RRM2-targeted nanocarrier enhances radiofrequency ablation efficacy in hepatocellular carcinoma through ferroptosis amplification and immune remodeling

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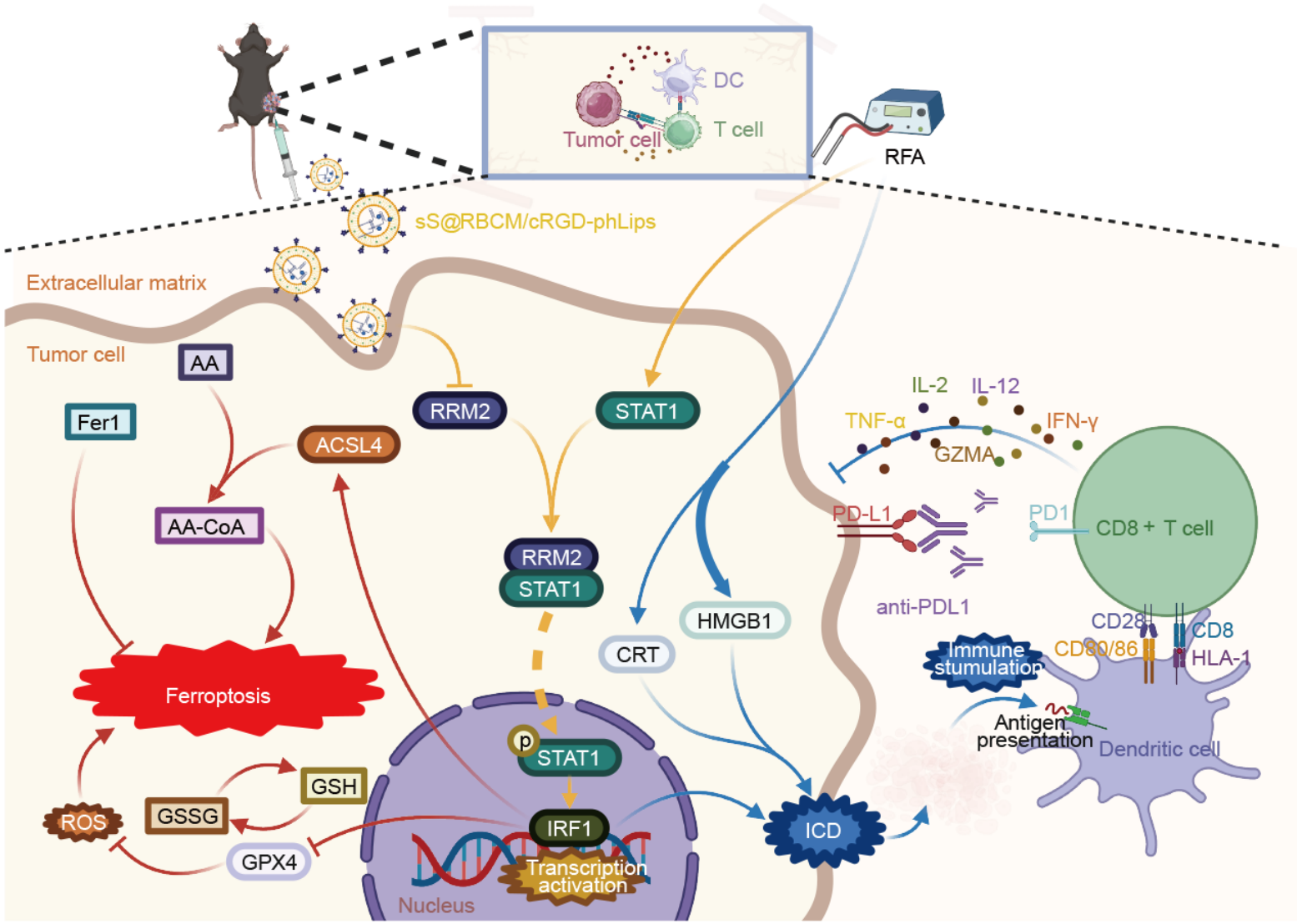
Introduction

The high incidence, mortality, heterogeneity, and recurrence of HCC limit single therapies. SPIO-enhanced MRI improves diagnosis, and RFA boosts survival, but incomplete ablation and recurrence require combination treatments.

RRM2 is vital for DNA synthesis, repair, and tumor immunity. In HCC, its overexpression inhibits ferroptosis by regulating GSH. While RRM2 knockout induces ferroptosis, its role in RFA-induced ablation and TME modulation is unclear.

This study developed a TME-responsive nanosystem (sgRRM2/SPIO@RBCM/cRGD-phLips) that integrates RRM2 knockout-induced ferroptosis and TME modulation to significantly enhance HCC treatment efficacy while elucidating its underlying molecular mechanisms.

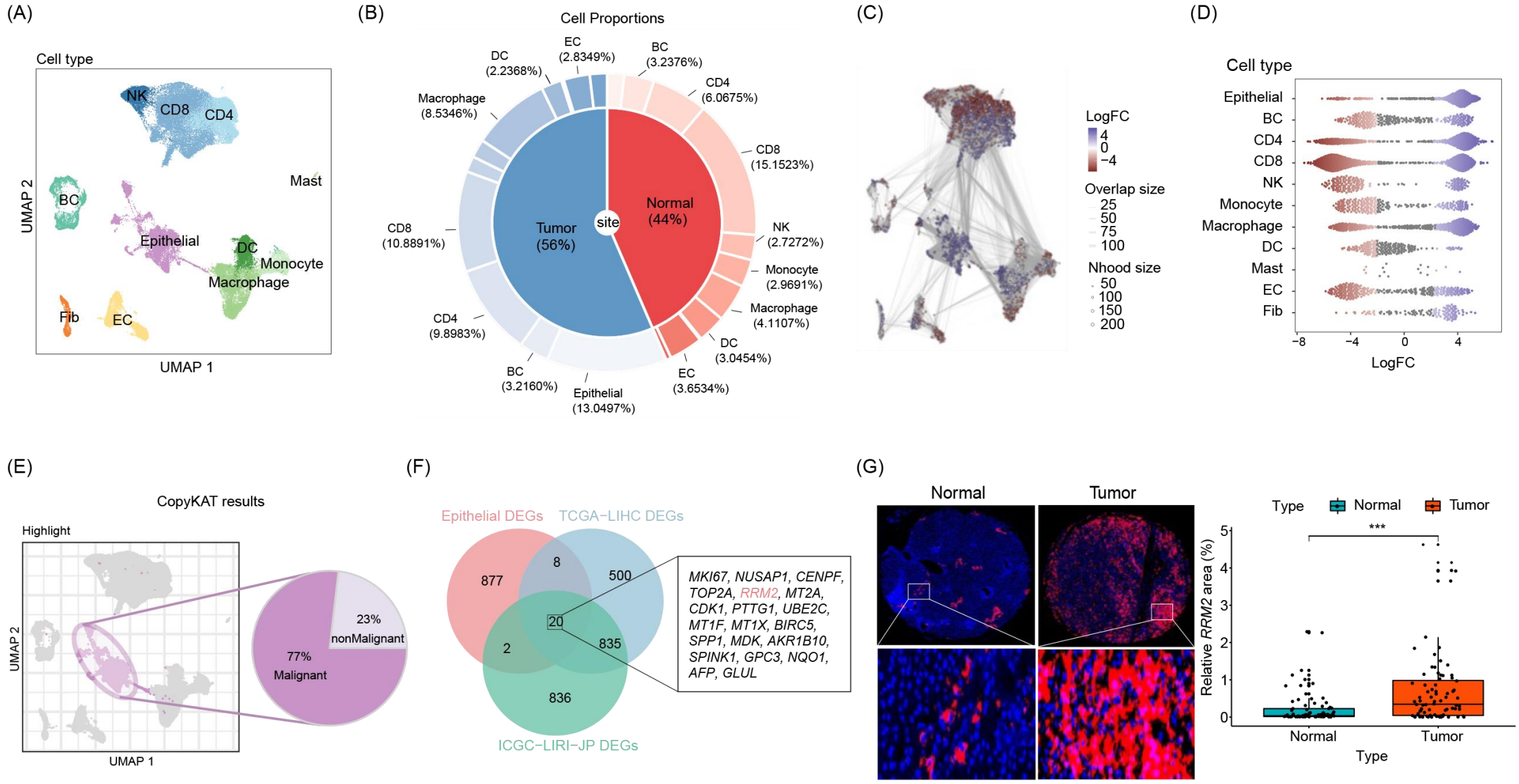
Highlights



- Targeting RRM2 with a nanocarrier boosts RFA efficacy in HCC by promoting ferroptosis.
- The sS@RBCM/cRGD-phLips nanoplatform activates the STAT1-IRF1-ACSL4 pathway to enhance ferroptosis.
- RRM2 knockout reshapes the tumor immune microenvironment by enhancing DC maturation and CD8+ T cell infiltration.
- Combining therapy with antiPDL1 improves tumor suppression and extends survival in HCC models.

Results

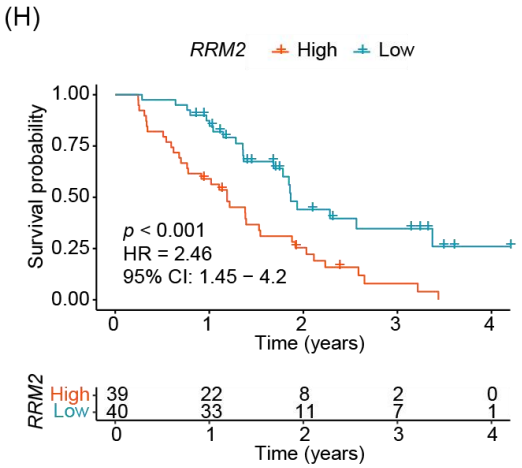
◆ High expression of RRM2 in HCC tissues after radiofrequency ablation (RFA) is closely associated with poor prognosis

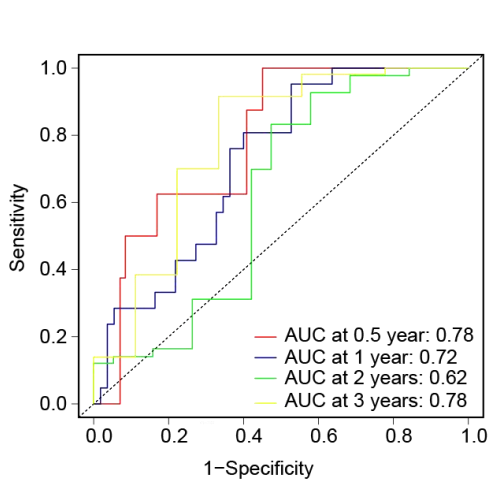


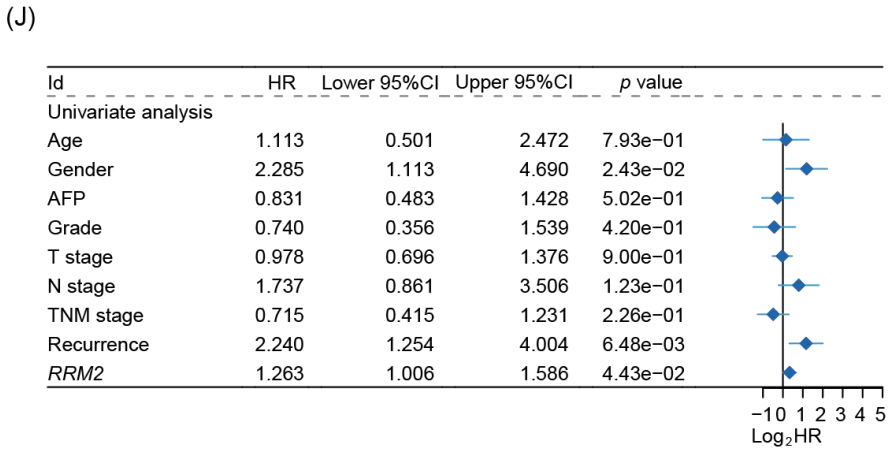
scRNA-seq analysis revealed increased proportions of epithelial cells and macrophages in HCC tissues, and identified 20 key genes.

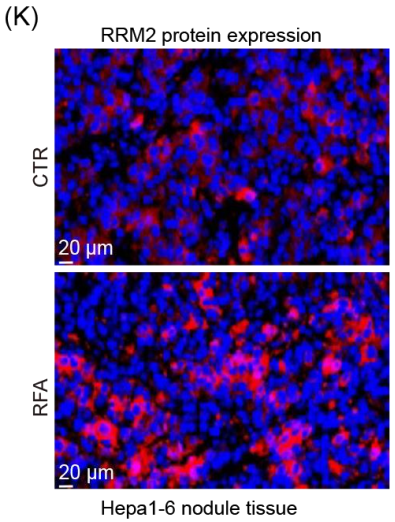
Results

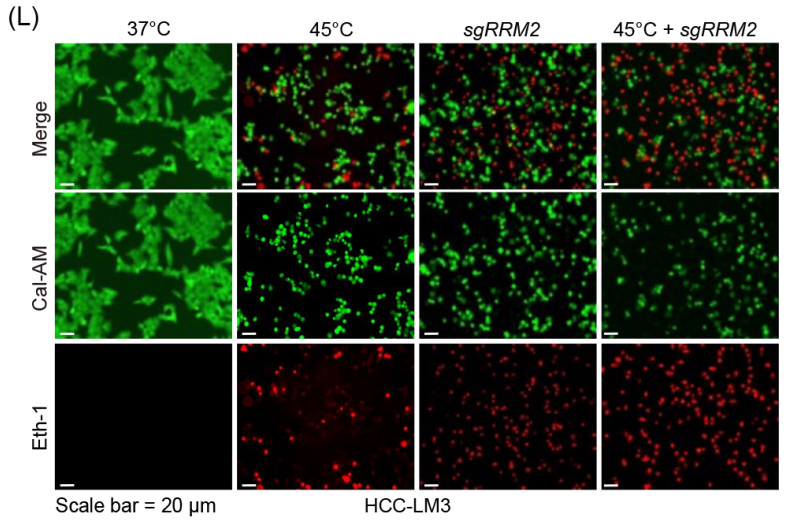
◆ High expression of RRM2 in HCC tissues after radiofrequency ablation (RFA) is closely associated with poor prognosis

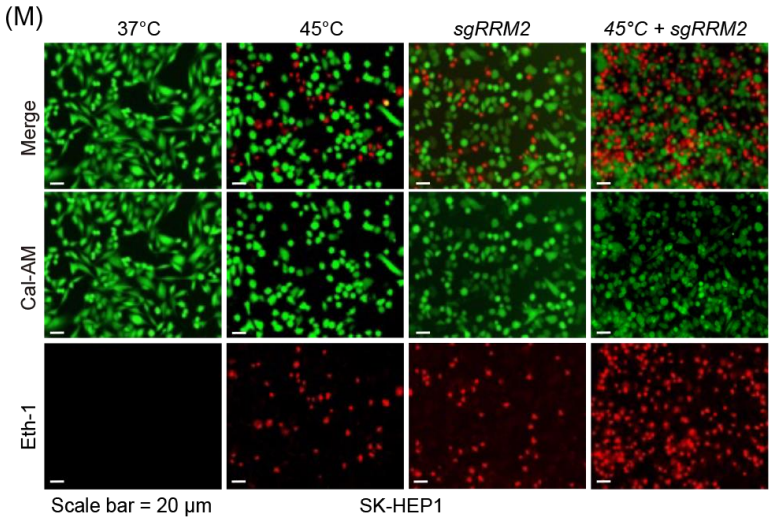








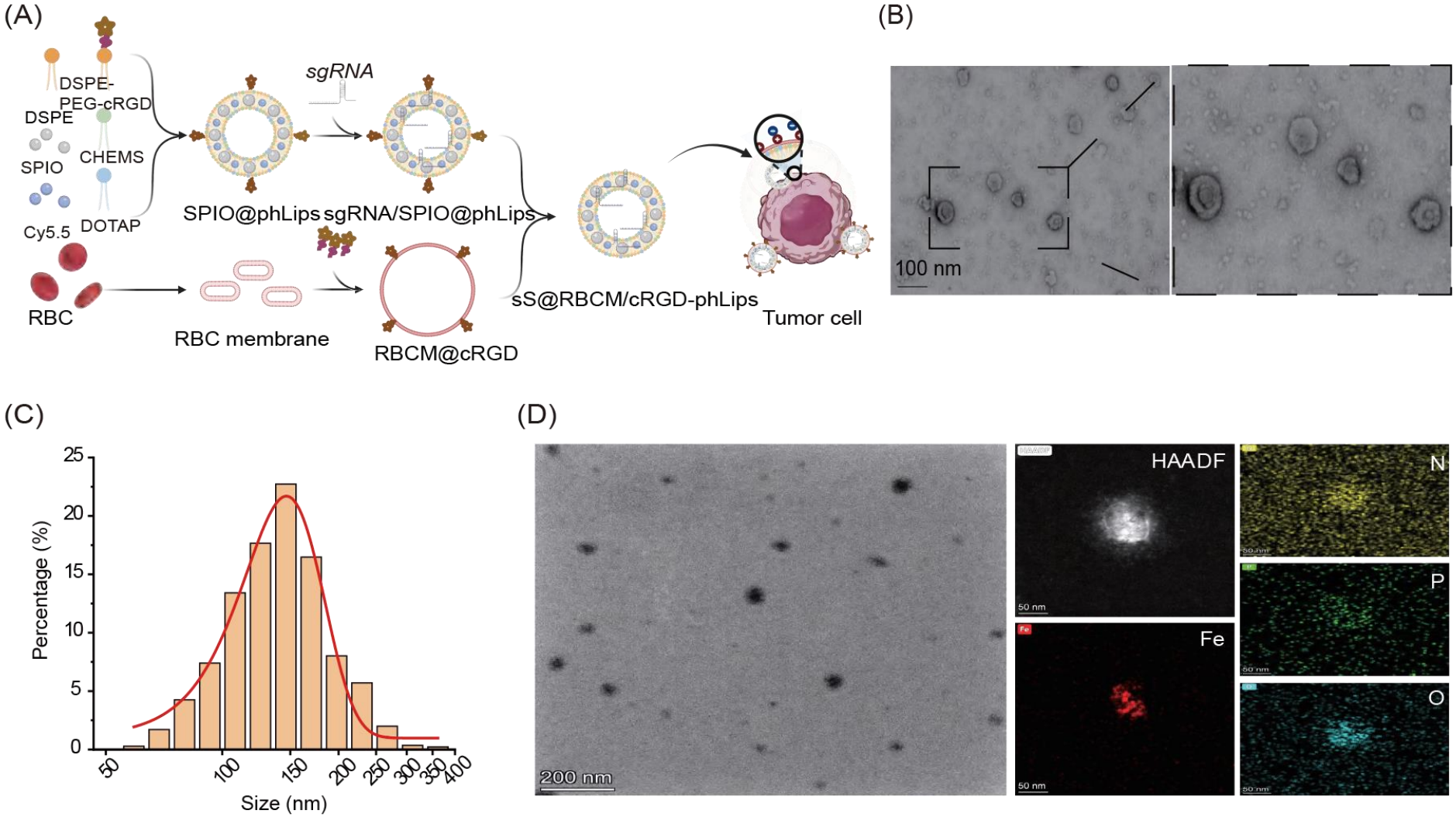




RRM2 is highly expressed in HCC and linked to poor prognosis. Its expression increases after RFA. RRM2 knockout with RFA significantly induces HCC cell death.

Results

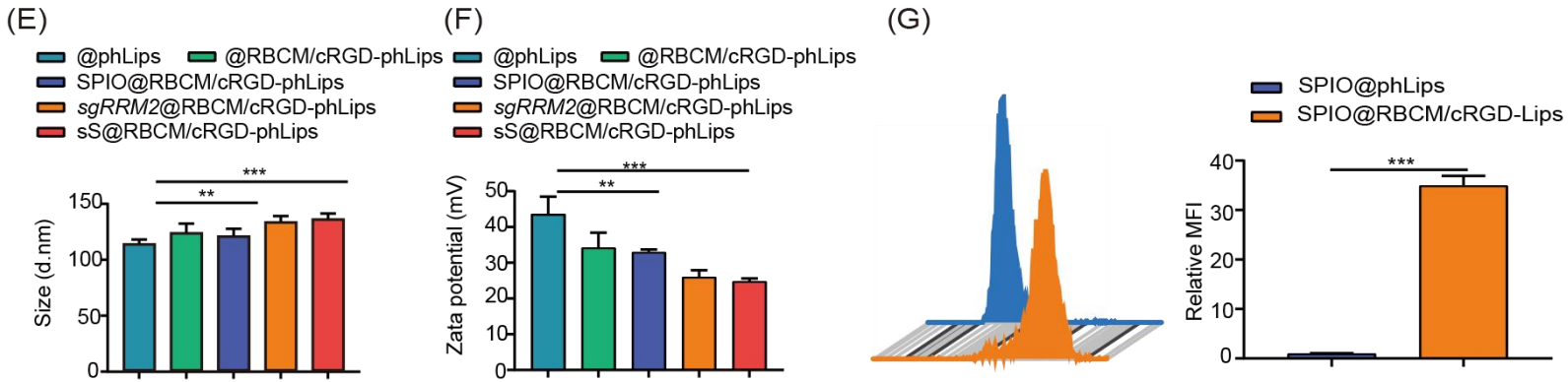
- **Liposomal nanocarriers efficiently and stably deliver sgRRM2, optimizing tumor targeting**

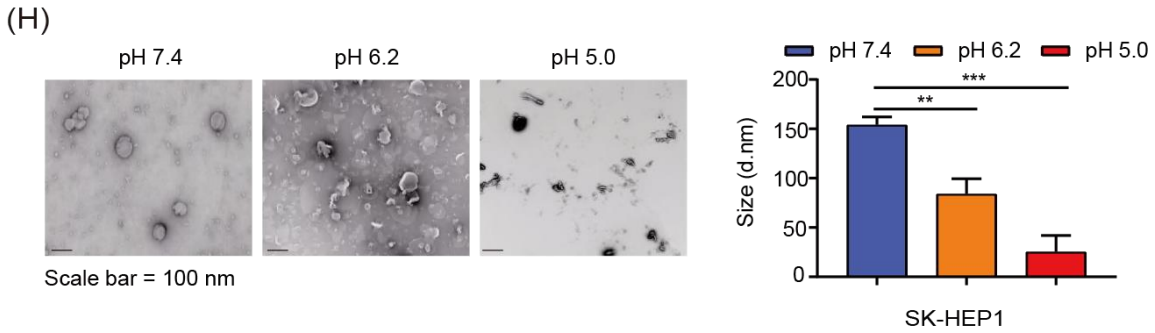


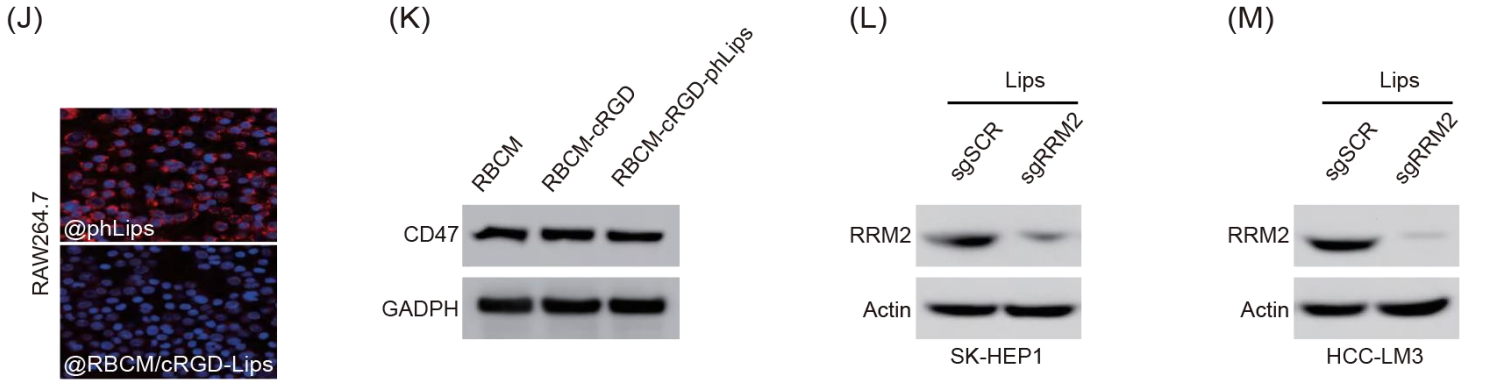
The modified nanoparticles exhibit superior tumor-targeting ability. Under the acidic tumor microenvironment, the nanoparticles undergo a morphological transformation and release their therapeutic payload.

Results

- **Liposomal nanocarriers efficiently and stably deliver sgRRM2, optimizing tumor targeting**



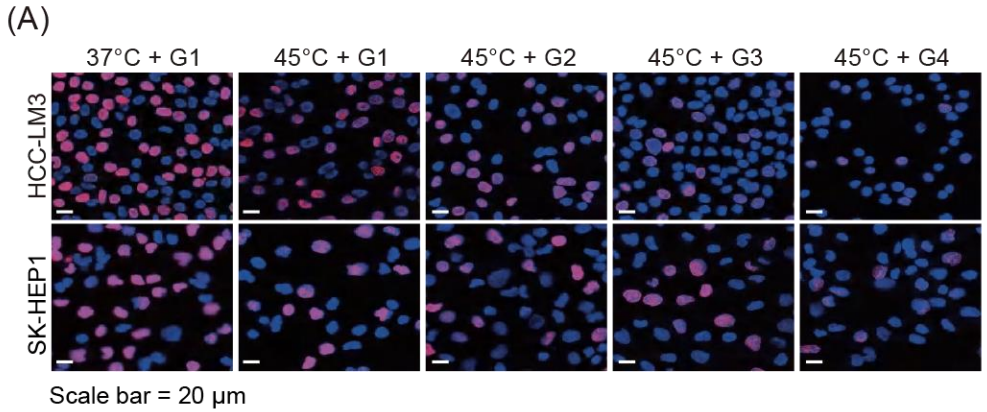


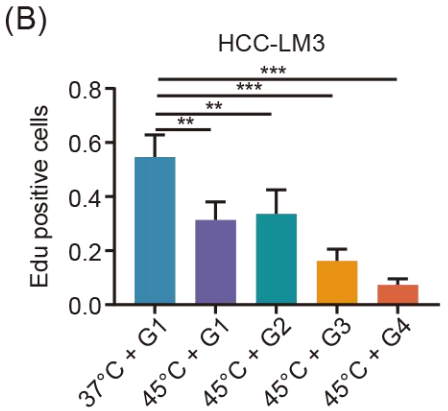


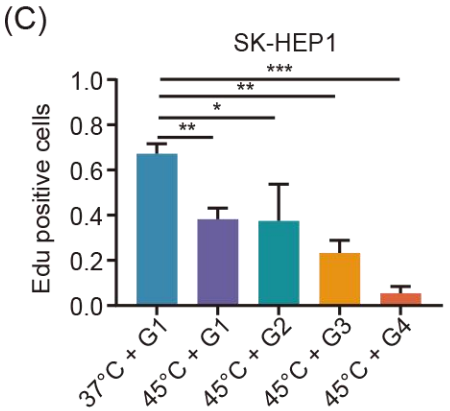
CD47 inhibits macrophage phagocytosis. sgRRM2 suppresses RRM2 expression. SPIO shows low toxicity and improves MRI diagnostics.

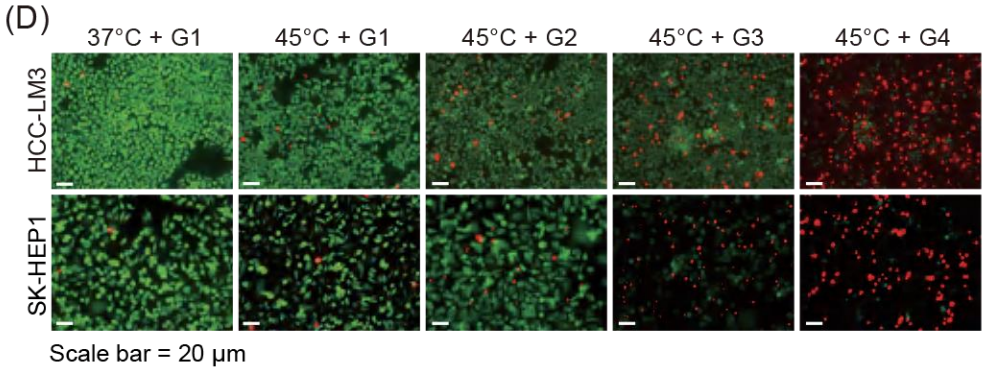
Results

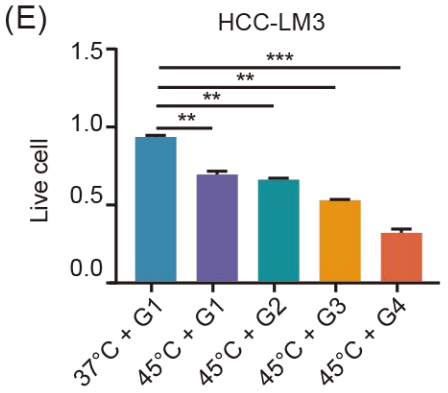
◆ Synergistic delivery of SPIO and sgRRM2 via nanocarriers enhances ferroptosis in HCC

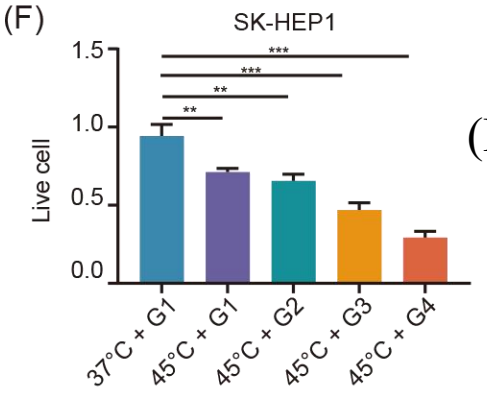


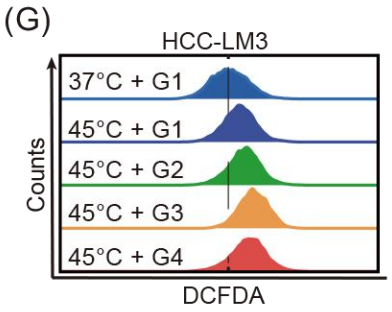


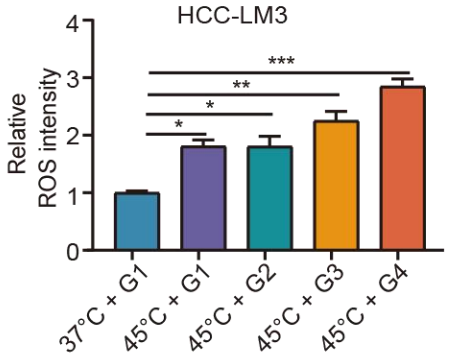


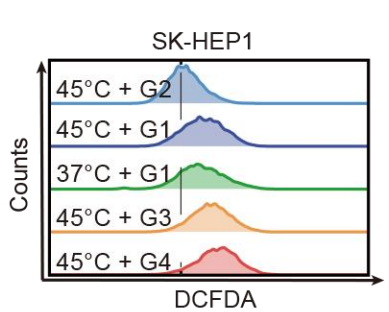


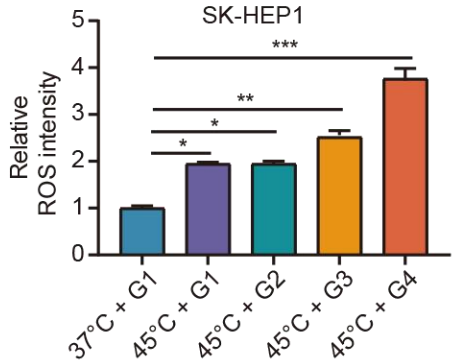








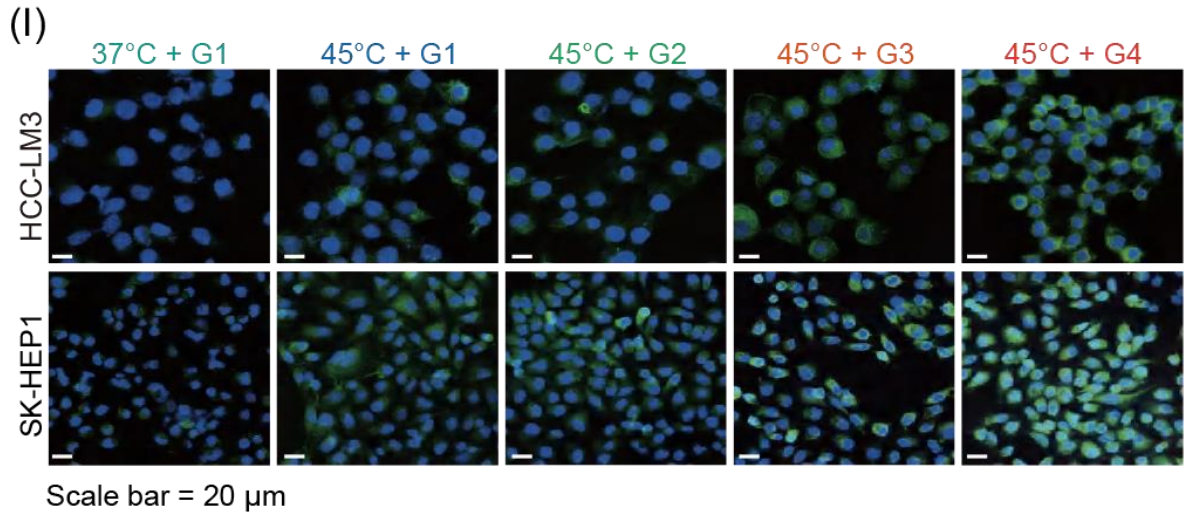


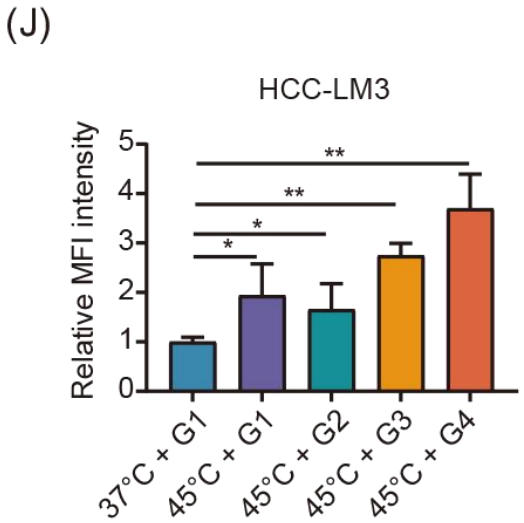


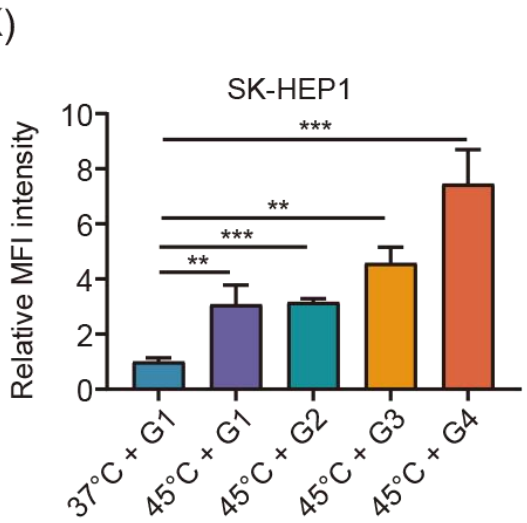
The dual-loaded nanoparticles (G4) exert their effects by triggering ferroptosis, increasing reactive oxygen species (ROS), lipid peroxidation, and iron levels.

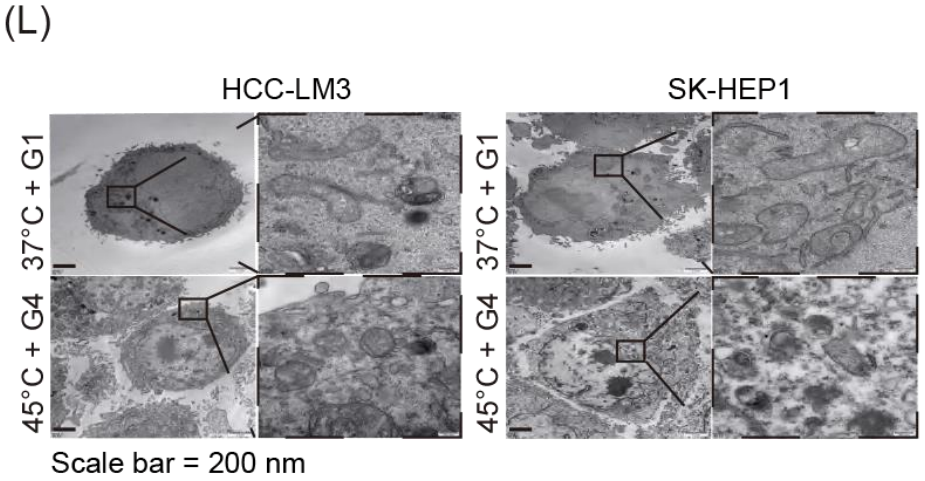
Results

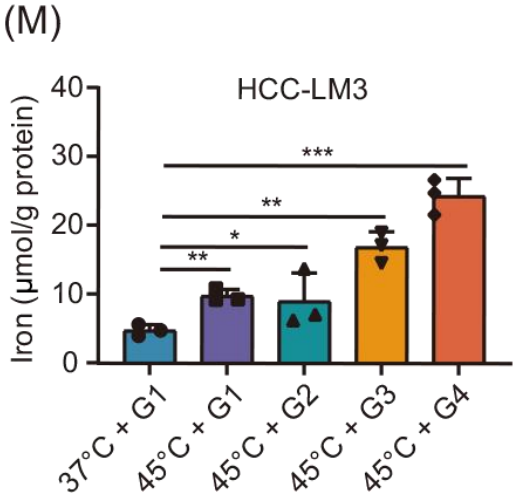
◆ **Synergistic delivery of SPIO and sgRRM2 via nanocarriers enhances ferroptosis in HCC**

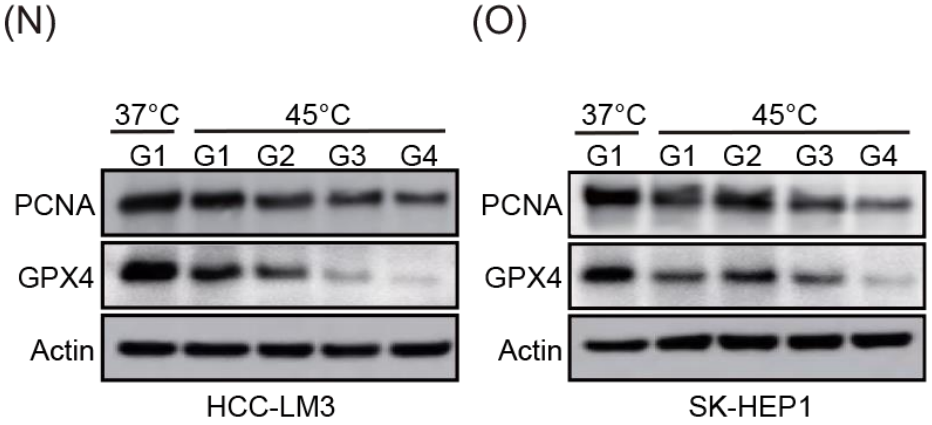








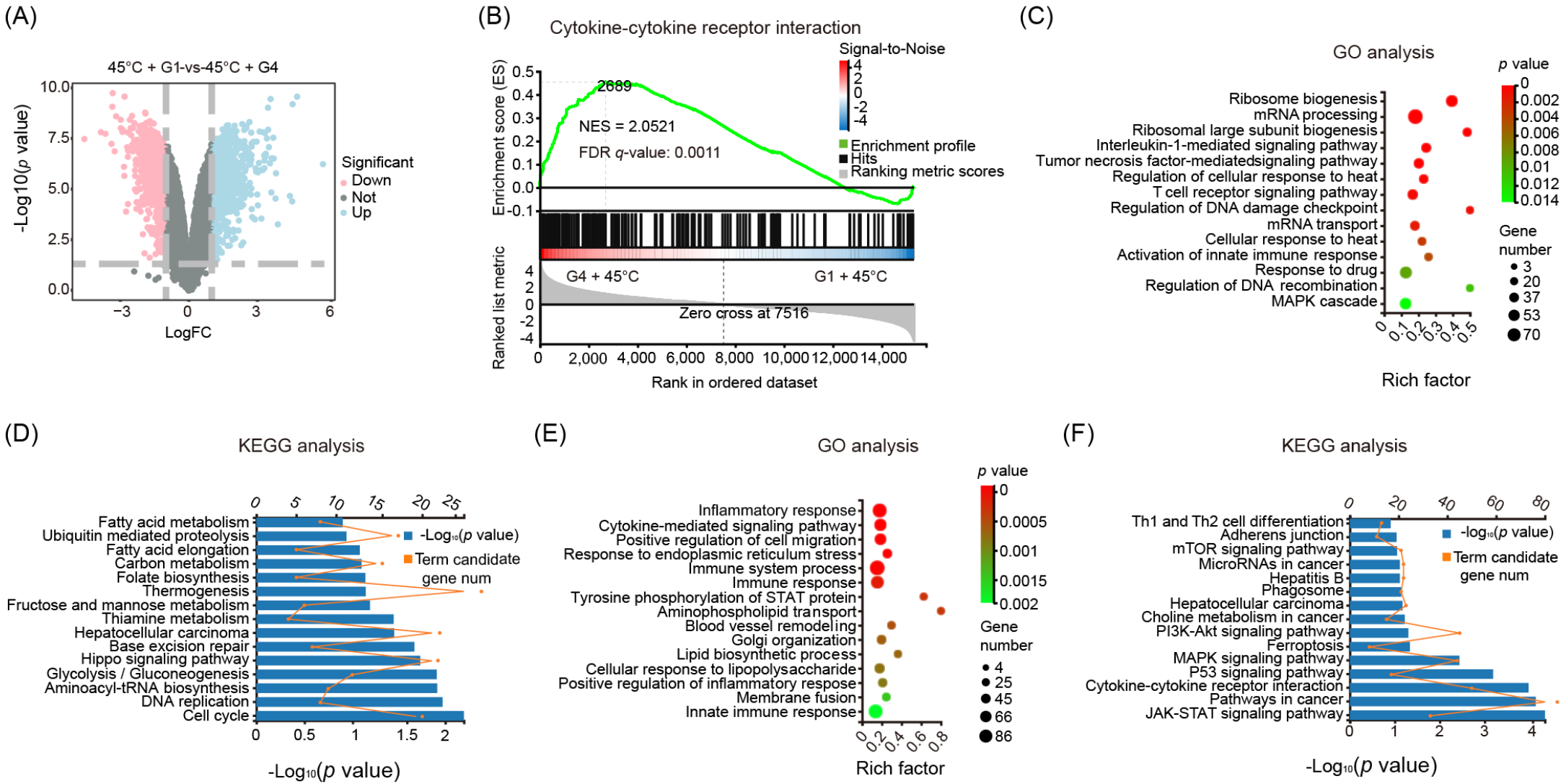




Simultaneously reducing glutathione (GSH) and glutathione peroxidase 4 (GPX4) significantly enhances antitumor effects, thereby inhibiting tumor growth and inducing cell death.

Results

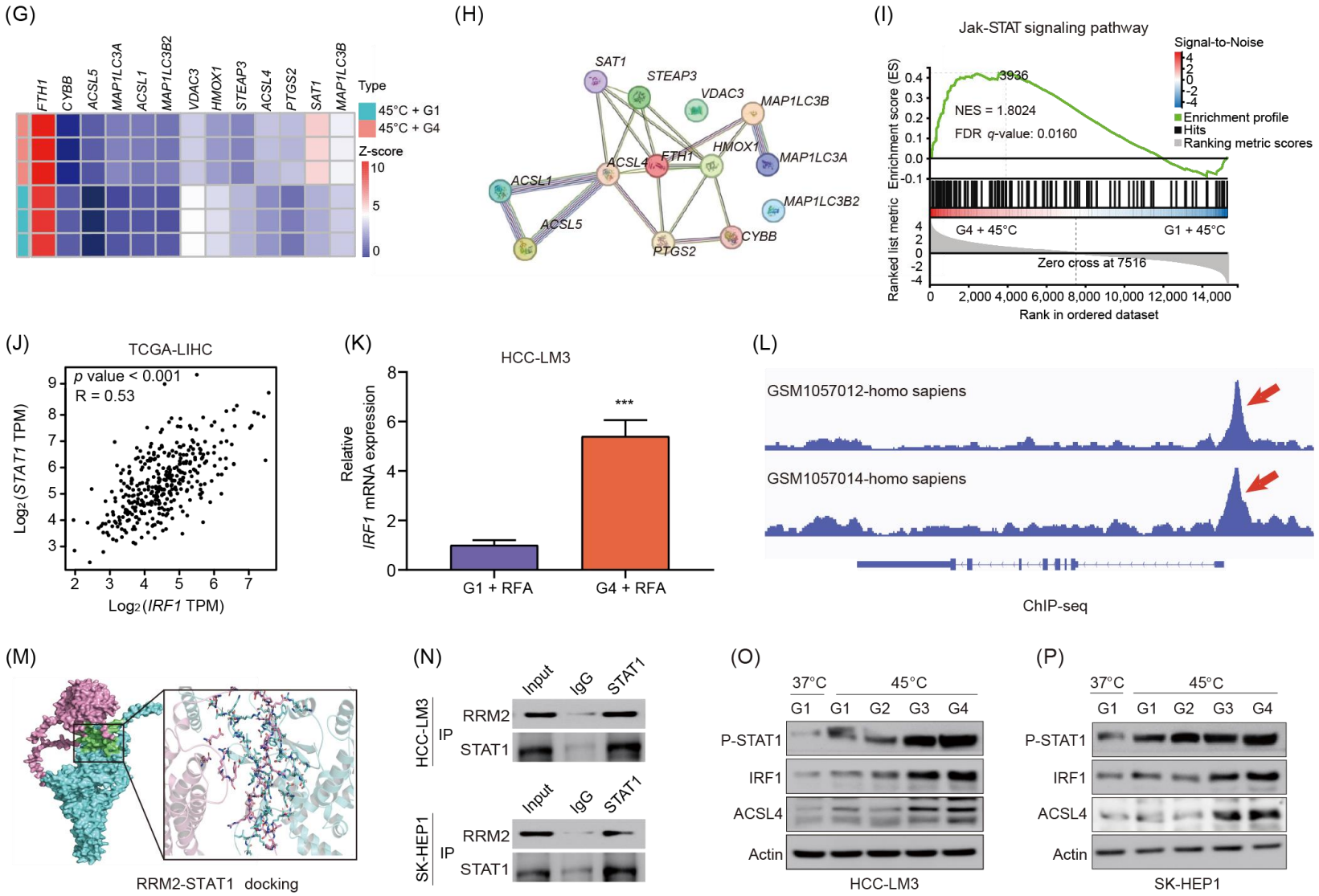
◆ RRM2-targeting nanocarriers upregulate the STAT1-IRF1-ACSL4 axis in HCC



G4 nanoparticles activate ferroptosis, cytokine signaling pathways, and fatty acid metabolism by knocking down RRM2 and upregulating ACSL4 expression.

Results

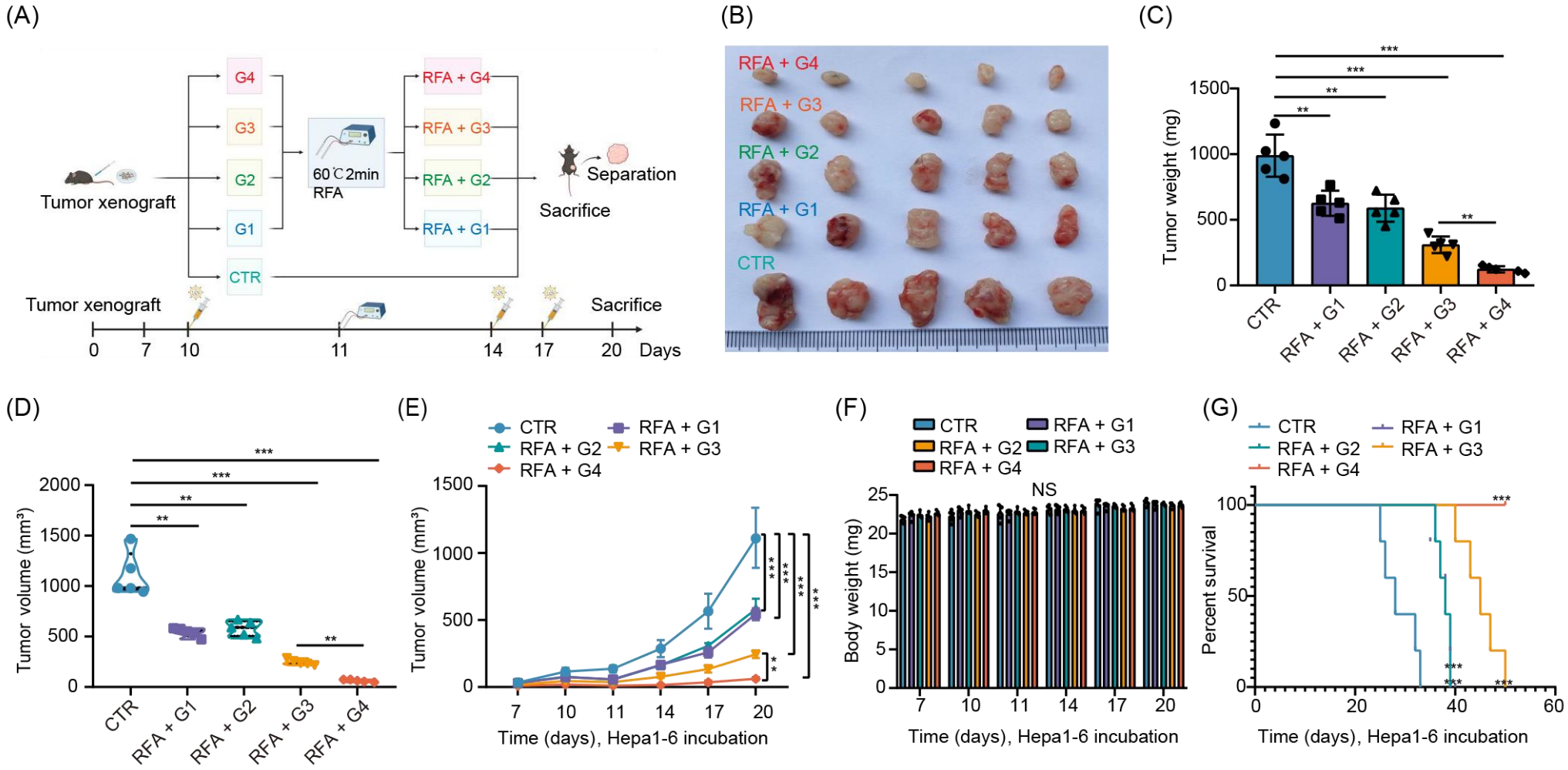
◆ RRM2-targeting nanocarriers upregulate the STAT1-IRF1-ACSL4 axis in HCC



In combination with RFA, they enhance the STAT1-IRF1-ACSL4 axis, thereby improving the antitumor effects against HCC.

Results

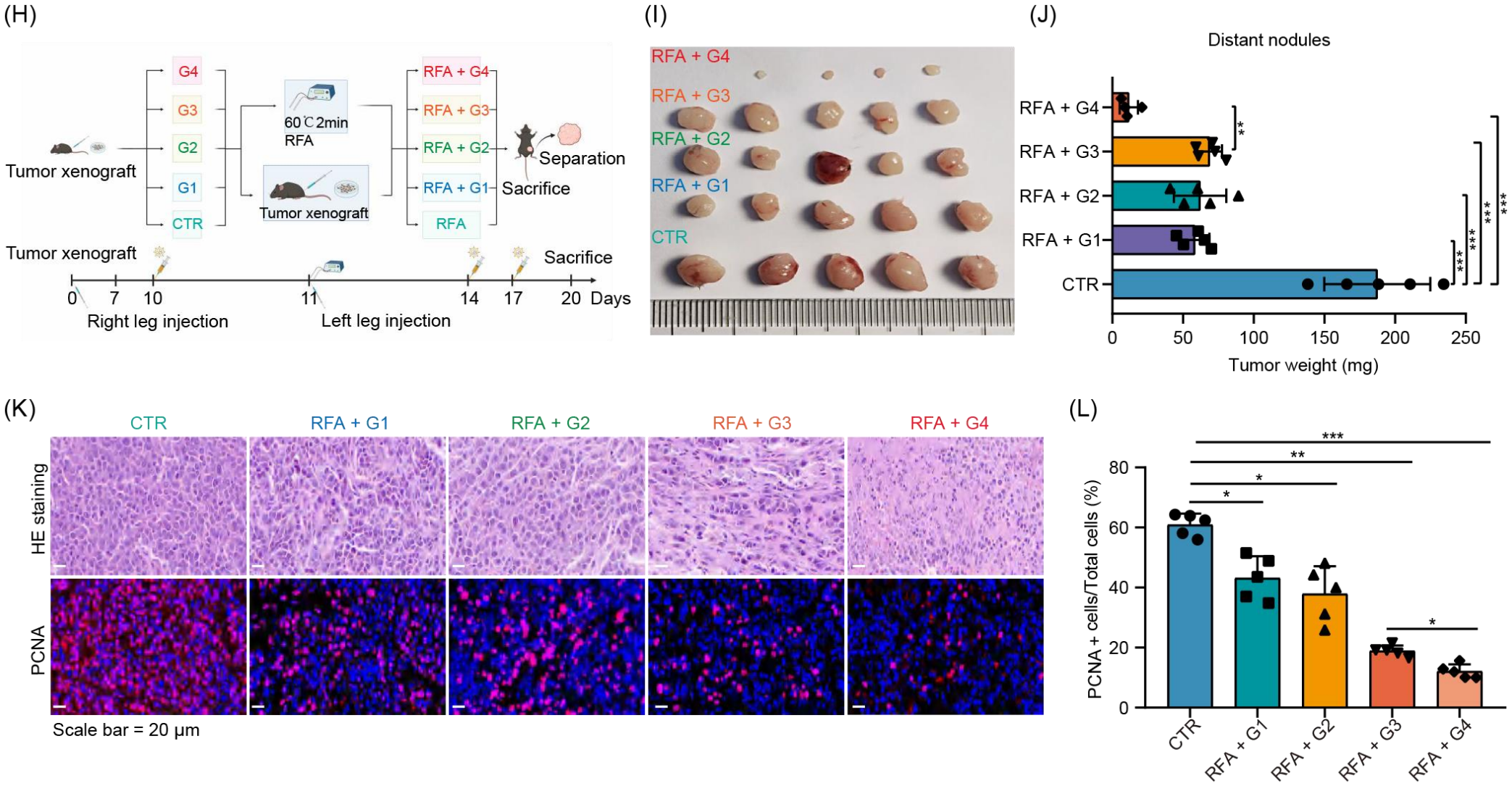
◆ The co-delivery nanocarrier system exhibits low toxicity and enhances the anti-tumor efficacy of RFA



In vitro, SPIO and RRM2 knockout nanoparticles enhanced antitumor effects. In vivo, they inhibited tumor growth, reduced tumor size, extended survival, and showed good biocompatibility.

Results

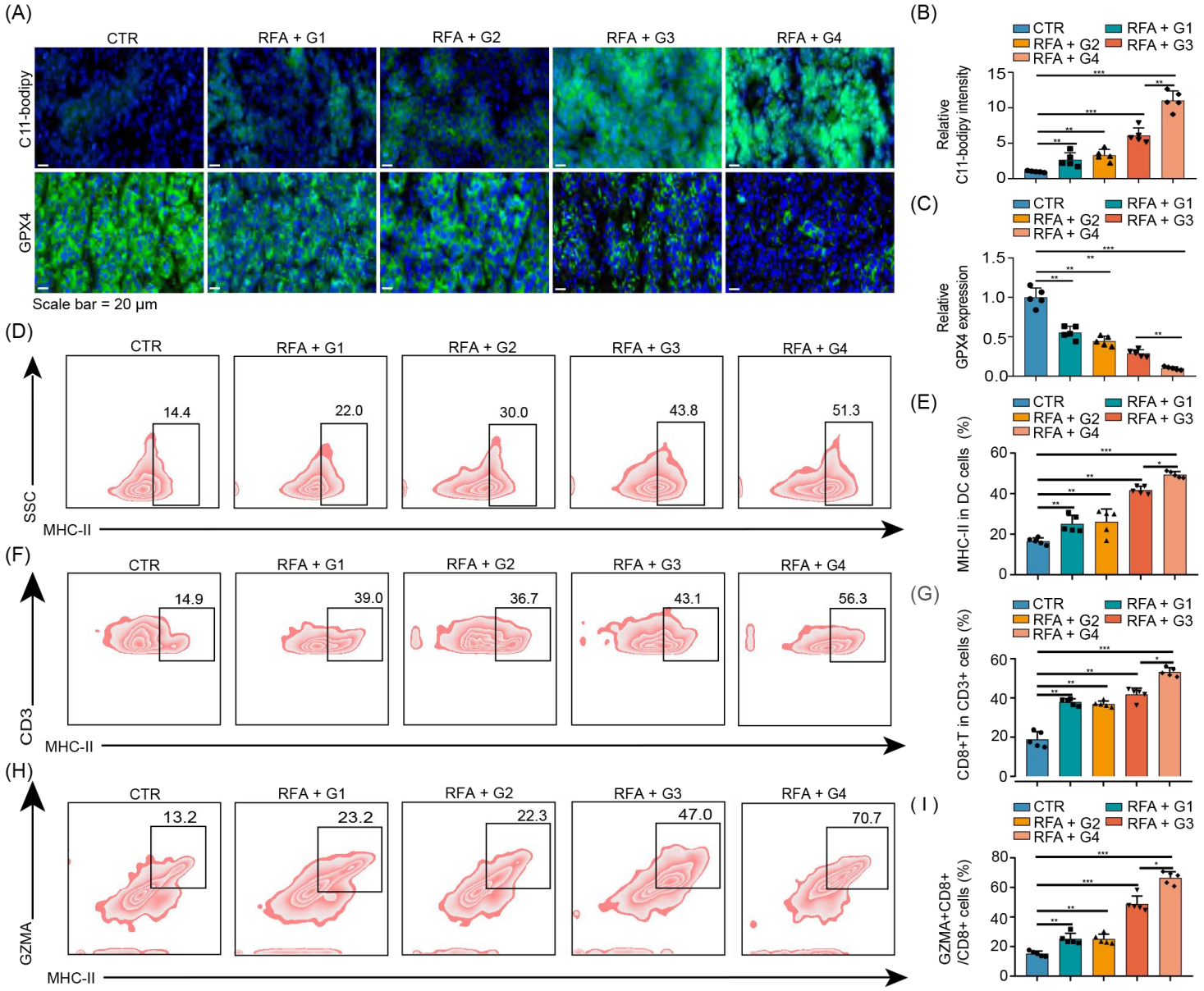
◆ The co-delivery nanocarrier system exhibits low toxicity and enhances the anti-tumor efficacy of RFA



Their efficacy was also validated in a metastasis model.

Results

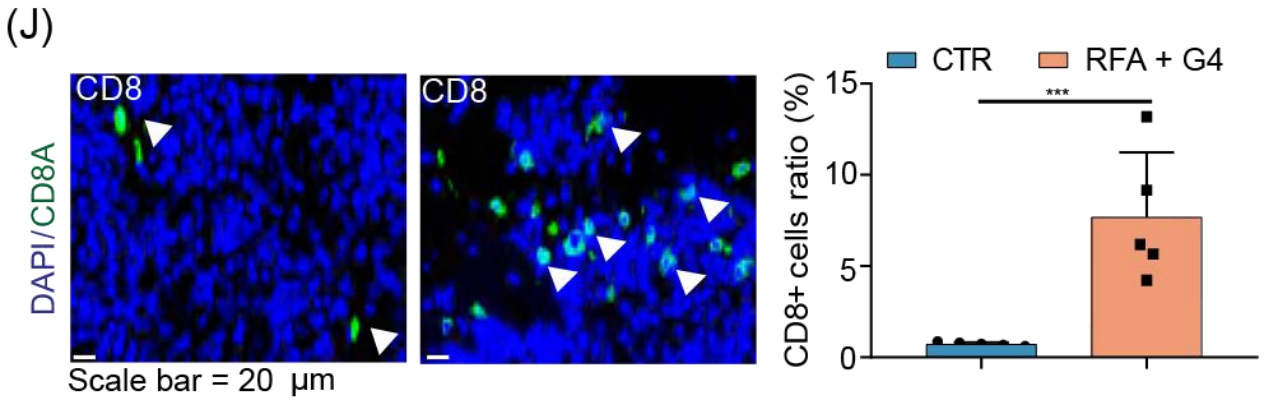
◆ The co-delivery nanocarrier system enhances anti-tumor immunity and modulates the TME

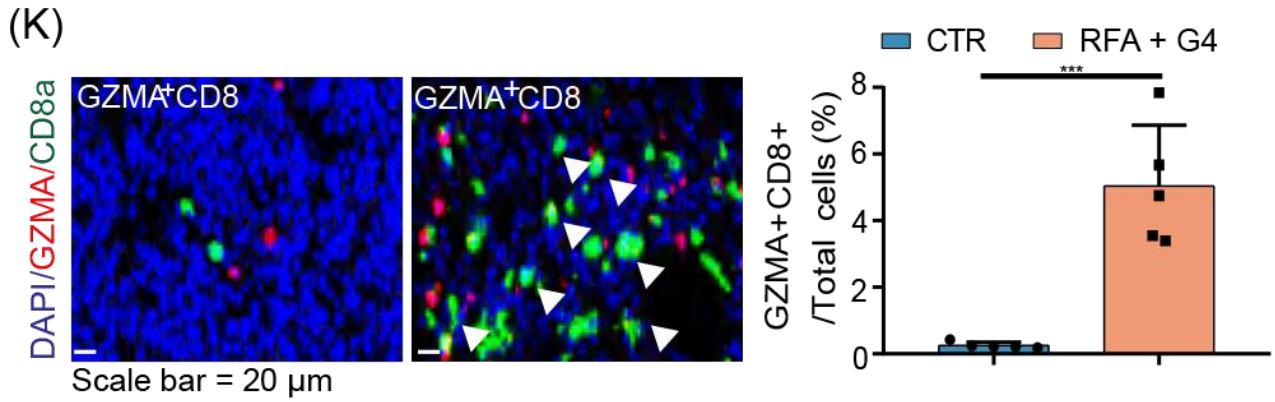


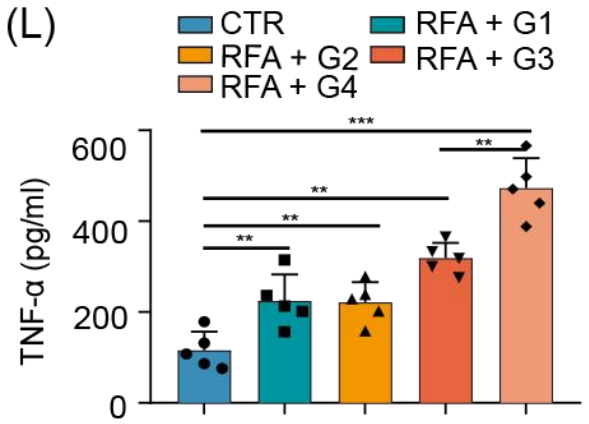
RFA-induced ferroptosis and immune responses inhibited tumor progression with lipid peroxidation and GPX4 inhibition.

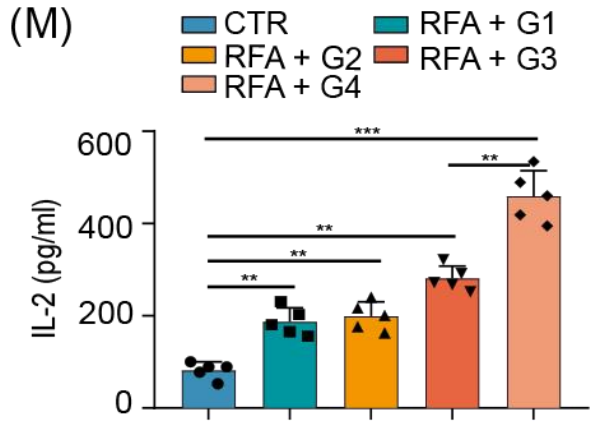
Results

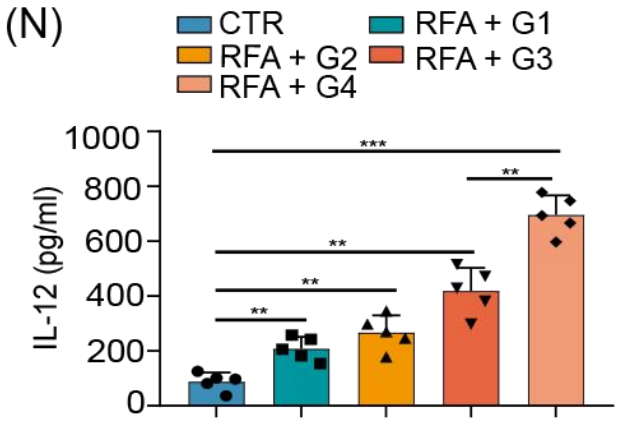
◆ **The co-delivery nanocarrier system enhances anti-tumor immunity and modulates the TME**

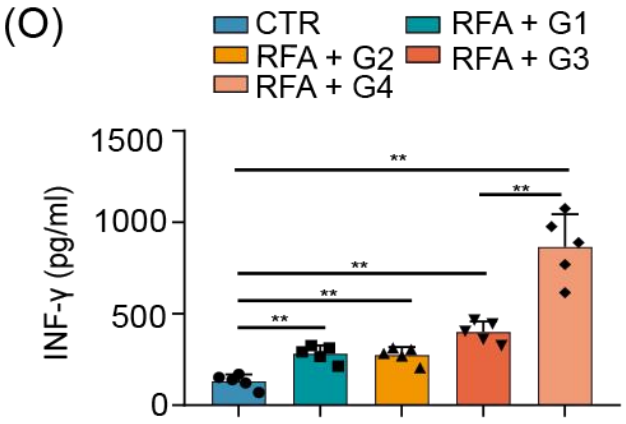








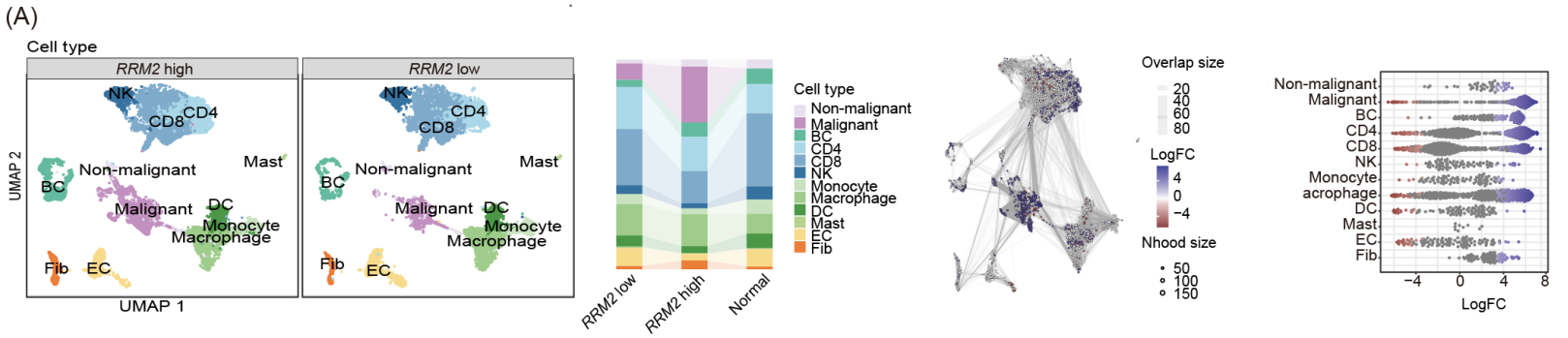


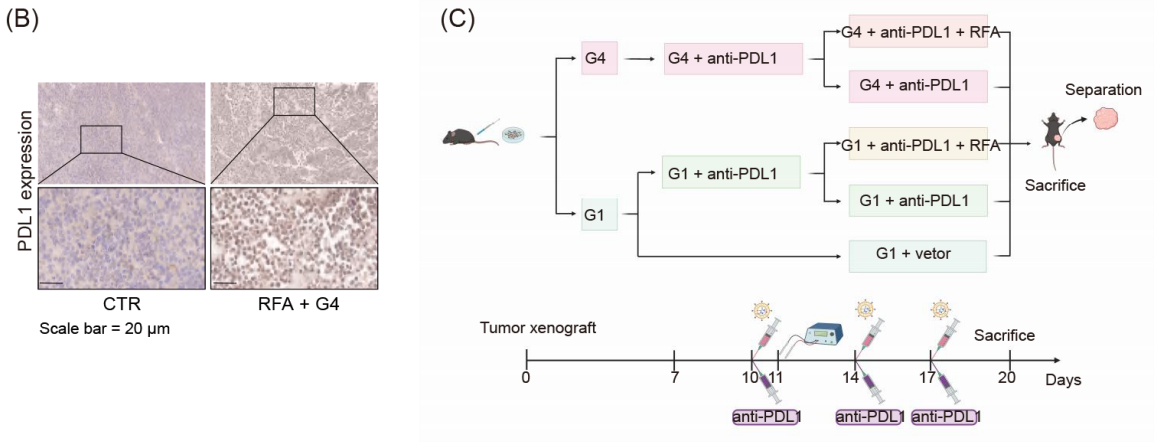


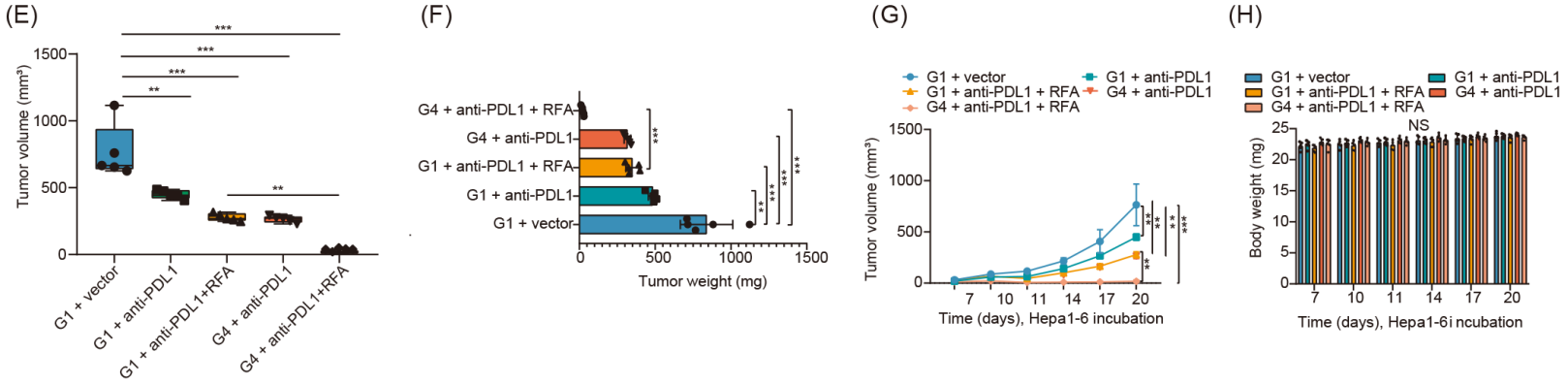
As well as a significant increase in CD8+ cytotoxic T cells and antitumor cytokines.

Results

◆ RRM2-targeted nanoparticles combined with RFA enhance anti-PD-L1 efficacy in HCC



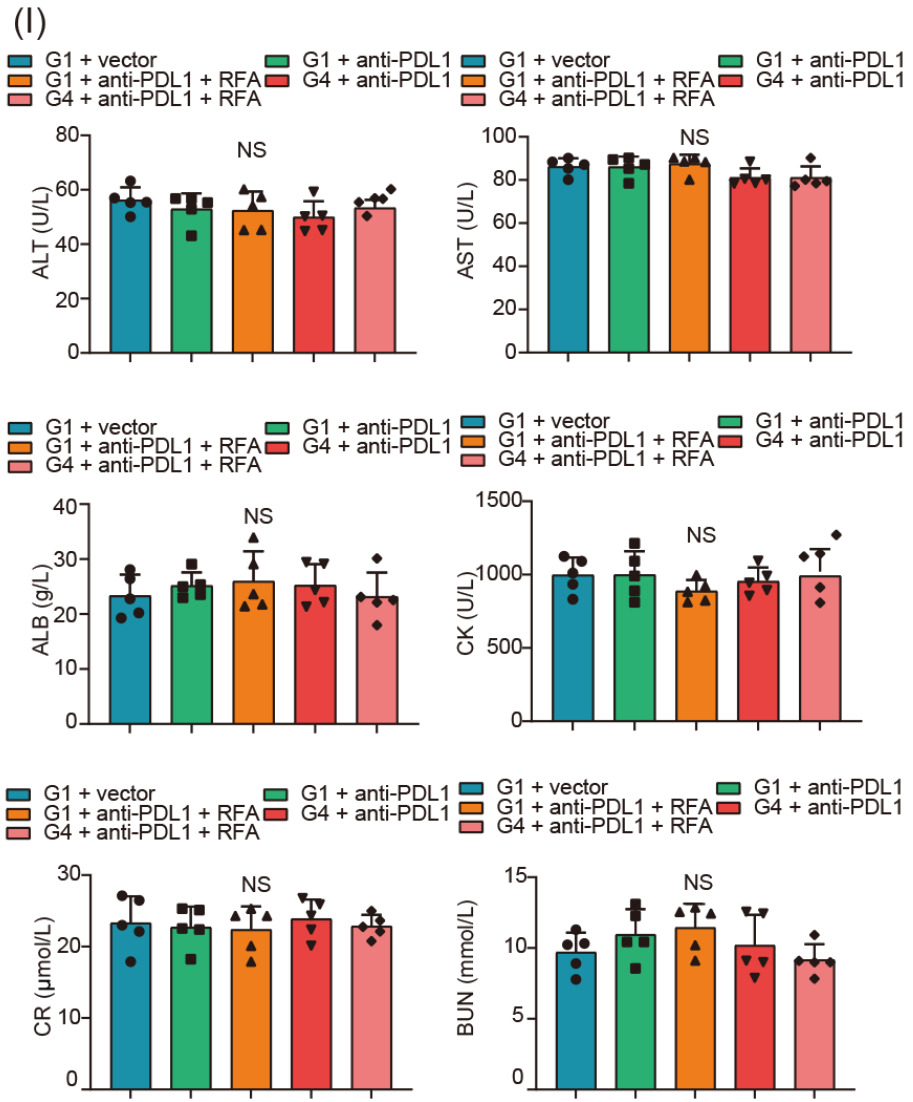


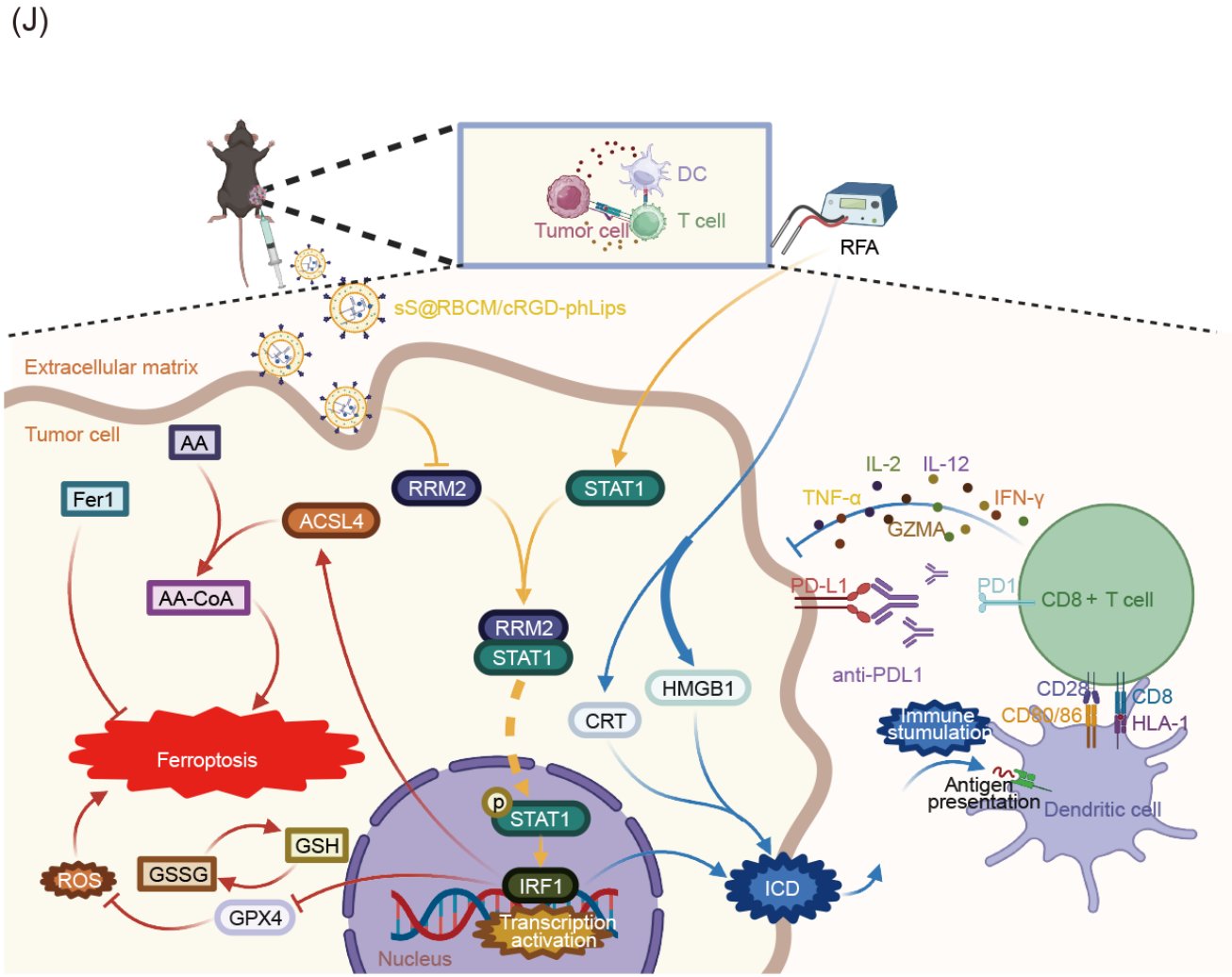


RRM2 knockout reduced malignant cells, increased CD8+ T cells and dendritic cells, and elevated PDL1 expression.

Results

RRM2-targeted nanoparticles combined with RFA enhance anti-PD-L1 efficacy in HCC





The combination of nanoparticles with anti-PDL1 therapy effectively inhibited the progression of HCC. The optimized nanoparticles further improved immune response and therapeutic efficacy.

Summary

- RRM2-targeted nanoparticles combined with RFA enhanced HCC treatment by inducing ferroptosis, promoting ICD, and modulating the TME to inhibit tumor growth and recurrence.

- The nanoparticles boosted RFA-induced PDL1 upregulation, and combining this with PDL1 inhibition activated DCs and CD8+ T cells, improving the anti-tumor immune response.

- The nanoplatform, with high tumor targeting and controlled release, synergizes PDL1 blockade and RFA to improve HCC prognosis.

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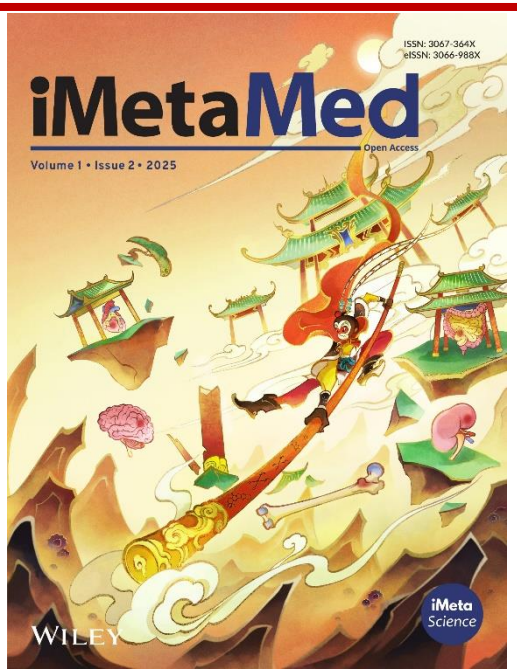

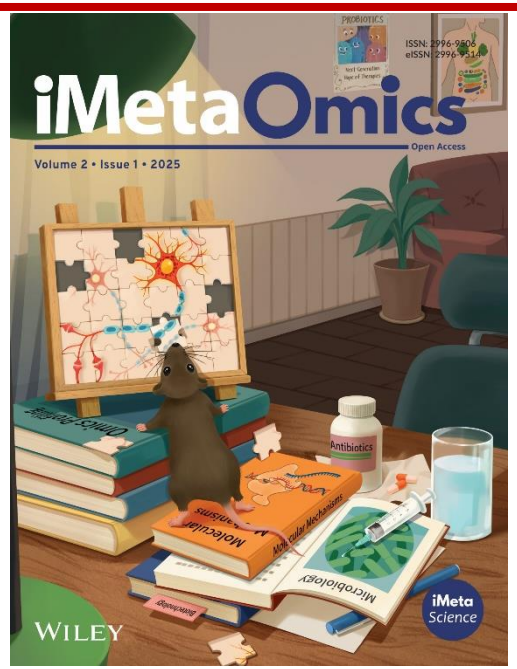

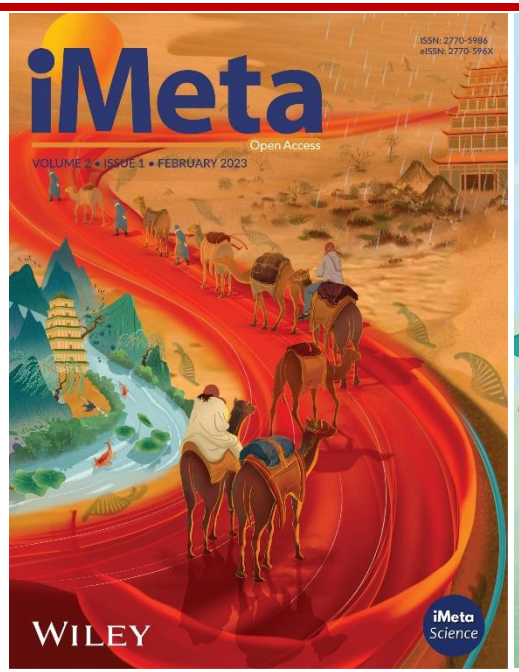

"***iMeta***" launched in 2022 by iMeta Science Society, impact factor (IF) **33.2**, ranking top 65/22249 in world and 2/161 in the microbiology. It aims to publish innovative and high-quality papers with broad and diverse audiences. **Its scope is similar to *Cell*, *Nature Biotechnology/Methods/Microbiology/Medicine/Food***. Its unique features include video abstract, bilingual publication, and social media with 600,000 followers. Indexed by **SCIE/ESI**, **PubMed**, **Google Scholar** etc.

"***iMetaOmics***" launched in 2024, with a **target IF>10, and its scope is similar to *Nature Communications*, *Cell Reports***, *Microbiome, ISME J, Nucleic Acids Research, Briefings in Bioinformatics,* etc.

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