A bioactive ginsenoside alleviates hepatocellular ferroptosis induced by oxidized phospholipid accumulation in nonalcoholic steatohepatitis.

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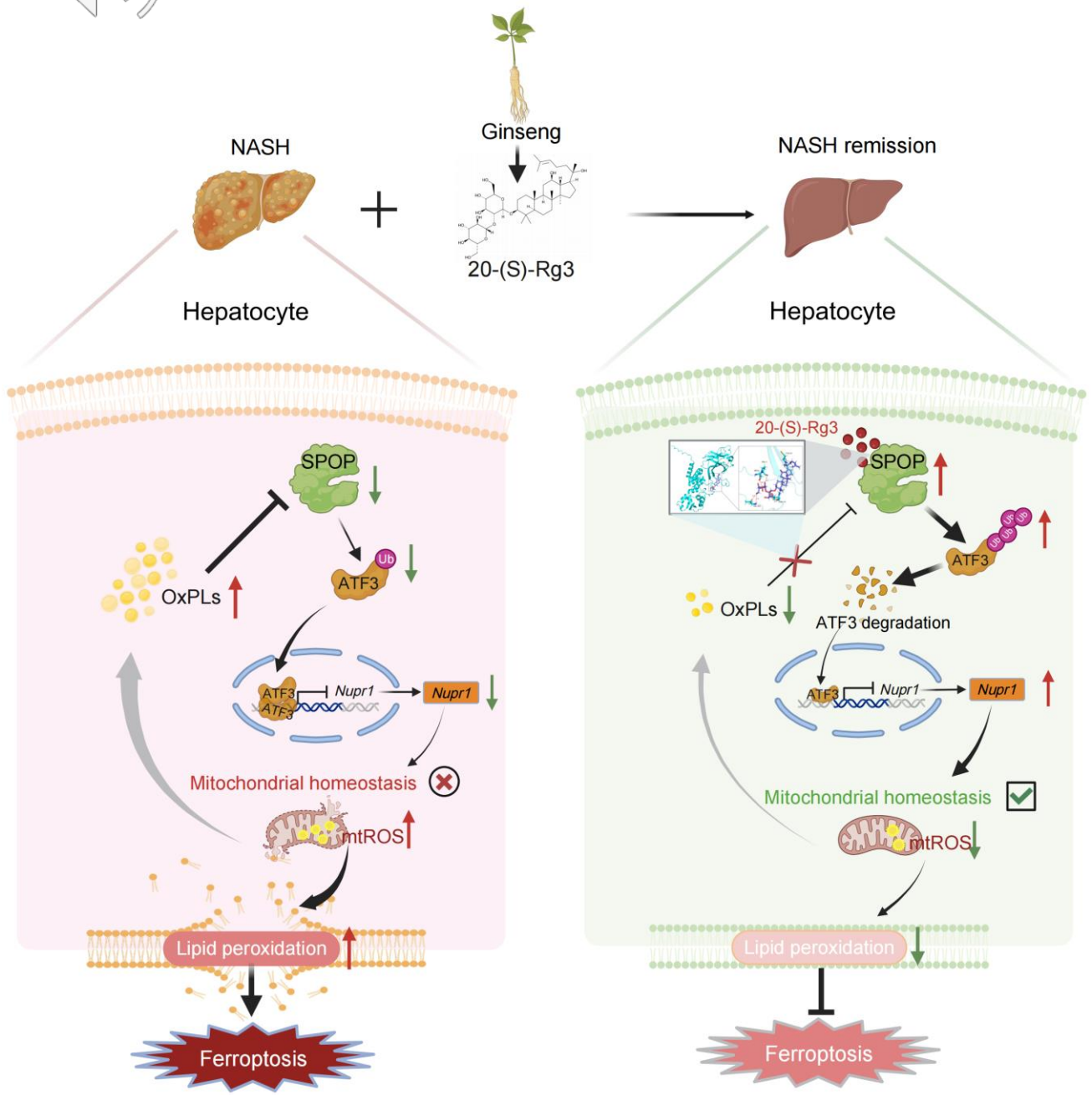
Yibo Zong, Guo Long, Tiantian Gu, Pan Huang, Yong Tian, Wenwu Xu, Xiheng Hu, et al. 2026. A Bioactive Ginsenoside Alleviates Hepatocellular Ferroptosis Induced by Oxidized Phospholipid Accumulation in Nonalcoholic Steatohepatitis. ***iMeta*** 5: e70114. https://doi.org/10.1002/imt2.70114

Introduction and Highlights



- The accumulation of OxPLs promotes the development of NASH, and 20(S)-Rg3 can reduce the content of OxPLs in mice.
- SPOP promotes ubiquitination of ATF3.
- 20(S)-Rg3 alleviates hepatocyte ferroptosis via the *Spop*/*Atf3*/*Nupr1* axis.

1. High-dose Rg3 ameliorates NASH and upregulates SPOP expression

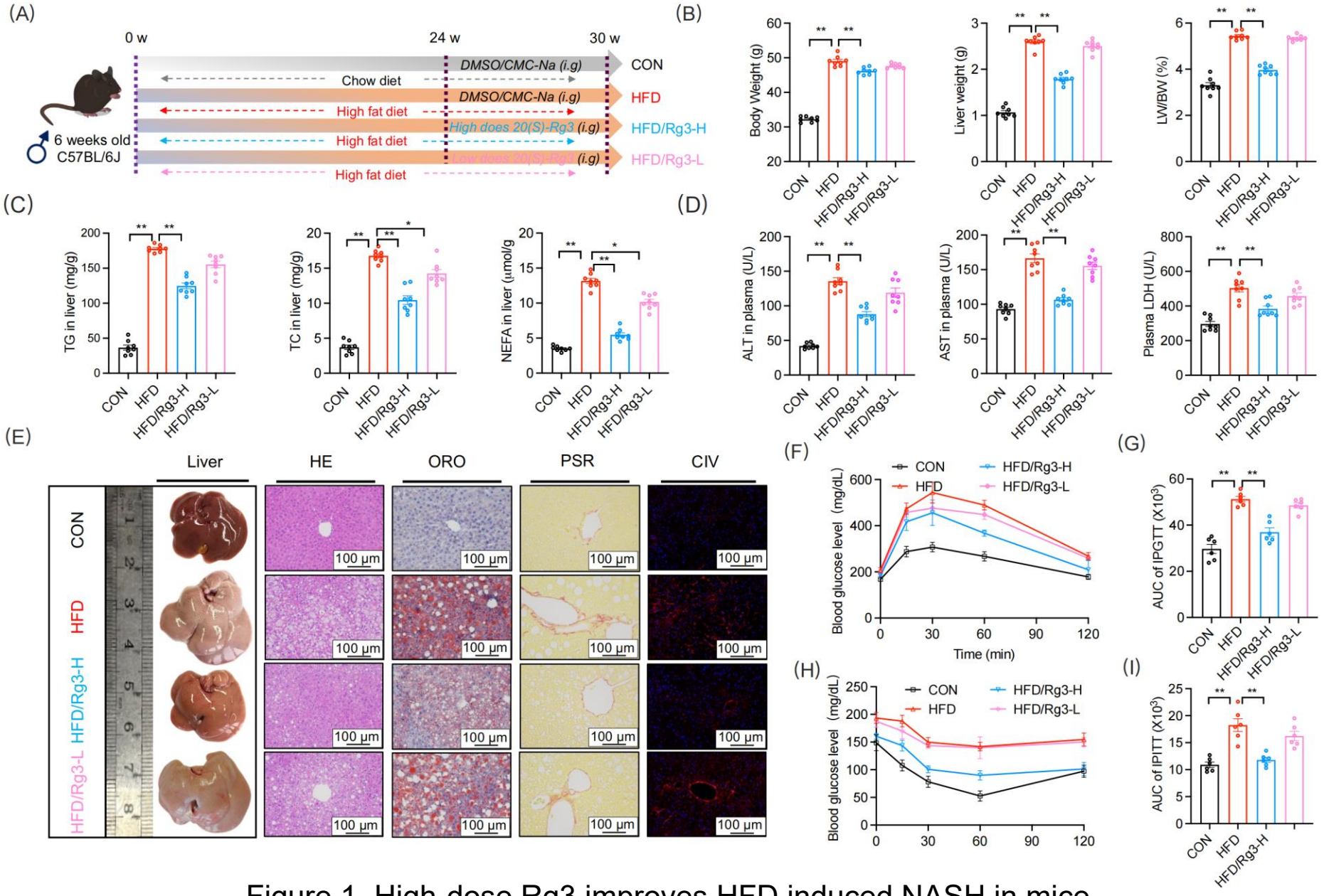


Figure 1. High-dose Rg3 improves HFD induced NASH in mice

1. High-dose Rg3 ameliorates NASH and upregulates SPOP expression

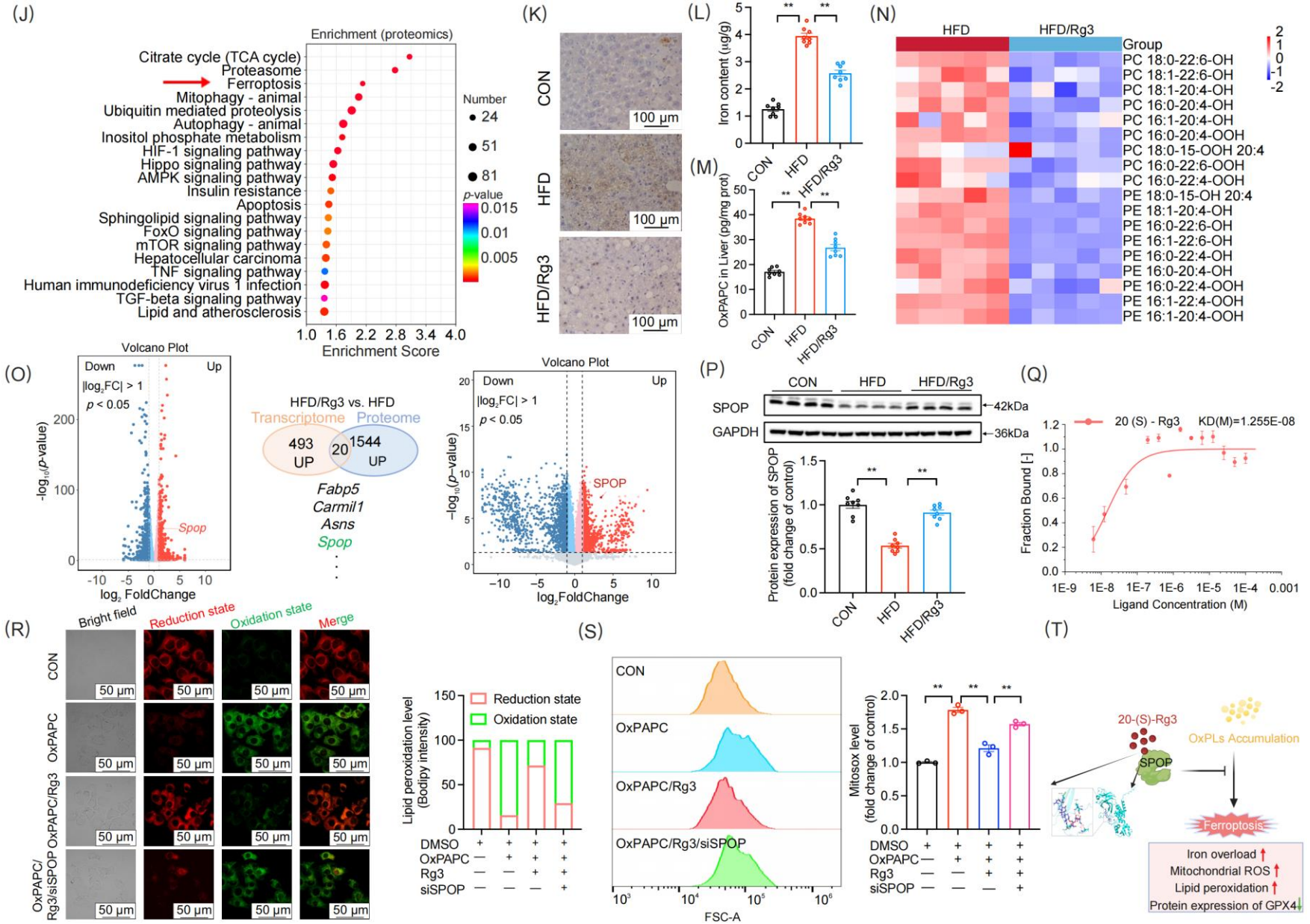


Figure 2. Rg3 alleviates ferroptosis and upregulates hepatic SPOP Expression

2. Rg3 Alleviates hepatocyte ferroptosis via the Spop/Atf3/Nupr1 axis

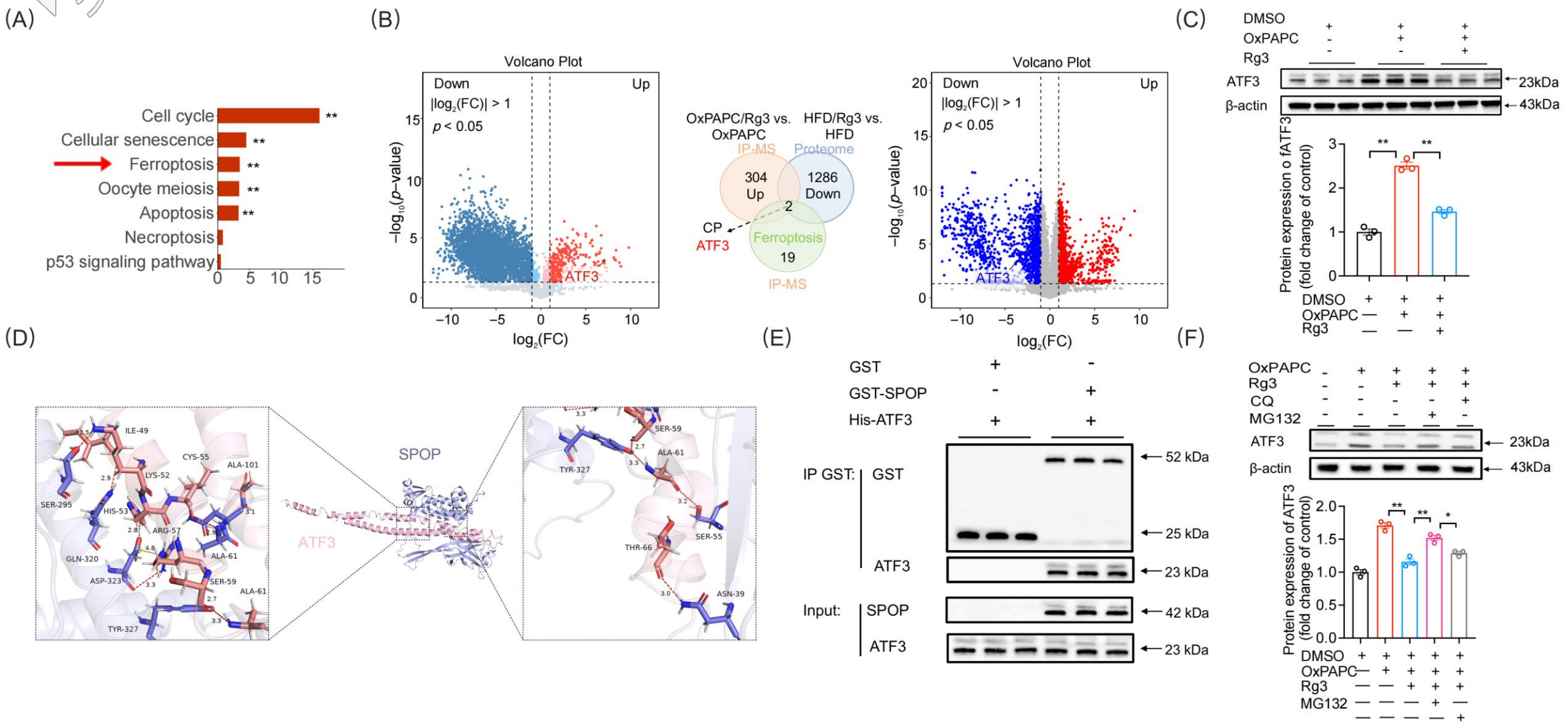


Figure 3. SPOP binds to ATF3 and promotes its ubiquitination

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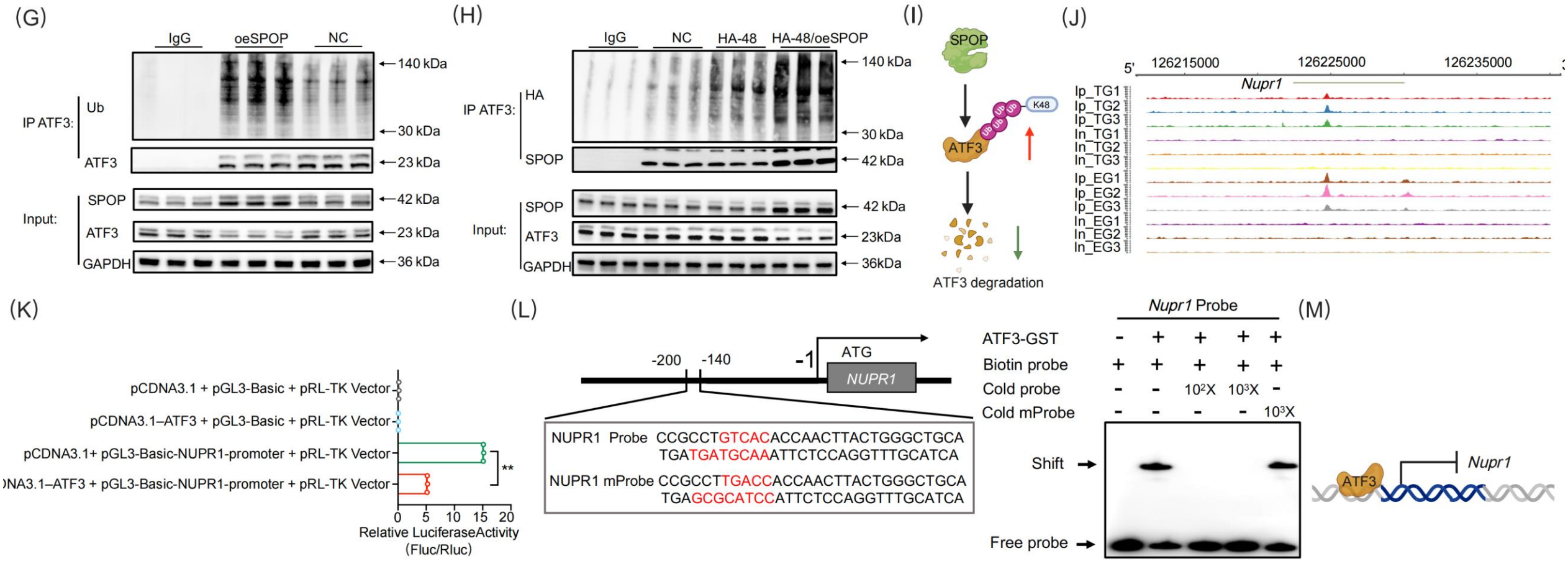

Figure 4. SPOP promotes K48-linked ubiquitination of ATF3

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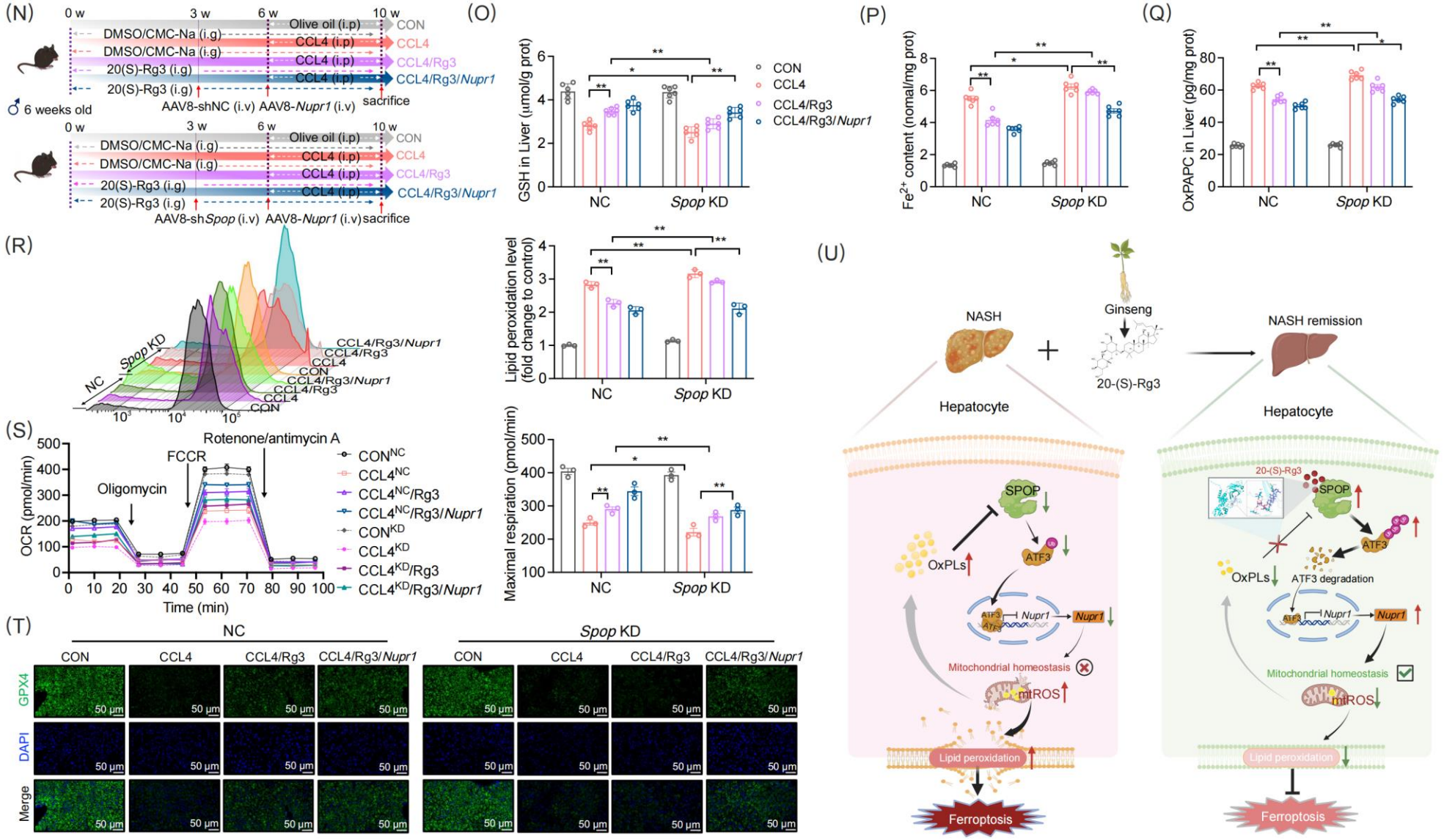

Figure 5. Nupr1 rescues the attenuation of Rg3-mediated anti-ferroptotic effects caused by SPOP knockdown in mouse liver

Summary

- This study systematically elucidates the molecular mechanism by which Rg3 alleviates NASH by suppressing OxPLs accumulation and hepatocellular ferroptosis;
- Rg3 activates SPOP to promote ATF3 ubiquitination and degradation, thereby relieving the transcriptional repression of Nupr1, restoring mitochondrial homeostasis, reducing lipid peroxidation, and ultimately inhibiting ferroptosis;
- OxPL levels are markedly elevated in the livers of patients with NASH as well as in mouse models, suggesting their potential as noninvasive biomarkers.

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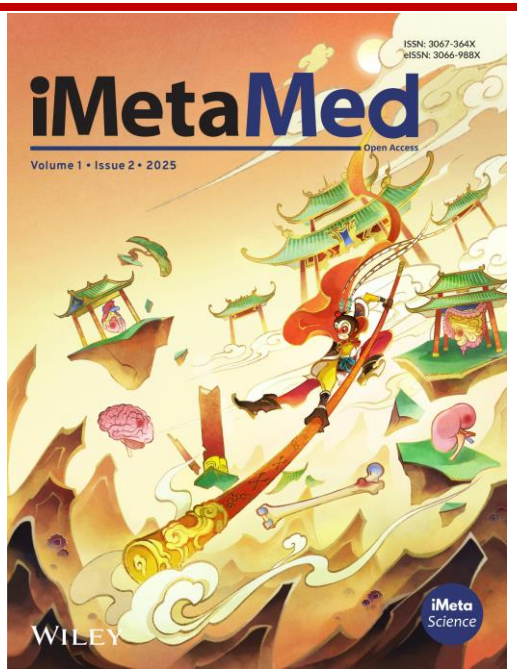

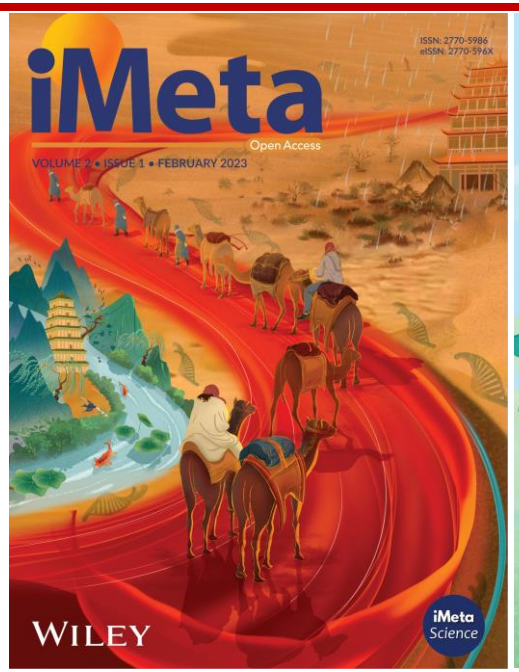

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