



# Inhibition of ferroptosis by microbiota-derived lithocholic acid underlies the intestinal radioprotection of a host defensin-derived oligopeptide

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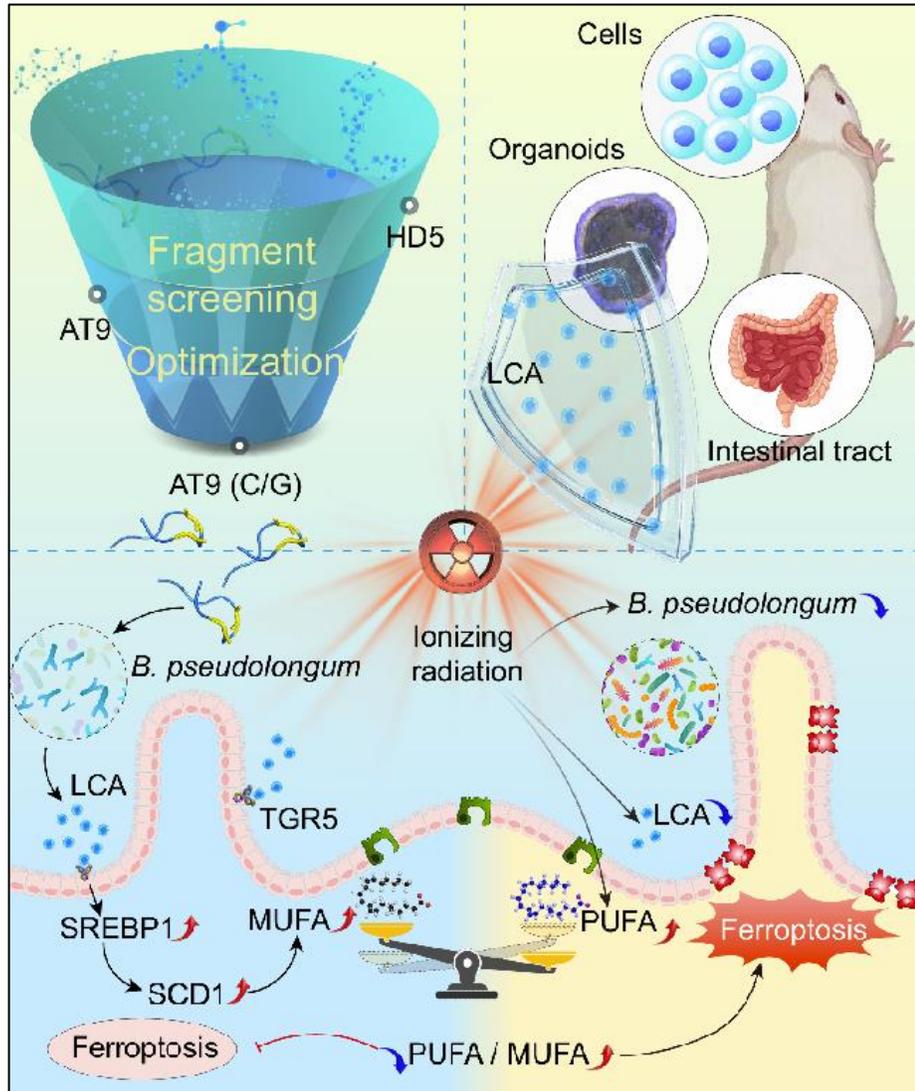
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# Graphical Abstract



- Human defensin 5-derived oligopeptide AT9(C/G) enriches the intestinal *Bifidobacterium pseudolongum* and increases the lithocholic acid (LCA) levels.
- In cell, mouse, and human small intestinal organoid models, LCA demonstrates radioprotective effects.
- Mechanistically, LCA activates TGR5 and upregulates SREBP1, which transcriptionally regulates the SCD1 expression and remodels lipid metabolism, thereby inhibiting ionizing radiation (IR)-induced ferroptosis.



# Highlights

- Human defensin 5-derived oligopeptide AT9(C/G) alleviates IR-induced intestinal injury (IRII).
- AT9(C/G) enriches intestinal *Bifidobacterium pseudolongum* and increases LCA levels.
- LCA upregulates SCD1 through the TGR5 receptor and inhibits IR-induced ferroptosis by reprogramming lipid metabolism..

# Result 1: HD5-derived oligopeptide AT9(C/G) effectively alleviates IRIII

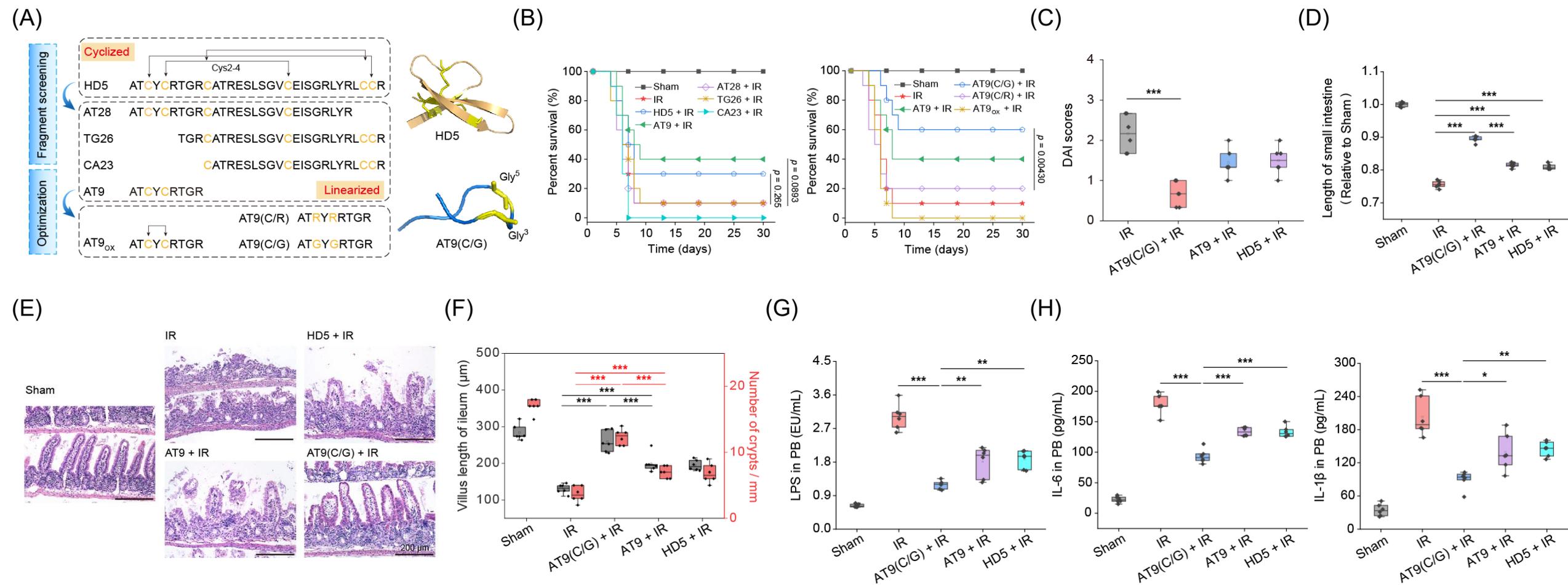


Figure 1. Evaluation of the effect of HD5 and its active fragments in alleviating IRIII.

# Result 2: AT9(C/G) alleviates IRII by reshaping the gut microbiota

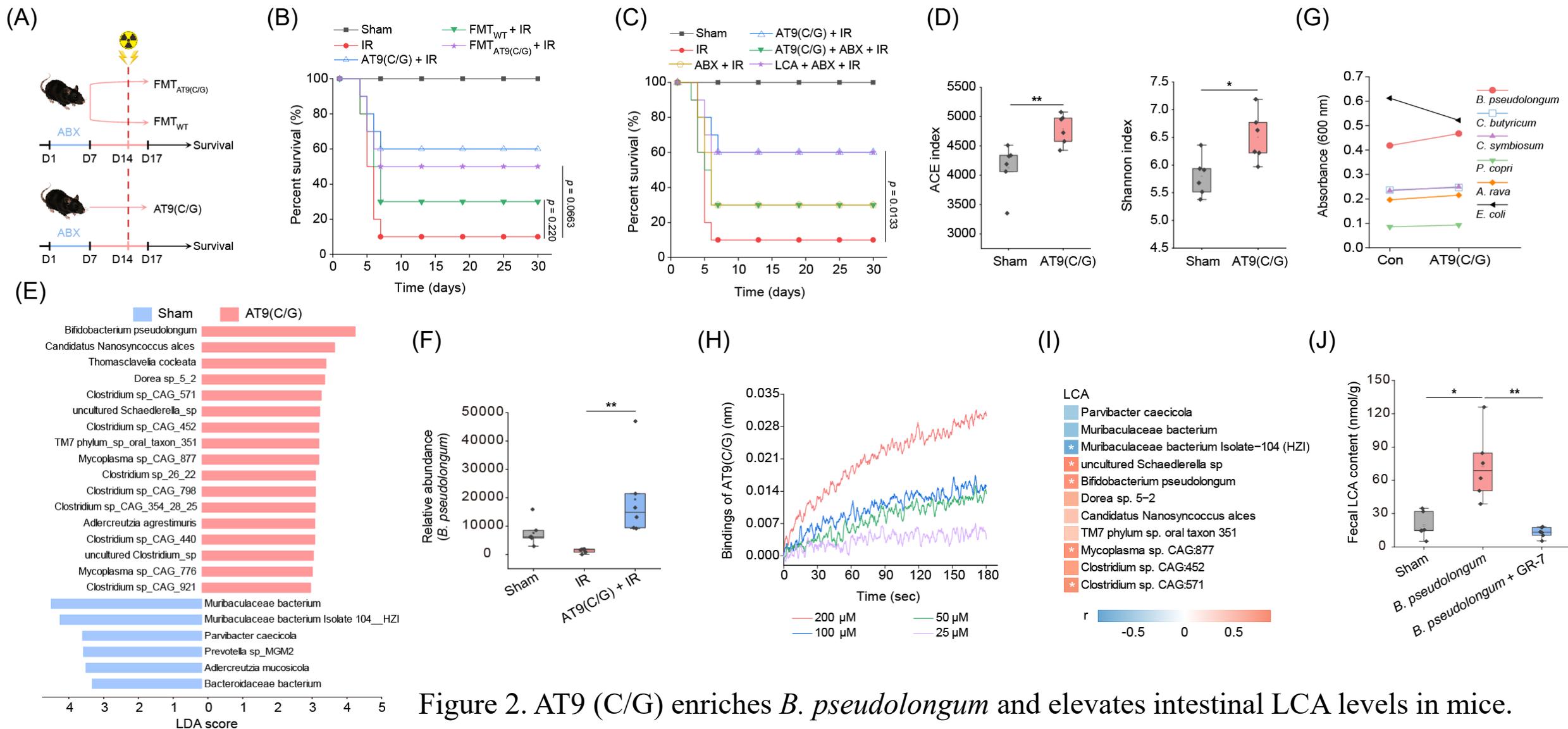


Figure 2. AT9 (C/G) enriches *B. pseudolongum* and elevates intestinal LCA levels in mice.

# Result 3: AT9(C/G) increases the radioprotective LCA in the gut

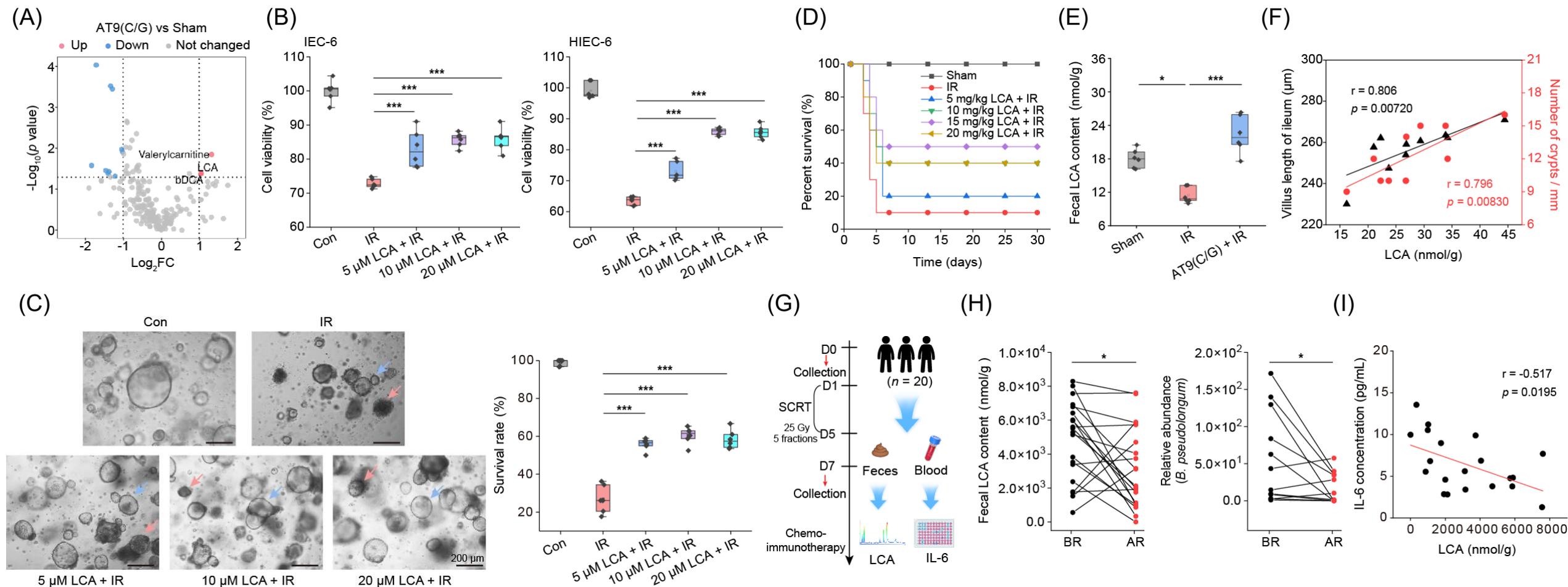


Figure 3. Evaluation of the ameliorative effects of LCA on IRIII *in vitro* and *in vivo*.

# Result 4: LCA reduces IR-induced cell death by upregulating SCD1 expression to inhibit ferroptosis

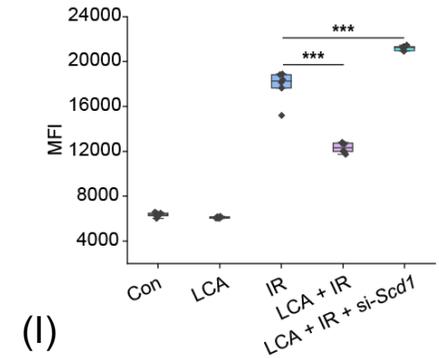
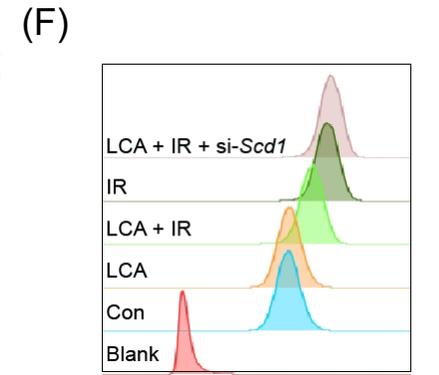
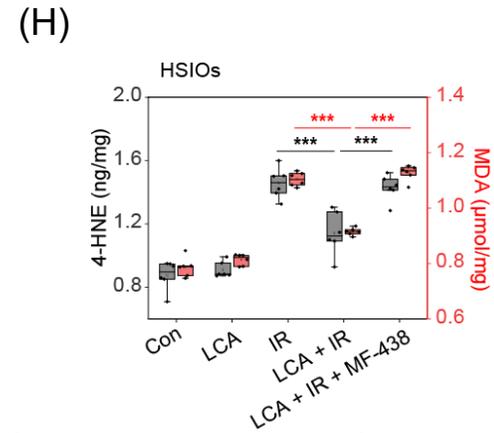
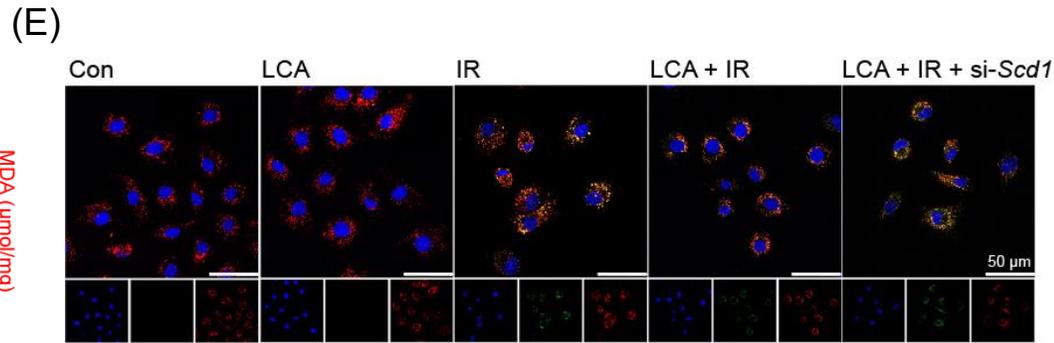
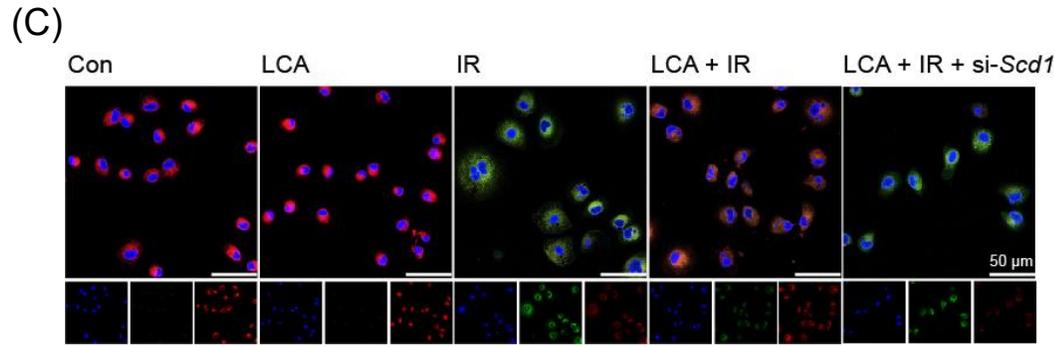
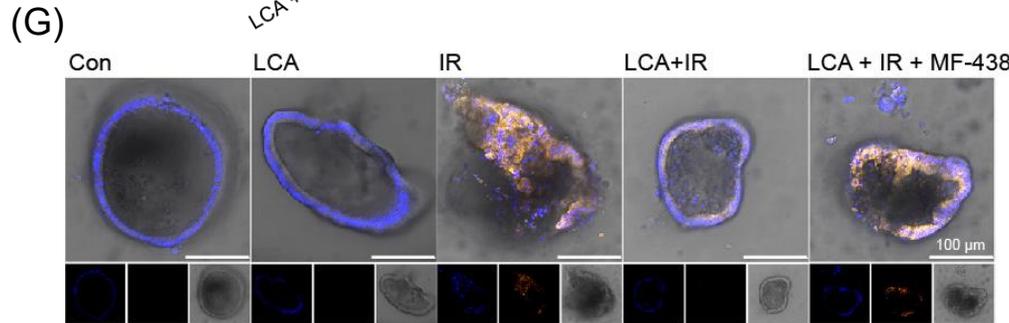
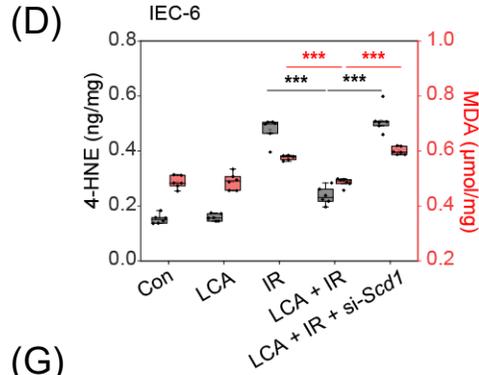
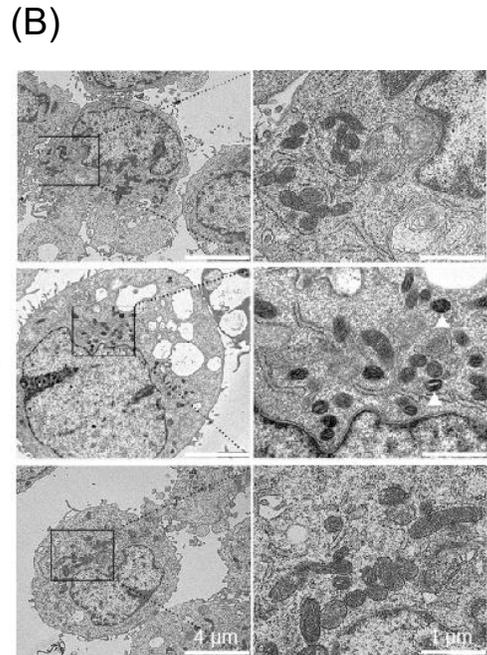
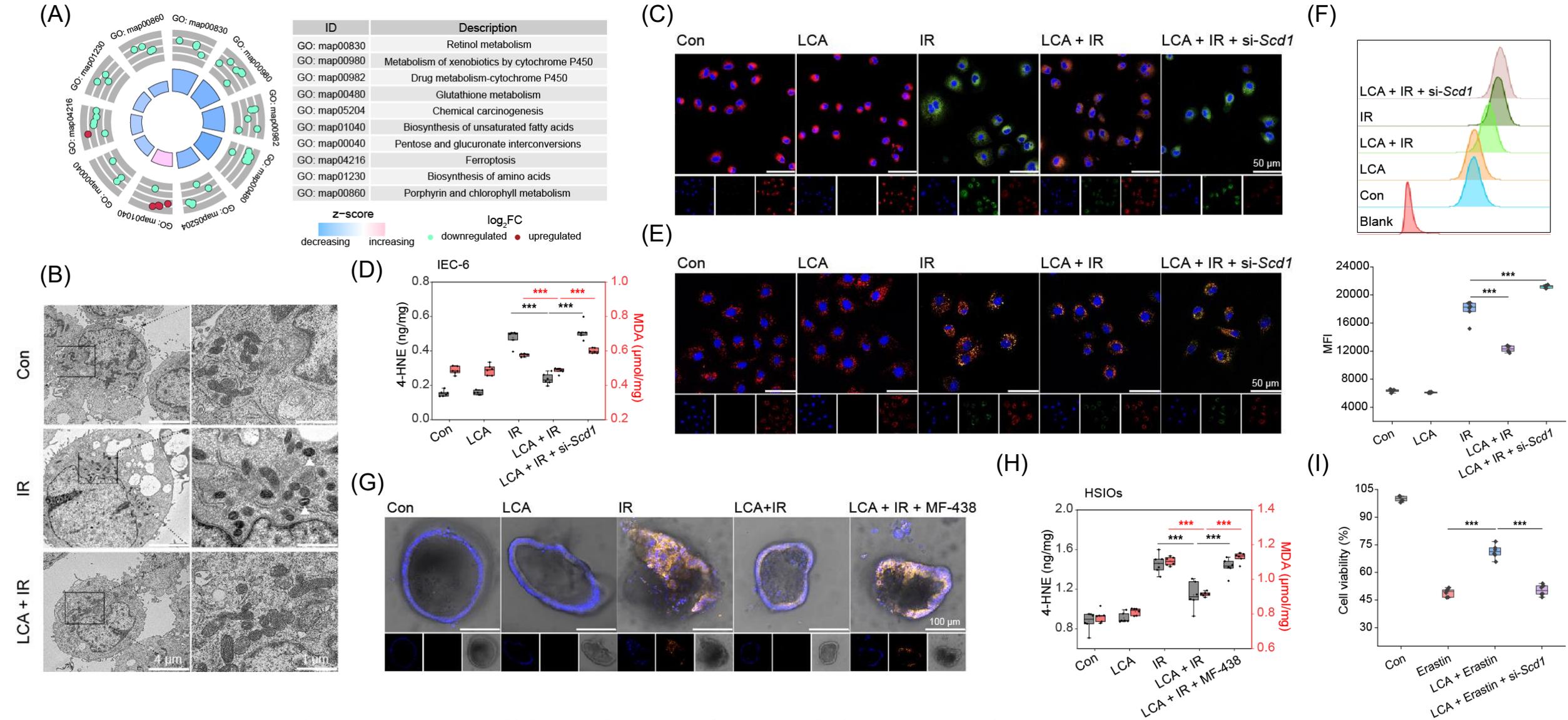


Figure 4. LCA inhibits IR-induced ferroptosis by upregulating SCD1 expression.

# Result 4: LCA reduces IR-induced cell death by upregulating SCD1 expression to inhibit ferroptosis

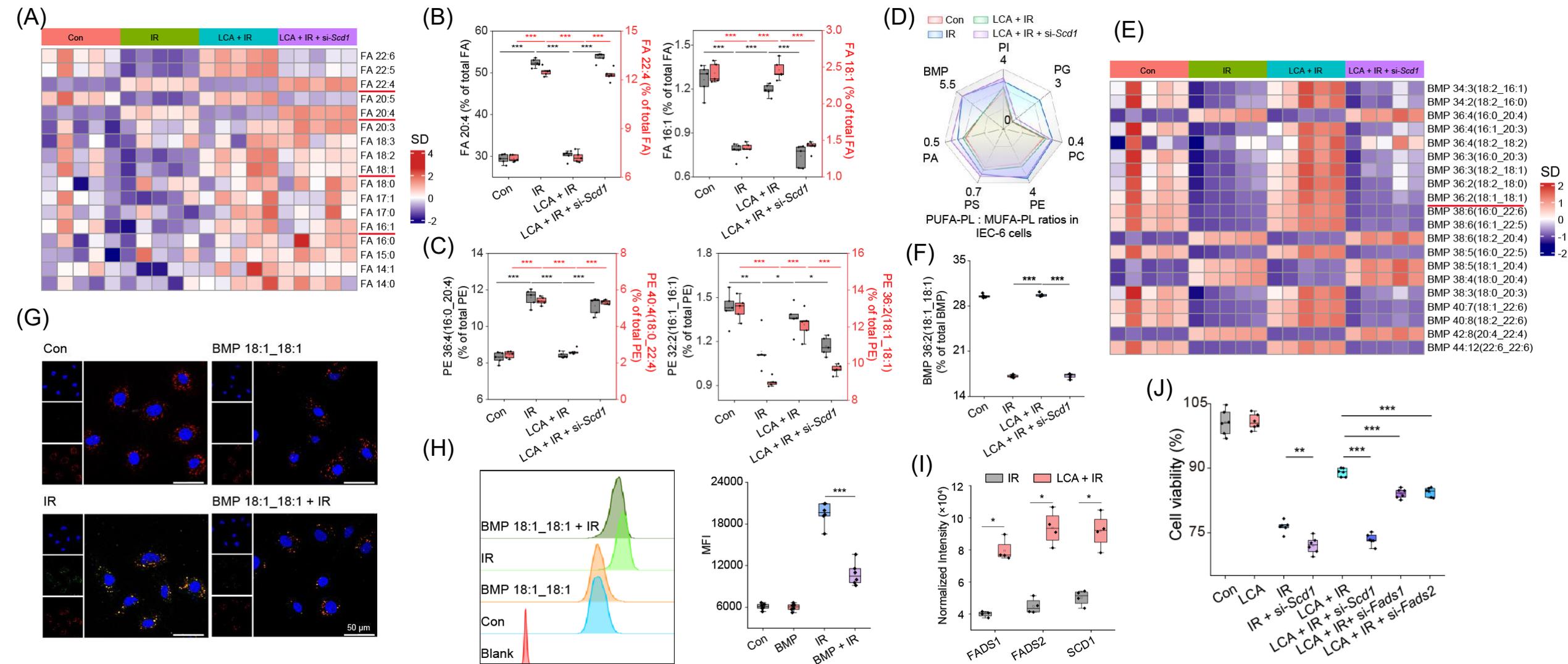


Figure 5. LCA remodels lipid metabolism in irradiated cells by upregulating SCD1 expression.

# Result 5: LCA upregulates SCD1 expression by activating TGR5-SREBP1 signaling

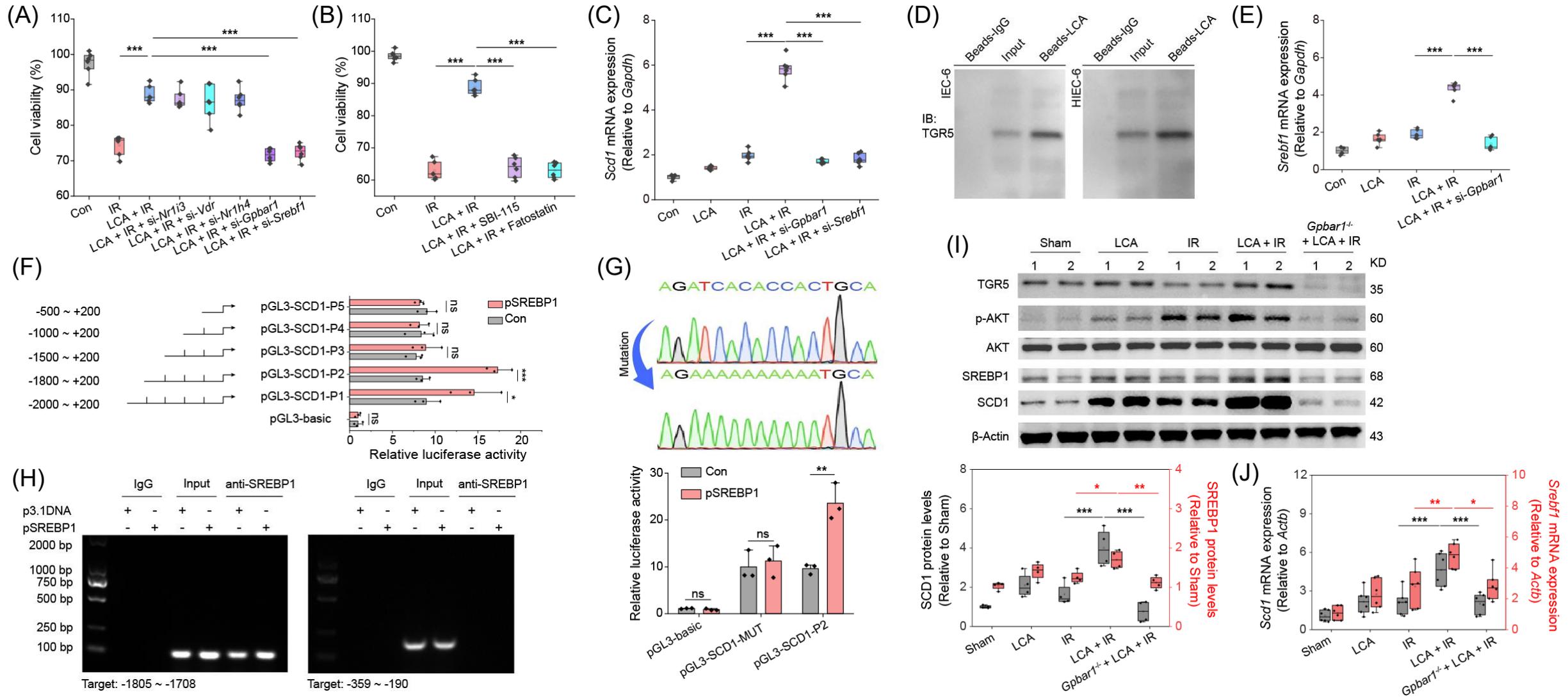


Figure 6. Investigation of the mechanism by which LCA upregulates SCD1 expression via TGR5.

# Result 6: SCD1 inhibition or *Gpbar1* knockout diminishes the radioprotective effect of AT9(C/G)

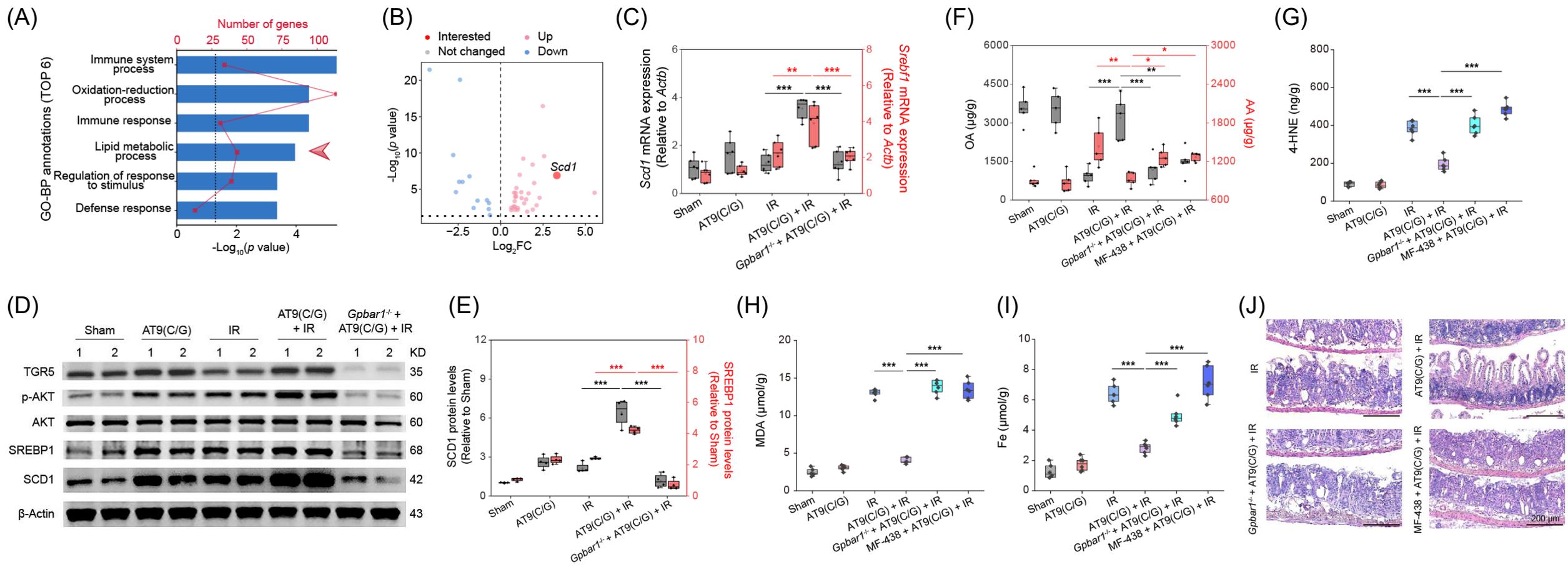


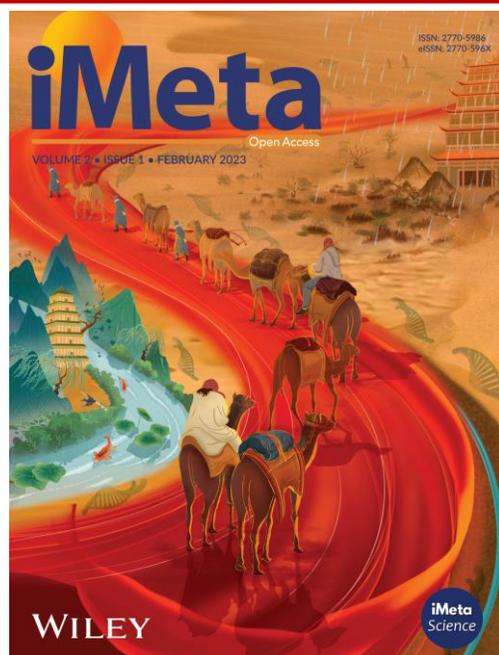
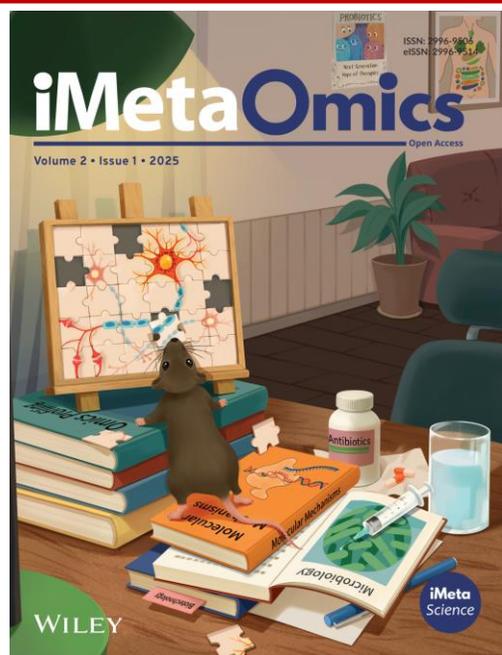
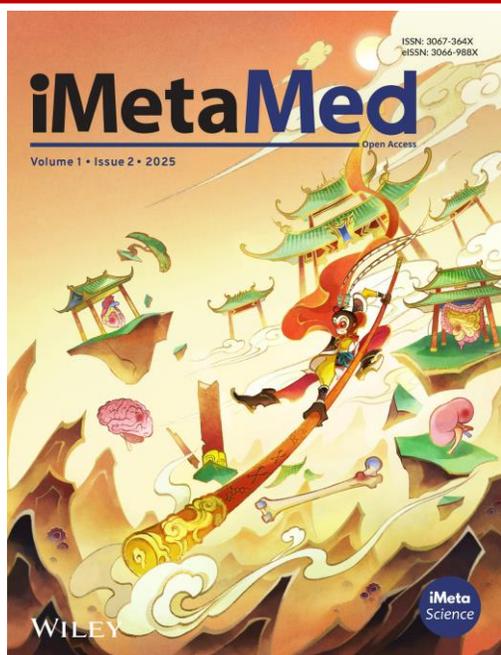
Figure 7. Activation of the TGR5–SREBP1–SCD1 signaling mediates the radioprotective effects of AT9(C/G) in the intestine.



# Conclusion

- Human defensin-derived oligopeptide AT9(C/G) alleviates IRIII by enriching *Bifidobacterium pseudolongum* in the gut and elevating LCA levels.
- LCA upregulates SCD1 through activation of the TGR5 receptor signaling pathway. This promotes monounsaturated fatty acid synthesis and reprograms lipid metabolism in irradiated cells, ultimately suppressing IR-induced ferroptosis.

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