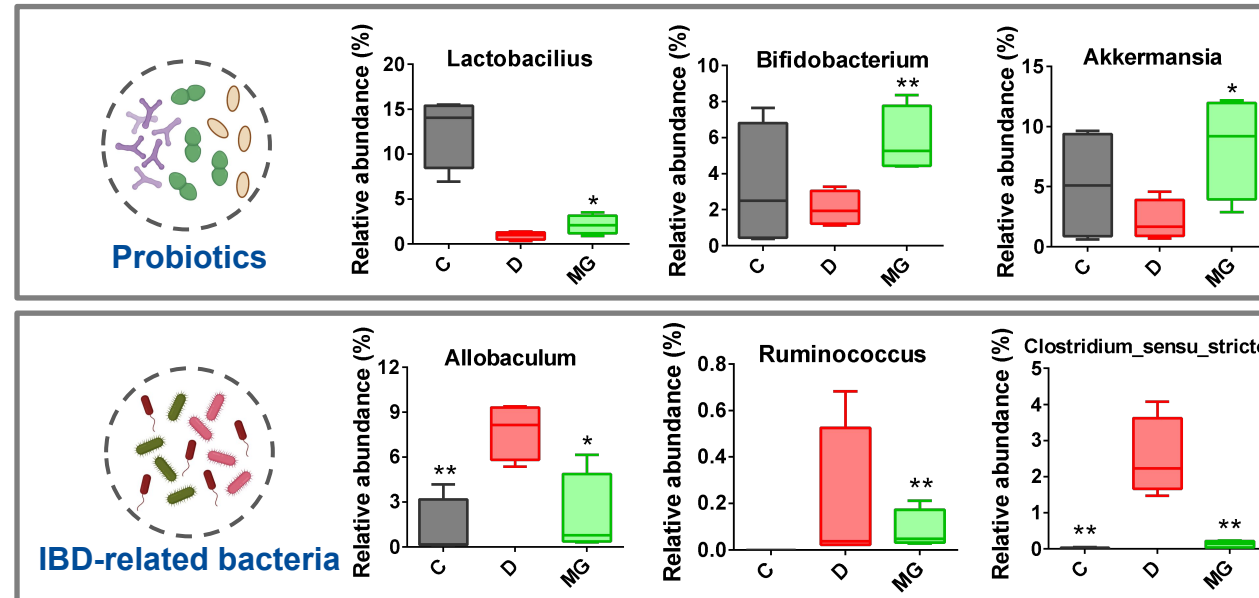
Res MT Lip@Gel inherited the microbiota-regulation of



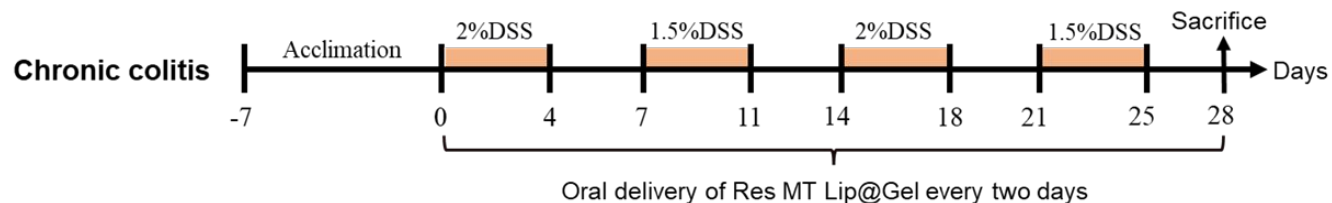
C: Healthy control

D: DSS control

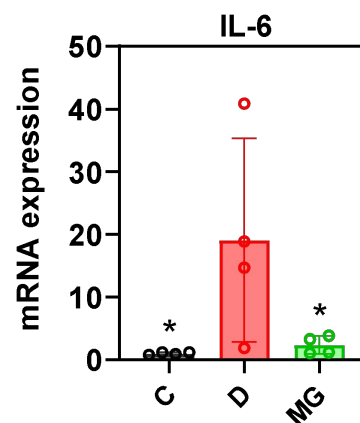
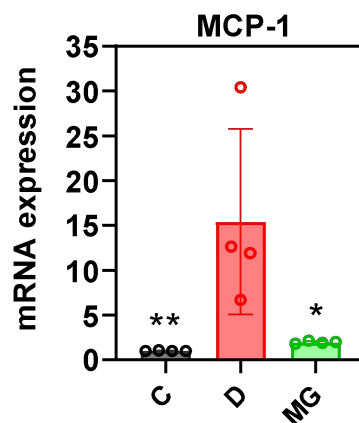
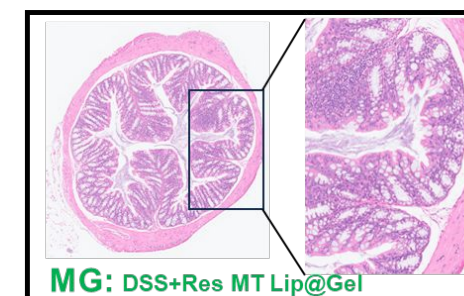
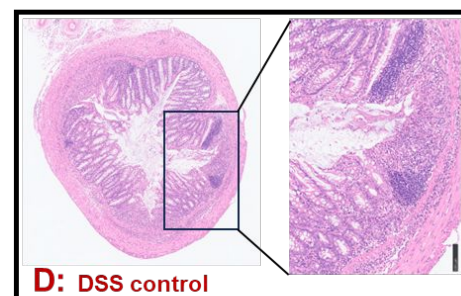
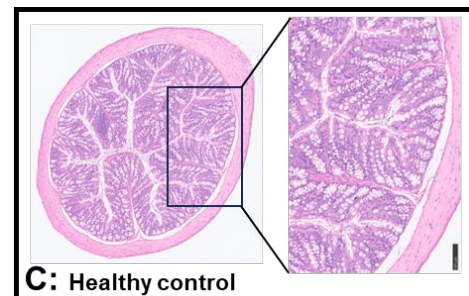
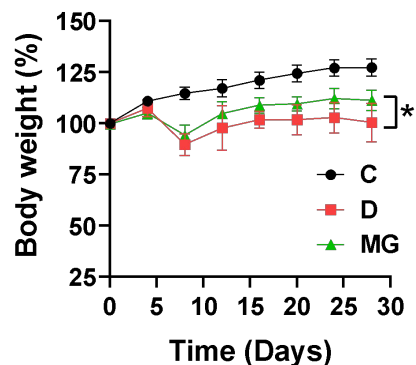
MG:DSS+Res MT Lip@Gel



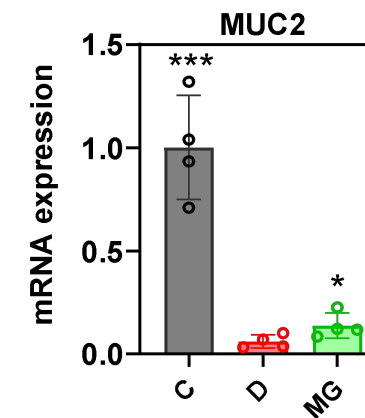
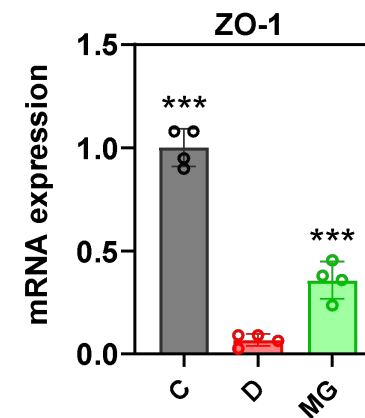
Res MT Lip@Gel relieved DSS-induced chronic colitis



C: Healthy control
D: DSS control
MG: DSS+Res MT Lip@Gel



Anti-inflammatory

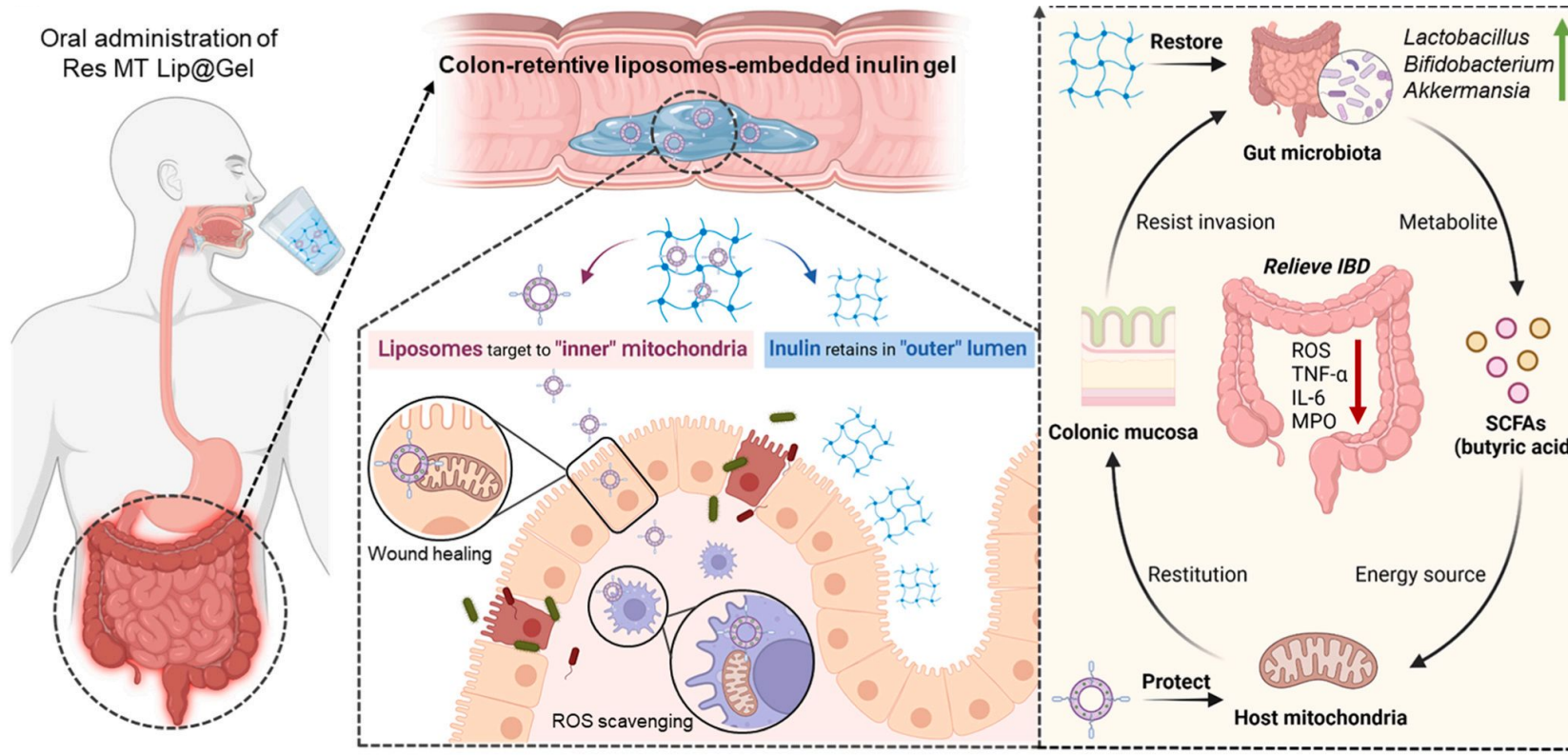


facilitated mucosal repairing

Orally cascade targeting delivery system



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- ◆ Targeted delivery to colonic mitochondria
- ◆ Protect mitochondria and regulate gut microbiota
- ◆ Alleviating acute and chronic colitis

Acknowledgement 613 Huang's Lab



Prof. Yuan Huang

Mucosal delivery systems

- Oral drug delivery
- Inhaled drug delivery
- Mucosal delivery of protein and peptide drugs

Subcellular-targeted delivery systems

- Mitochondrial targeted delivery
- Endoplasmic reticulum targeted delivery
- Nuclear targeted delivery



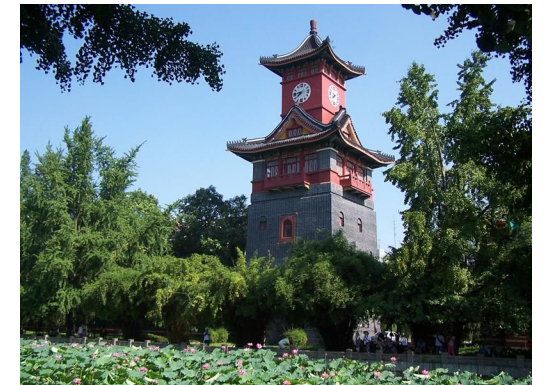
A.P. Zhou Zhou



A.P. Lian Li



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the Regional Innovation and Development Joint Fund of National Natural Science Foundation of China (U22A20356)

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Thanks for listening



INTEGRATING
Delivery Science
ACROSS DISCIPLINES

