Oral proton-reprogrammed nanomedicine to break the inflammatory bowel disease-*Clostridium difficile* infection vicious cycle

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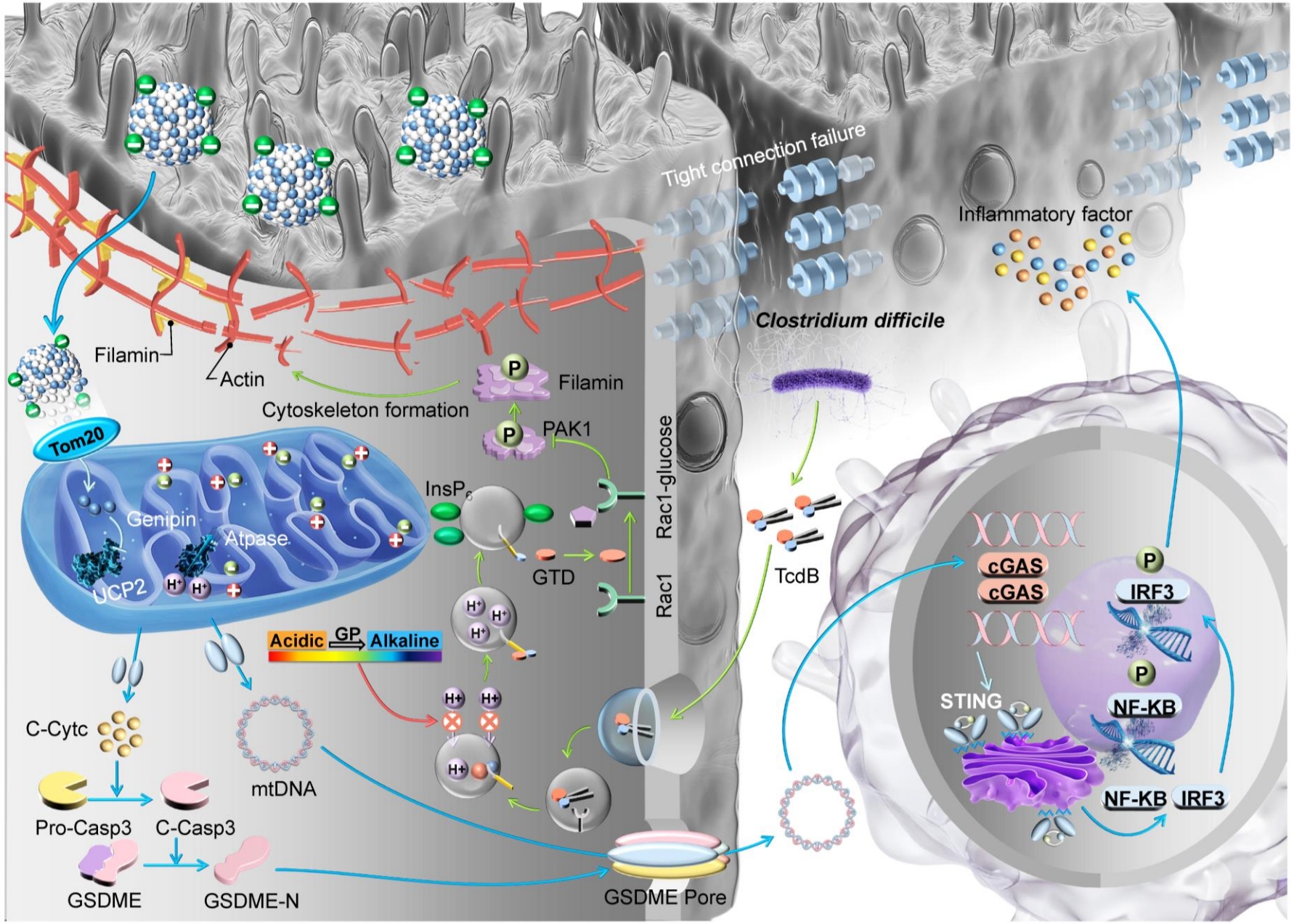
Introduction

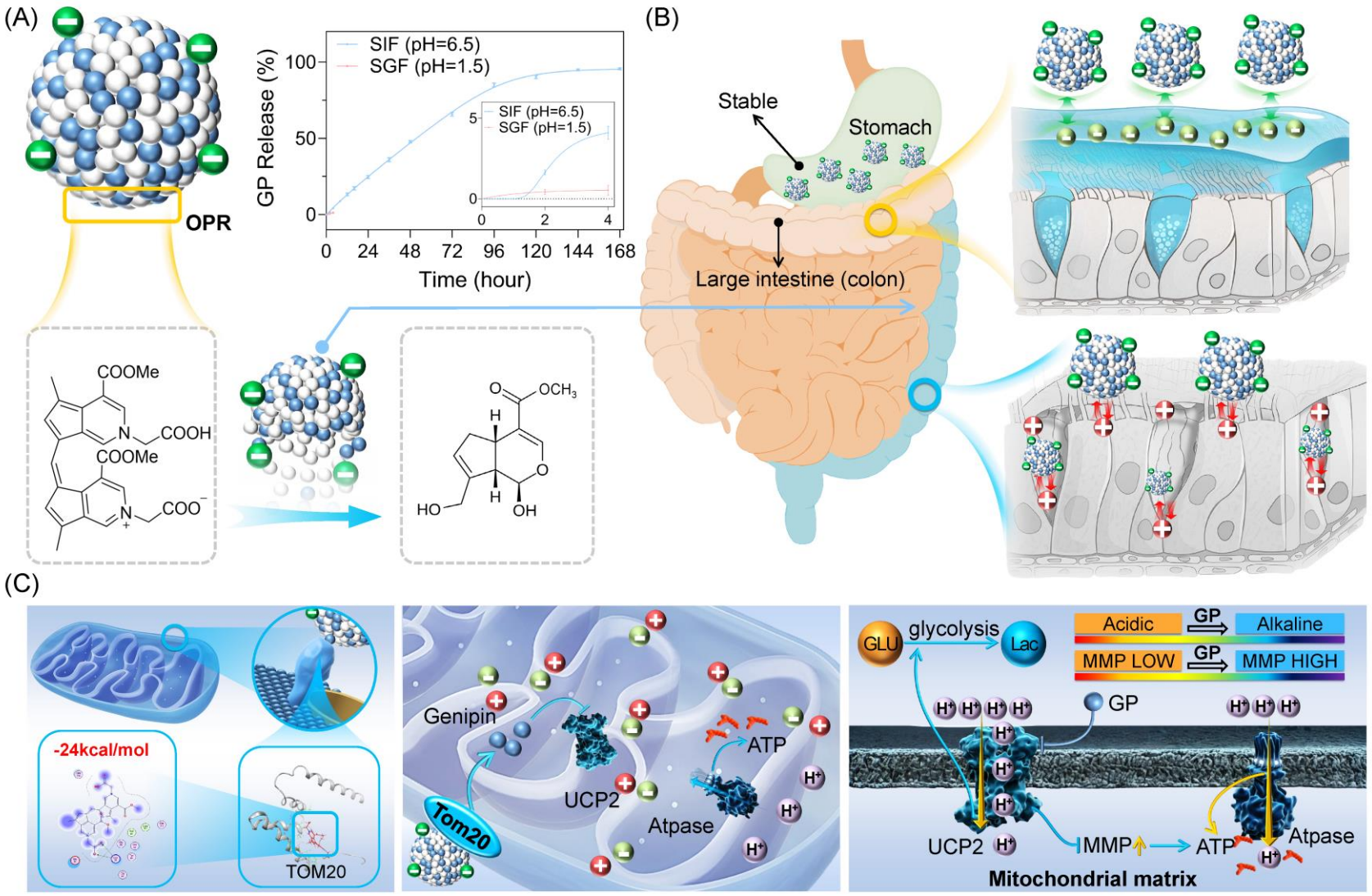


IBD

Cell pHi ⇅ TcdB

CDI

Highlights



- This study revealed that UCP2 is highly expressed in the intestinal epithelial cells of IBD patients, leading to mitochondrial dysfunction and metabolic reprogramming toward glycolysis.
- We developed an orally administered proton-reprogramming nanodrug (OPR). Through a hierarchical delivery system targeting intestinal lesions, mitochondria, and UCP2, it effectively alleviated symptoms of both IBD and concurrent CDI.

1. Oral proton reprogramming nanomedicine (OPR) targeting UCP2

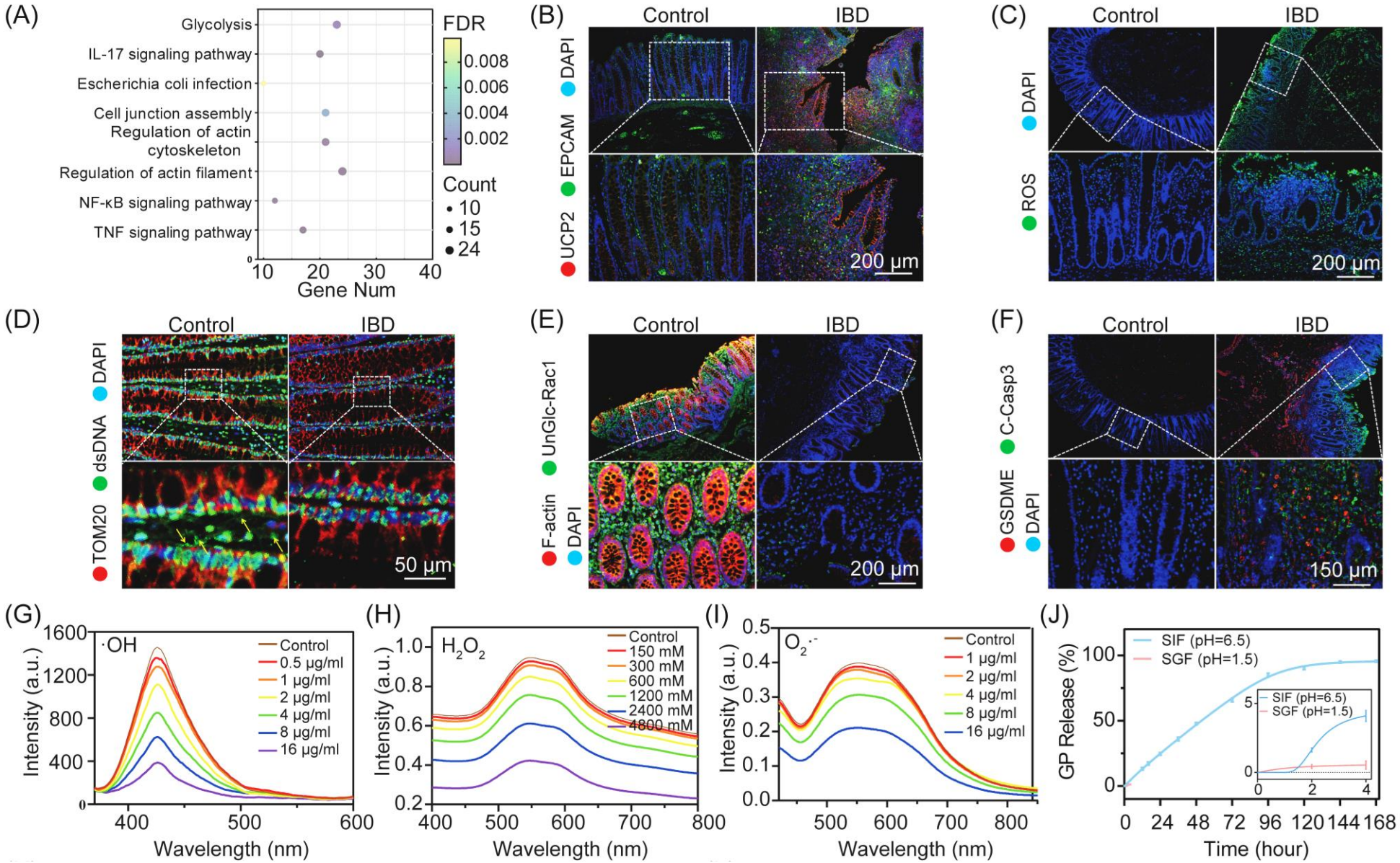


Figure 1-1. Screening of IBD-associated molecules/pathways

1. Oral proton reprogramming nanomedicine (OPR) targeting UCP2

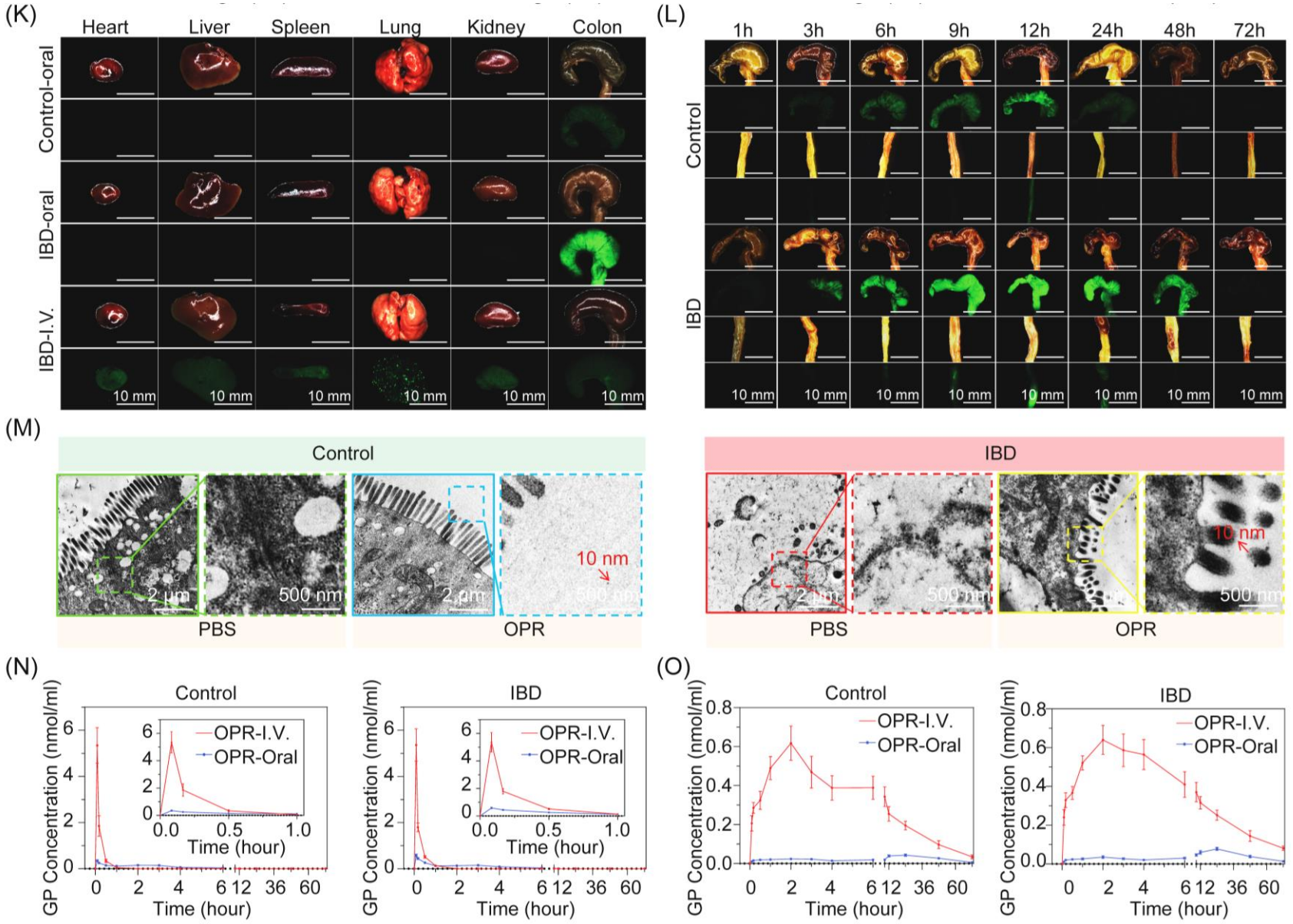


Figure 1-2. Synthesis, characterization, and *in vivo* distribution of OPR

2. The efficacy of OPR in IBD mouse model is superior to that of first-line drugs

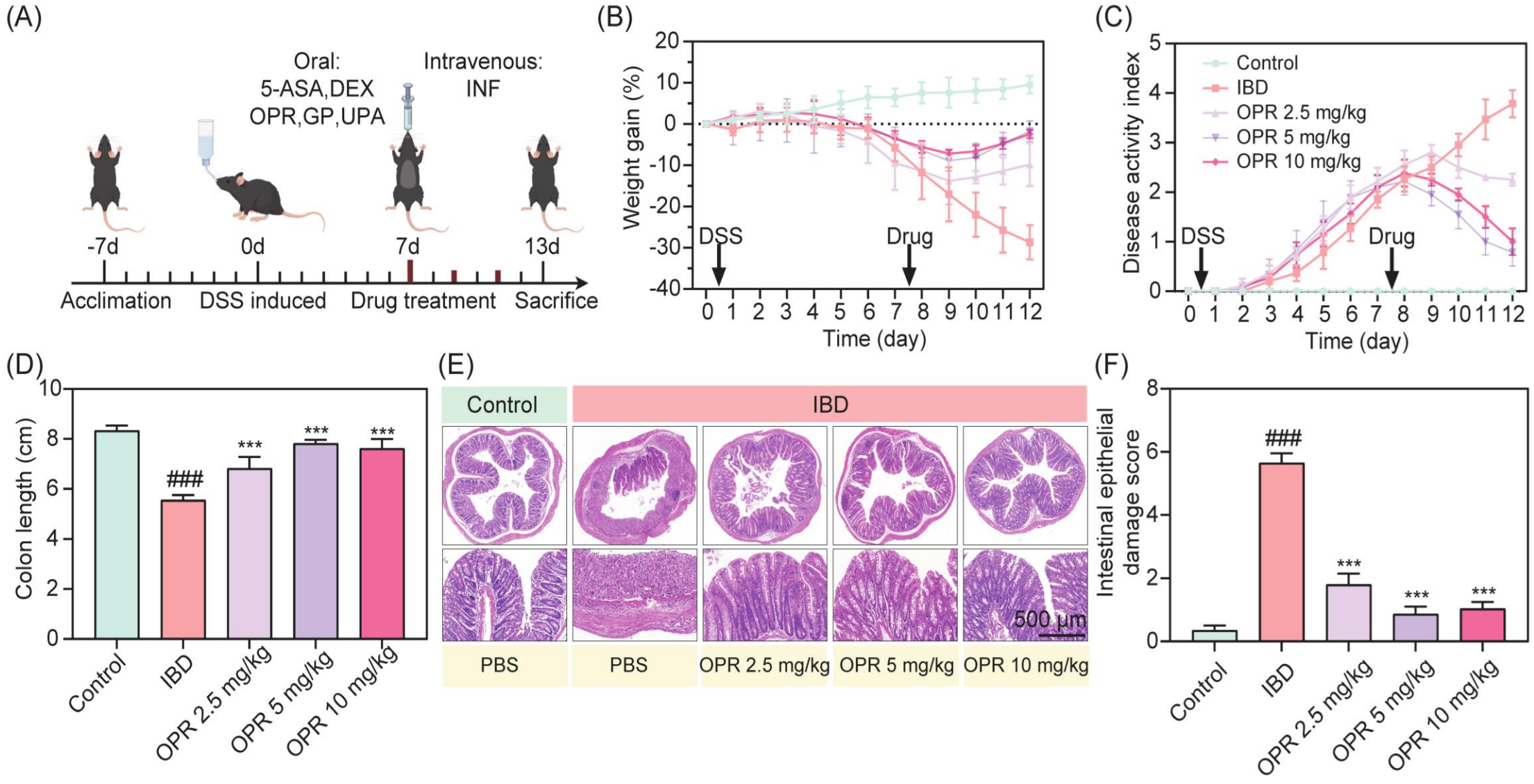


Figure 2-1. Dosage screening of OPR in IBD mouse model

2. The efficacy of OPR in IBD mouse model is superior to that of first-line drugs

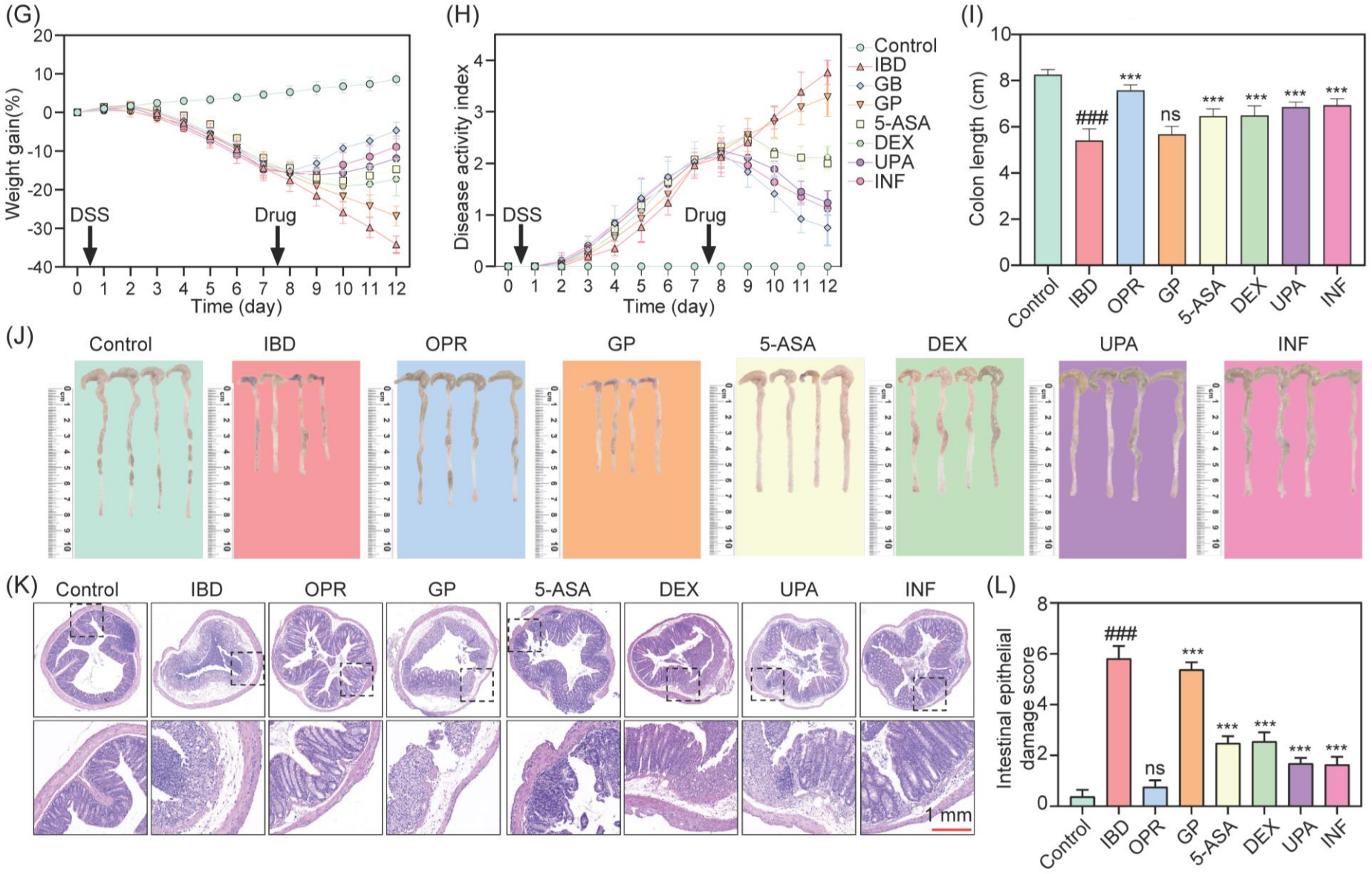


Figure 2-2. Efficacy of OPR in IBD mouse model

3. OPR modulates the gut microbiota and suppresses the toxicity of TcdB

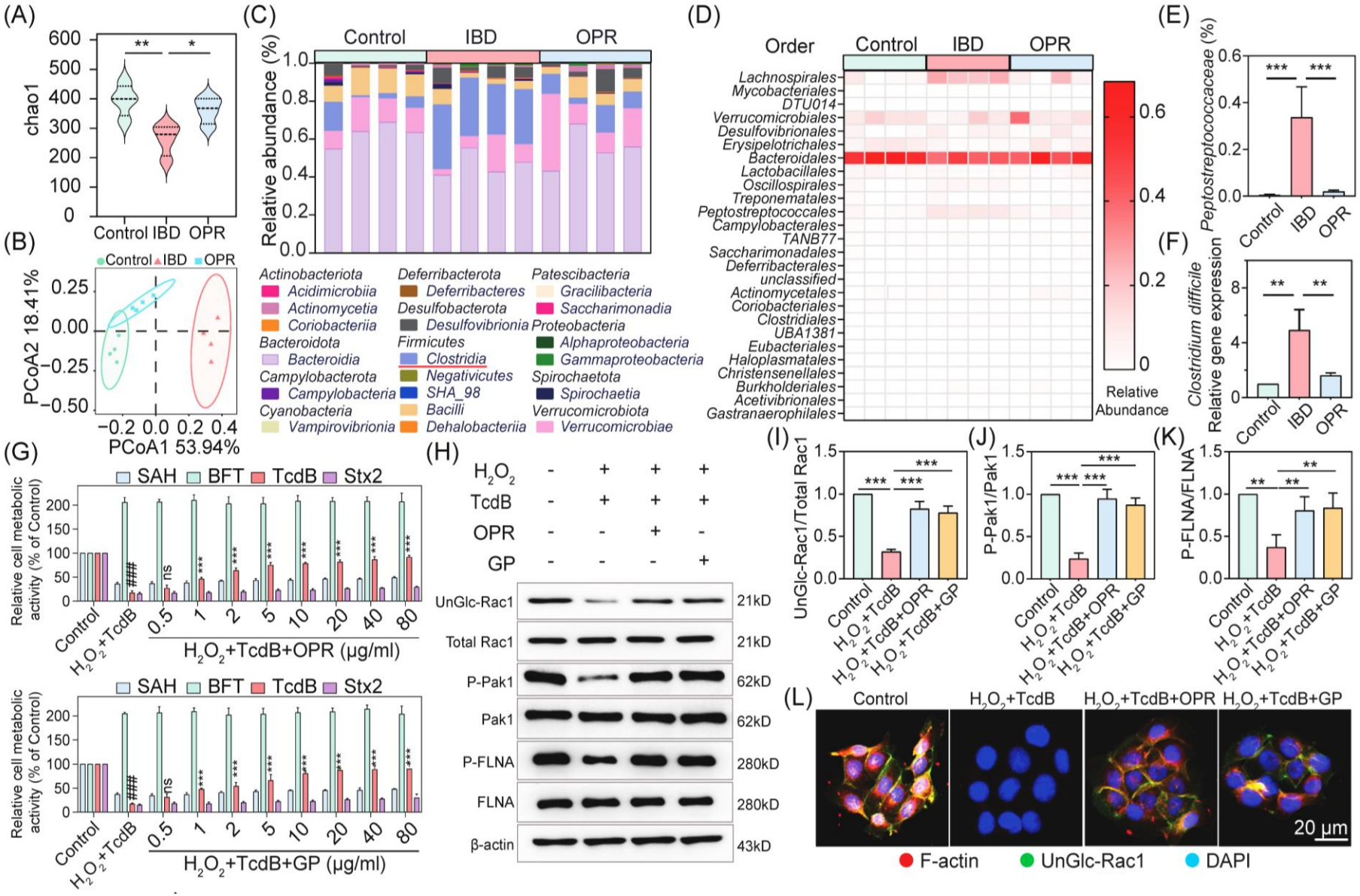


Figure 3-1. The regulatory effects of OPR on gut microbiota in mice

3. OPR modulates the gut microbiota and suppresses the toxicity of TcdB

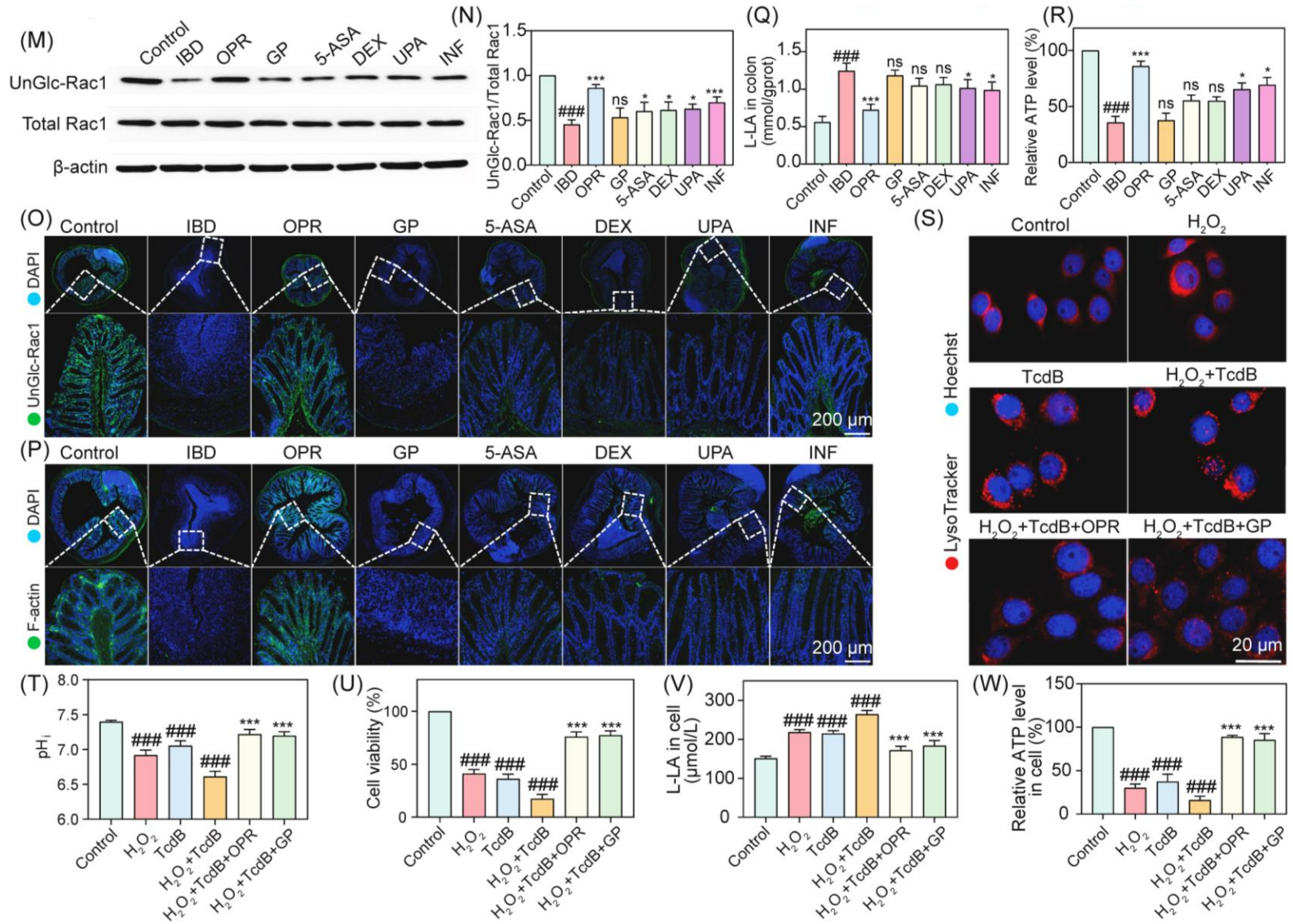


Figure 3-2. The underlying mechanisms of OPR on gut microbiota regulation

4. OPR demonstrates significant efficacy in the IBD-CDI mouse model

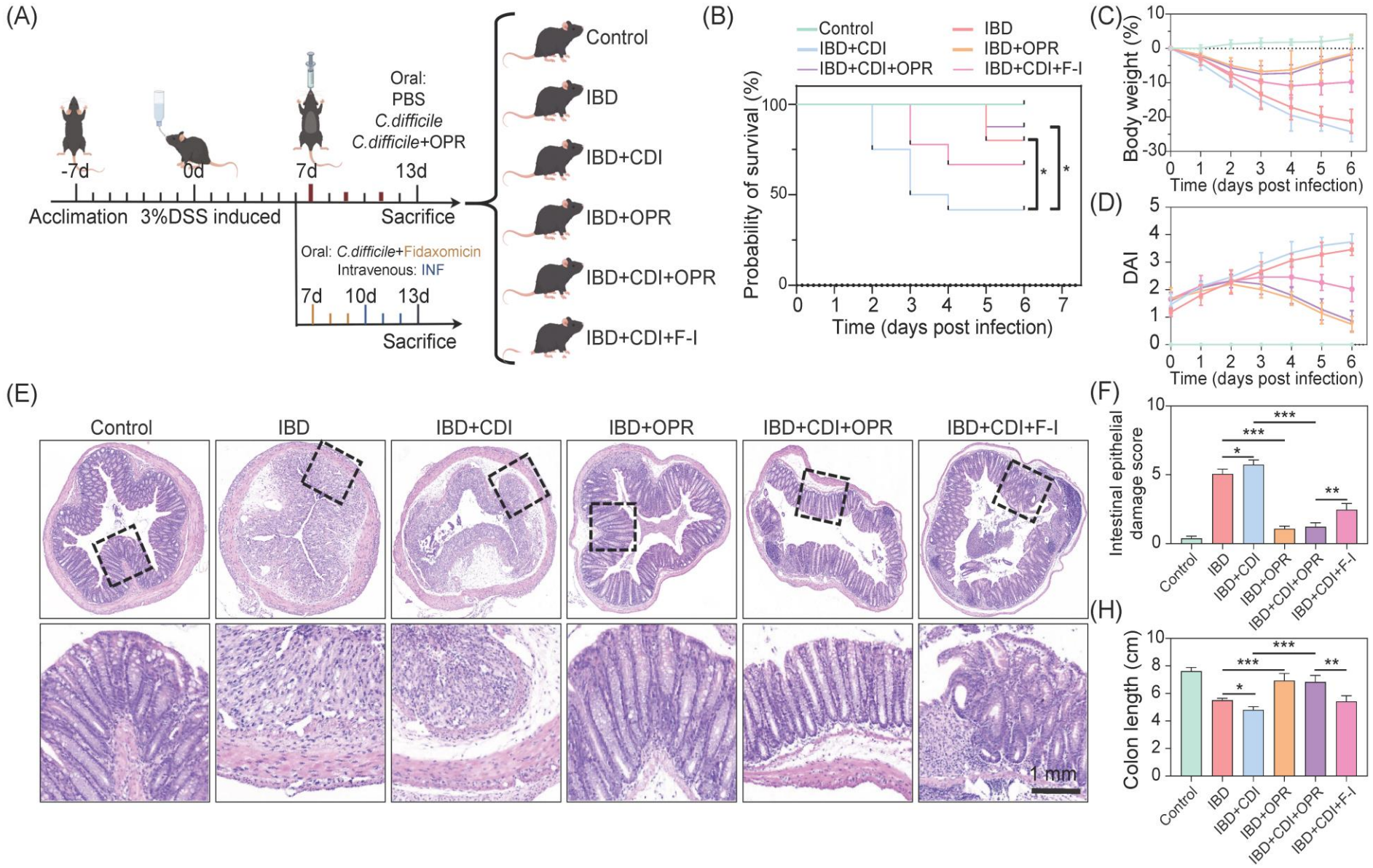


Figure 4-1. Efficacy of OPR in the IBD-CDI mouse model

4. OPR demonstrates significant efficacy in the IBD-CDI mouse model

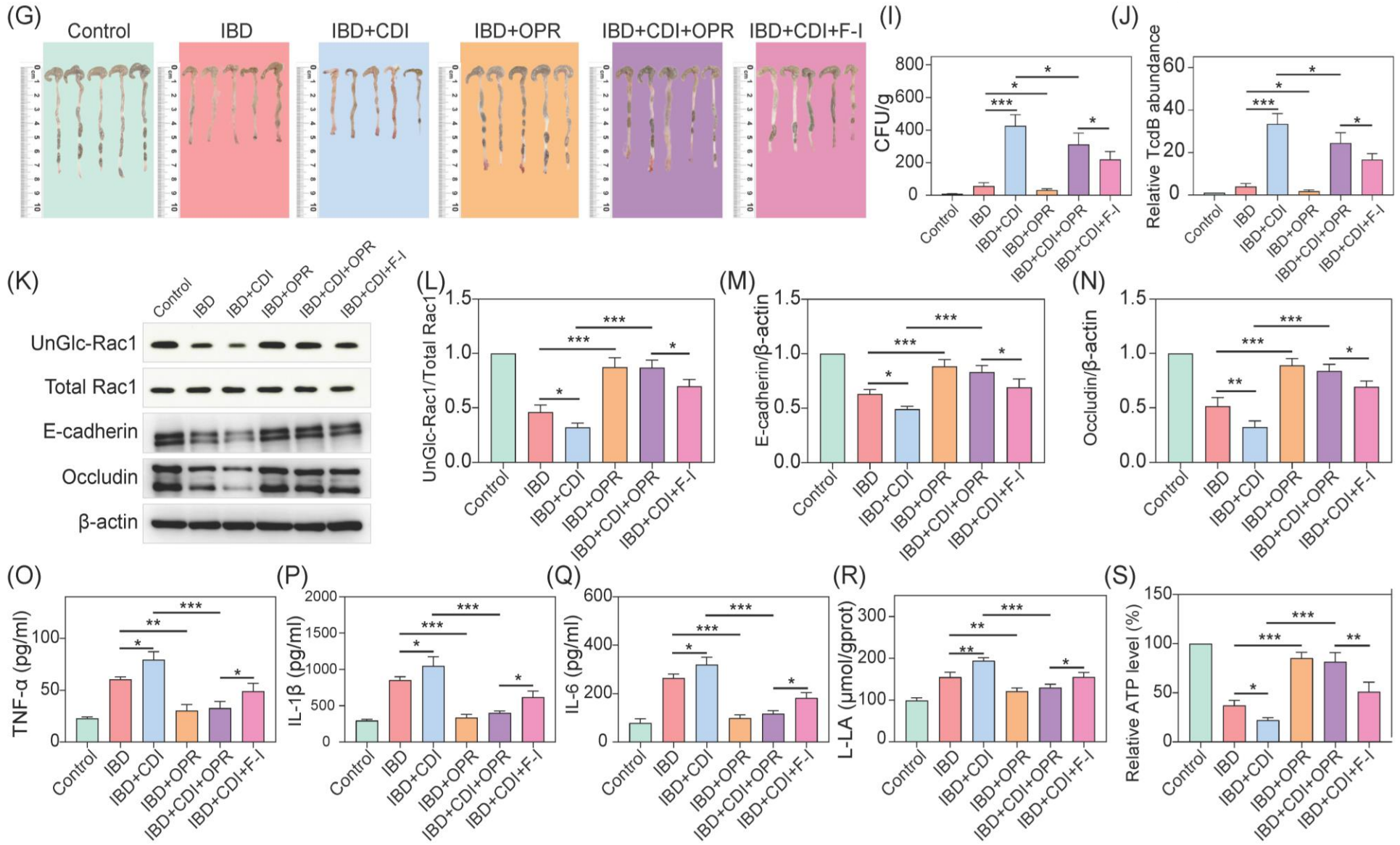


Figure 4-2. Efficacy of OPR in the IBD-CDI mouse model

5. OPR ameliorates mitochondrial dysfunction and suppresses pyroptosis

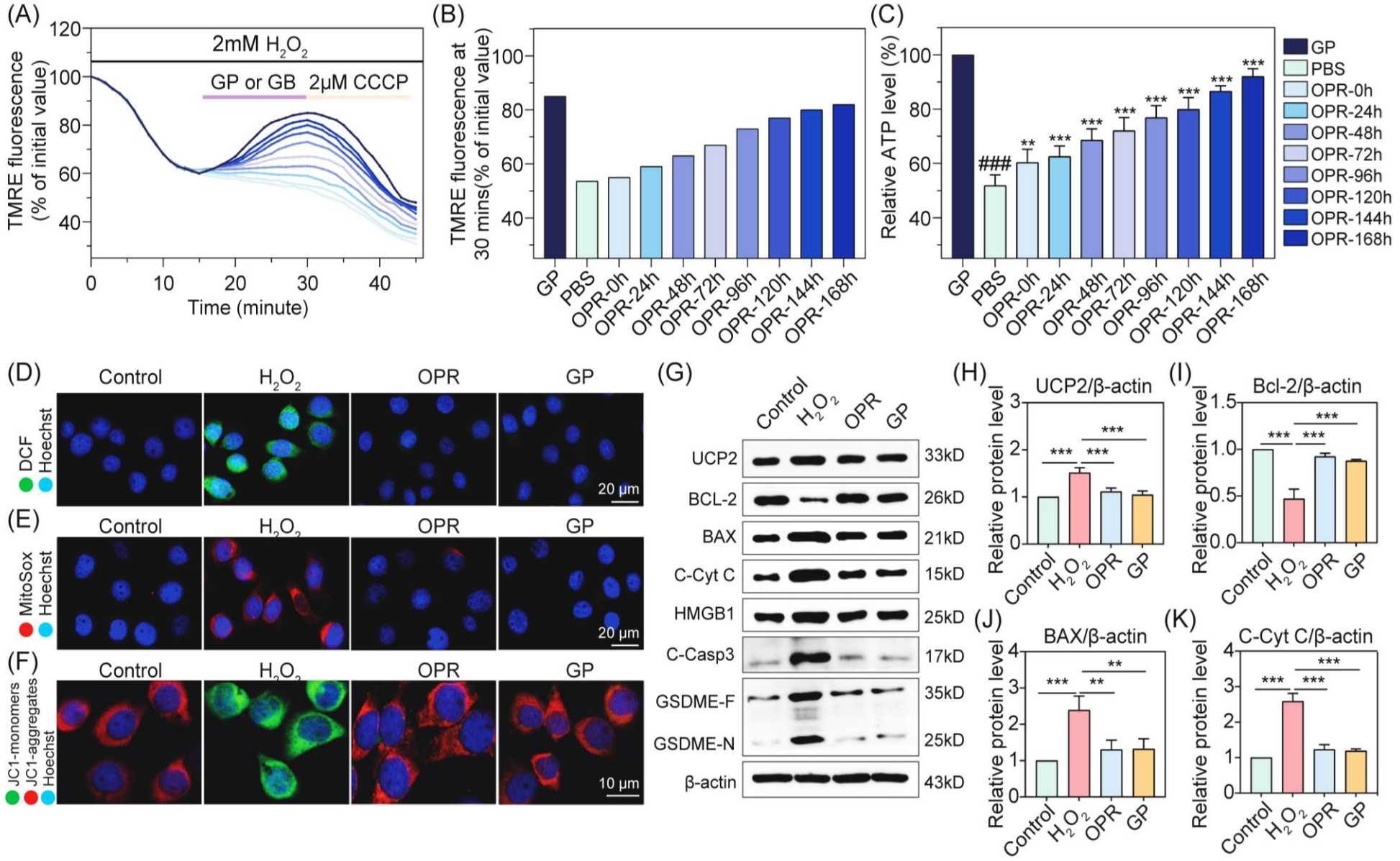


Figure 5-1. OPR alleviates oxidative stress and repairs mitochondrial function

5. OPR ameliorates mitochondrial dysfunction and suppresses pyroptosis

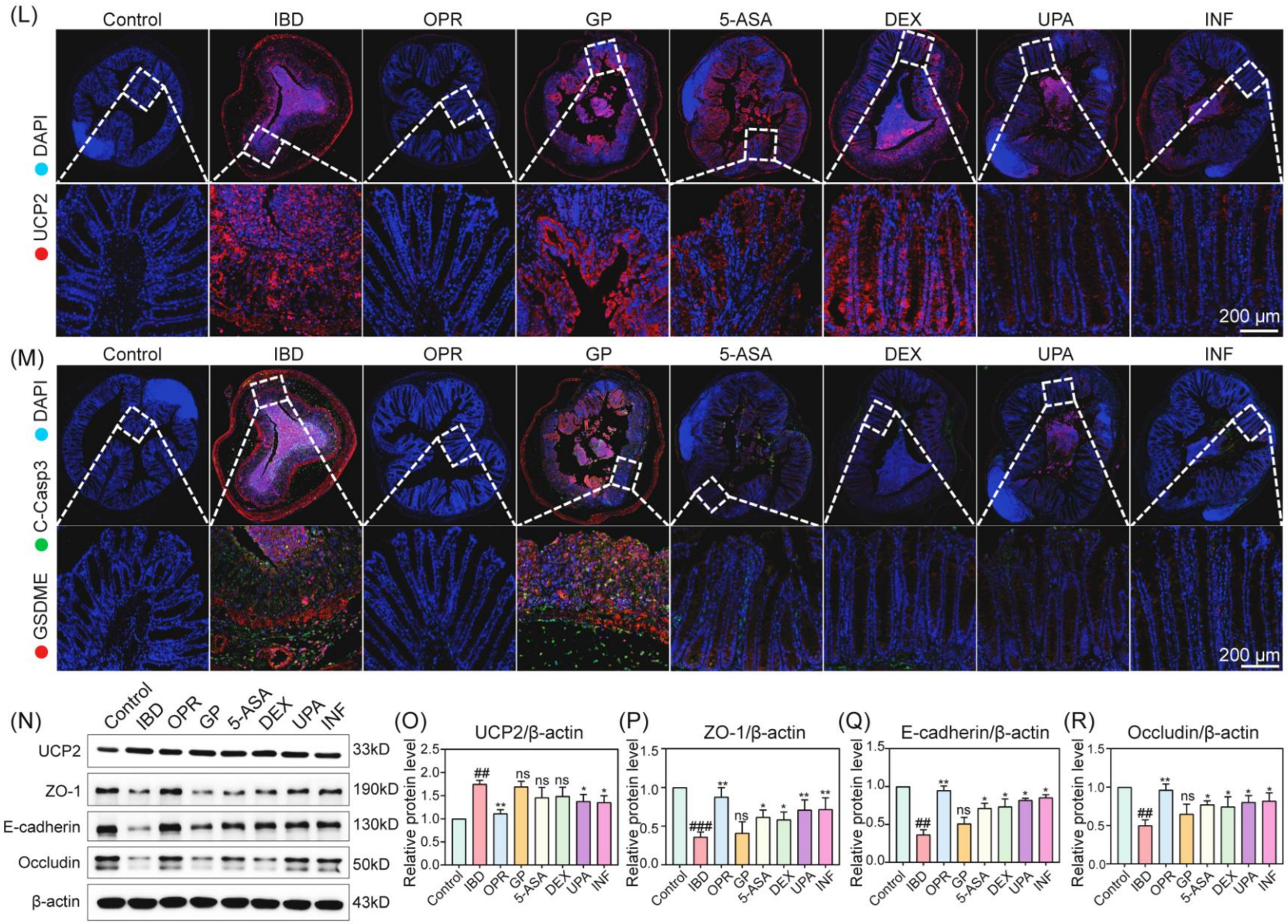


Figure 5-2. OPR restores the intestinal barrier

6. OPR suppresses mtDNA-mediated macrophage activation

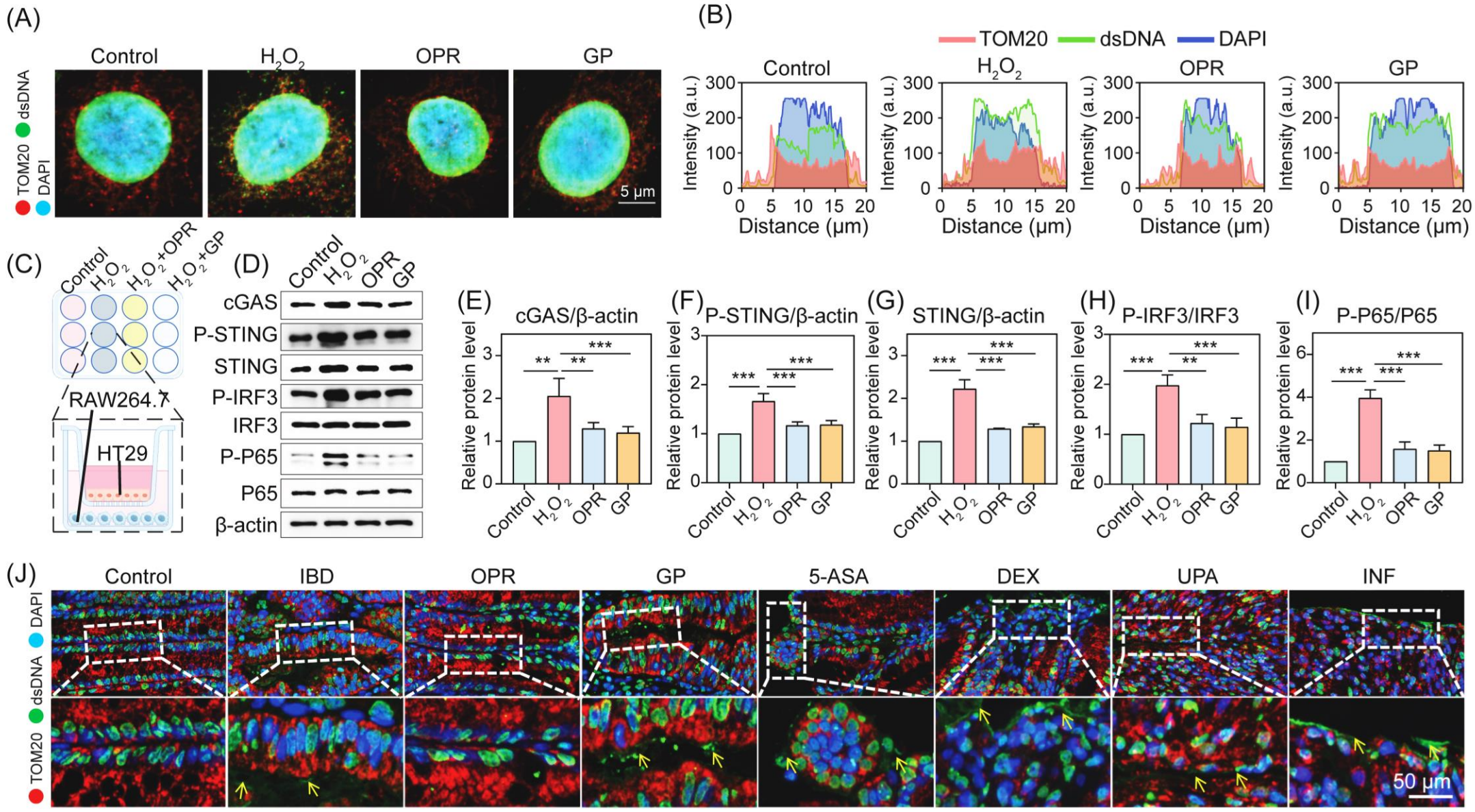


Figure 6-1. OPR inhibits epithelial mtDNA-mediated aberrant activation of the macrophage cGAS-STING pathway

6. OPR suppresses mtDNA-mediated macrophage activation

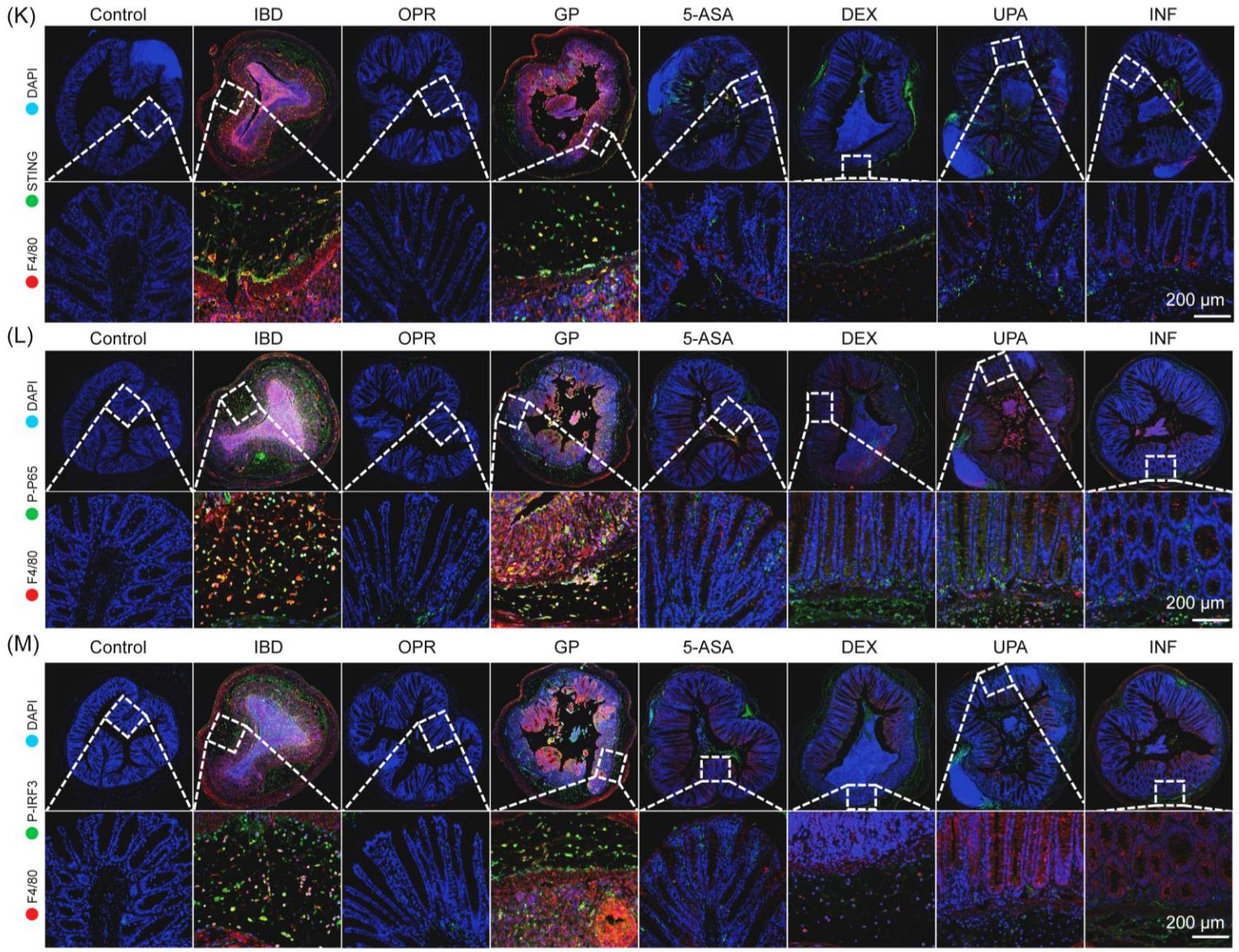


Figure 6-2. OPR inhibits epithelial mtDNA-mediated aberrant activation of the macrophage cGAS-STING pathway

7. Validation: Single-cell sequencing and transcriptome analysis

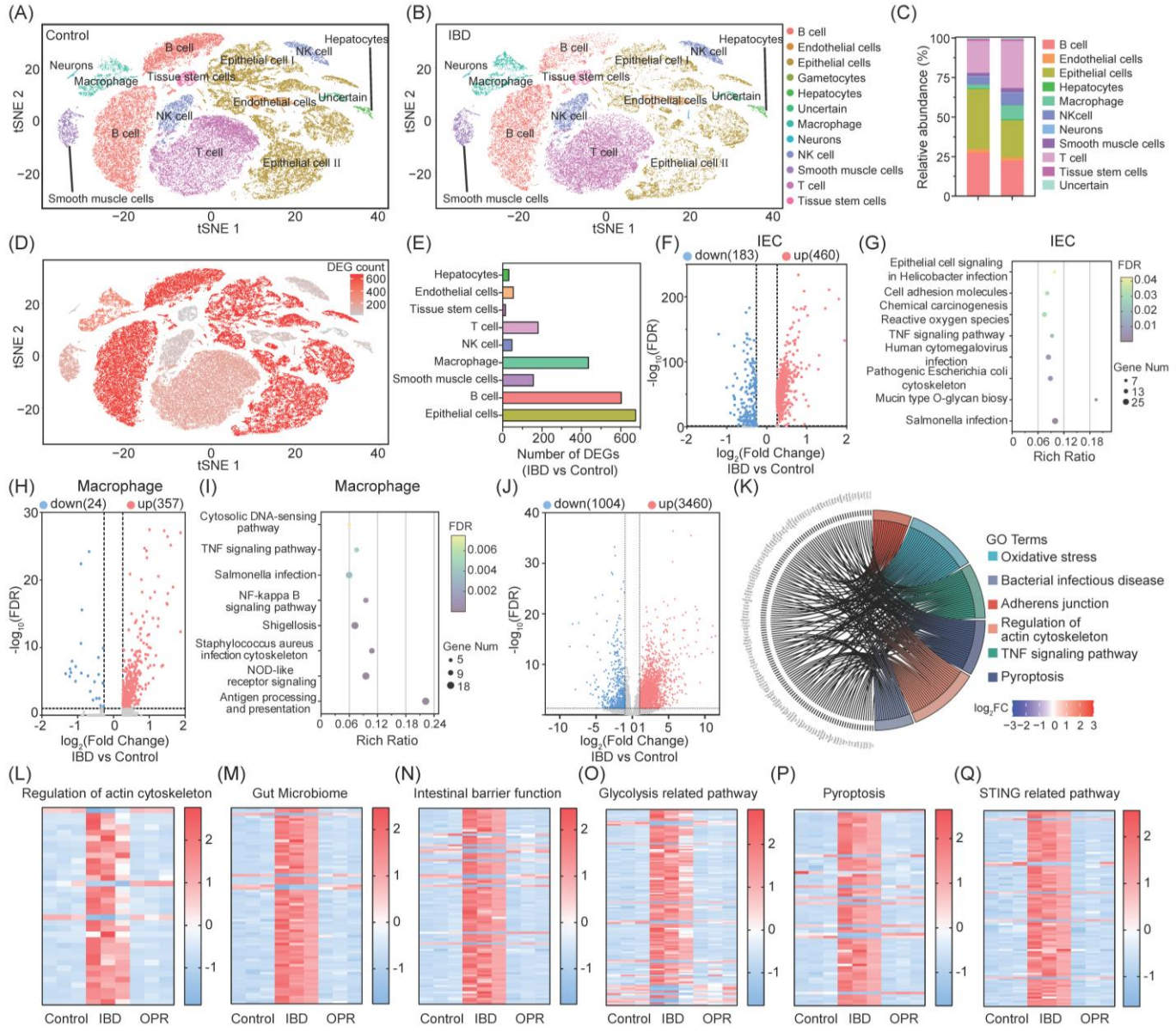


Figure 7. Single-cell sequencing dataset of human colon and mouse colon transcriptomic sequencing analysis

Summary

- This study reveals that UCP2 is highly expressed in IECs of IBD, impairs mitochondrial function, and reprograms cellular metabolism toward glycolysis, thereby reducing the resistance of IECs to TcdB.

- This study develops an oral proton-reprogramming nanomedicine (OPR) that switches the metabolism of IECs from glycolysis to oxidative phosphorylation, thereby effectively alleviating IBD and CDI syndromes.

- This study identifies UCP2-mediated mitochondrial dysfunction as a key mechanism through which TcdB exerts its effects, and reveals that metabolic reprogramming of IECs represents a potential therapeutic target for IBD-CDI.

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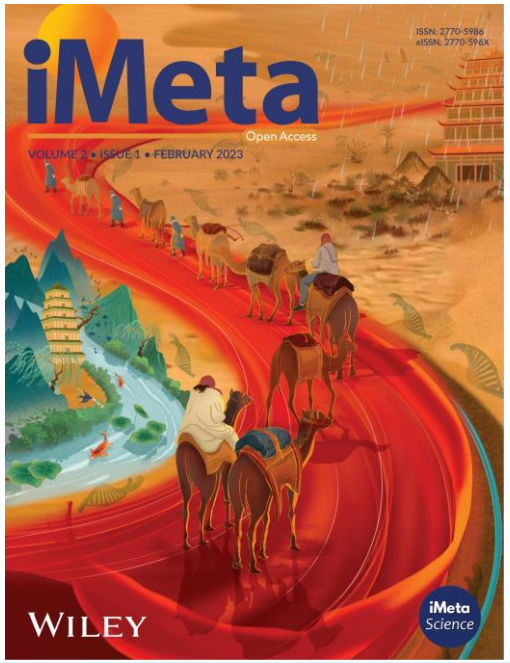

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