

Mechanistic Study of Ion-Exchange Strategy for Regulating Multi-Metal Homeostasis to Ameliorate Mitochondrial Dysfunction in Radiation-Induced Oral Mucositis

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INTRODUCTION & AIM

Radiation-induced oral mucositis (RIOM) is a common and severe complication of radiotherapy for head and neck cancers. Preliminary studies by the applicant revealed that RIOM is not merely characterized by isolated iron overload, but rather exhibits a novel pathological feature of multi-metal dyshomeostasis, specifically "iron overload accompanied by zinc/magnesium depletion." Accordingly, we propose the hypothesis that this multi-metal dyshomeostasis serves as a critical upstream mechanism driving RIOM repair failure by activating ferroptosis and inducing mitochondrial dysfunction. Consequently, the targeted reconstruction of local metal homeostasis is expected to achieve synergistic tissue repair. Based on the competitive displacement principle of coordination chemistry, this project proposes the design and synthesis of a magnesium/zinc-curcumin complex (MgZn-Cur), which is further integrated with a γ -polyglutamic acid/polylysine network to formulate an in situ hydrogel spray (MgZn-Cur@PP). Exploiting the high stability constant between iron and curcumin, this system competitively displaces Mg and Zn within the iron-overloaded microenvironment. This enables a sophisticated ion-exchange regulation strategy that simultaneously chelates excessive iron and supplements depleted magnesium and zinc. Specifically, this study will: (1) systematically characterize the physicochemical properties and the ion-exchange mechanism of the MgZn-Cur@PP hydrogel; (2) elucidate the underlying mechanisms by which multi-metal dyshomeostasis triggers ferroptosis and mitochondrial damage; and (3) evaluate the in vivo repair efficacy and biosafety of the hydrogel spray using animal models. By interpreting the pathogenesis of RIOM from the unprecedented perspective of multi-metal dyshomeostasis, this study is expected to provide novel insights and a solid theoretical foundation for the clinical treatment of RIOM.

METHOD

[(1) By expanding the sample size, setting dose gradients and key time points, we aim to explore the regularity of the steady-state imbalance of multiple metal elements (Fe, Zn, Mg) in the RIOM, and clarify the correlation between the degree of metal steady-state imbalance and the severity and repair ability of mucosal damage.
(2) By integrating metalomics and transcriptomics data, we aim to analyze the molecular mechanism by which Zn/Mg loss and Fe overload synergistically drive ferroptosis and mitochondrial dysfunction, providing experimental evidence for the role of multi-metal steady-state imbalance as a key upstream driving factor in RIOM.
(3) Based on the principles of coordination chemistry, we construct a MgZn-Cur@PP hydrogel delivery system with "chelating iron, supplementing zinc/magnesium" triple regulatory functions, to reveal the ion exchange rules in the oral microenvironment, and evaluate its efficacy, mechanism of action and safety in restoring metal homeostasis, inhibiting ferroptosis and promoting mucosal regeneration.]

RESULTS & DISCUSSION

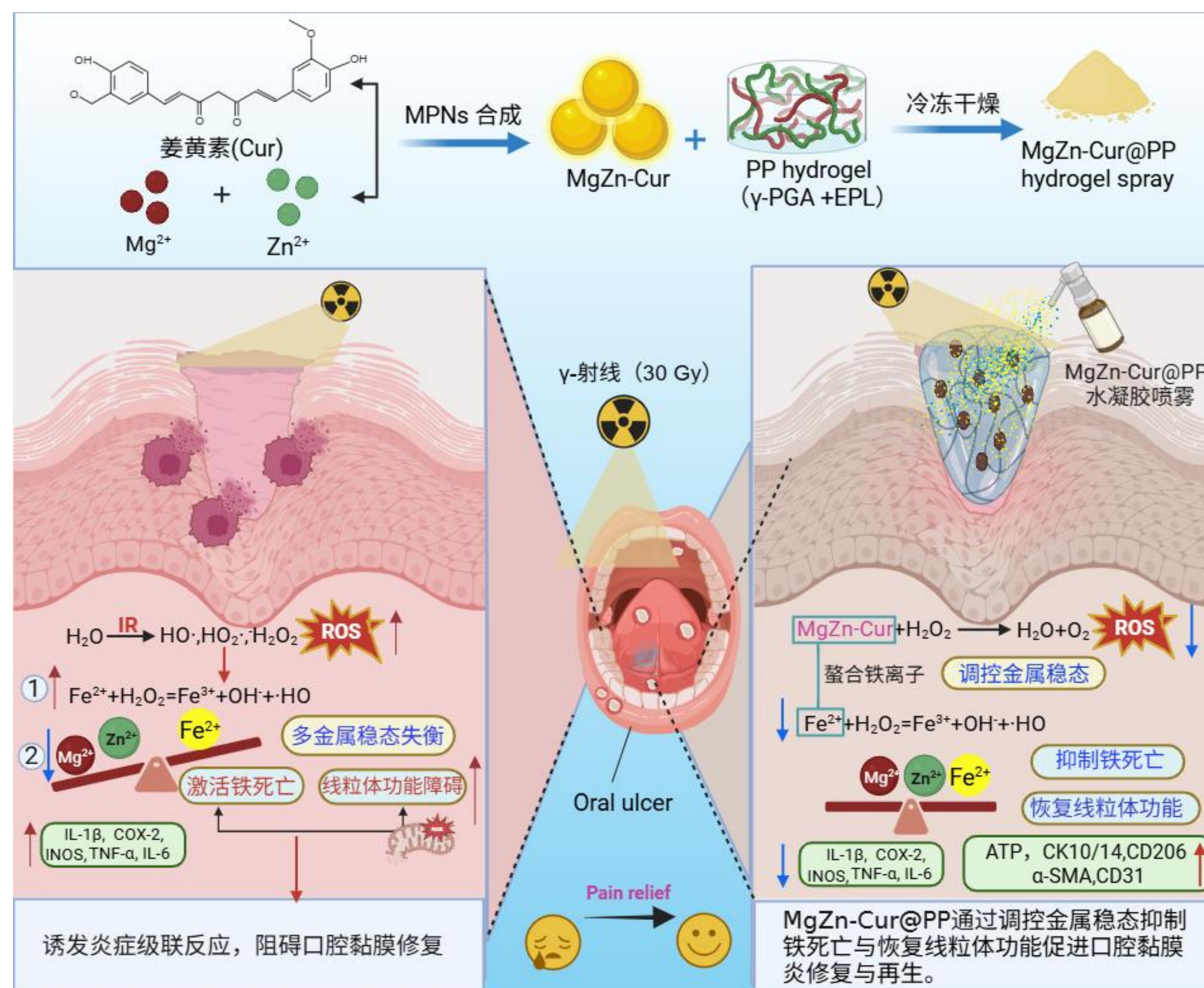


Fig 1. Schematic diagram of the treatment of radiation-induced oral mucositis with metal polyphenol hydrogel spray

[(1) Innovatively proposed to reveal the upstream pathogenic mechanism of RIOM from the perspective of "multielemental synergy imbalance", thereby expanding the limitations of the traditional "single-element" research. (2) A MgZn-Cur@PP sprayable hydrogel based on the principle of ion substitution was constructed to achieve multi-metal ion regulation (chelating iron and supplementing zinc/magnesium) using a single material system. (3) This strategy embodies the characteristics of interdisciplinary integration between medicine and engineering, providing a new perspective for the precise treatment research of tissue damage induced by radiotherapy.]

CONCLUSIONS

[(1) It reveals how the "iron overload and zinc/magnesium loss" multi-metal homeostatic imbalance induced by radiotherapy, through regulating ferroptosis and mitochondrial dysfunction, jointly mediates the occurrence and repair failure of RIOM.
(2) Based on the principle of ion substitution, the MgZn-Cur complex can precisely regulate the "chelation of iron and supplementation of zinc/magnesium" in the complex oral microenvironment.
(3) The MgZn-Cur@PP hydrogel inhibits ferroptosis and restores mitochondrial function by re-establishing the multielement homeostasis.]

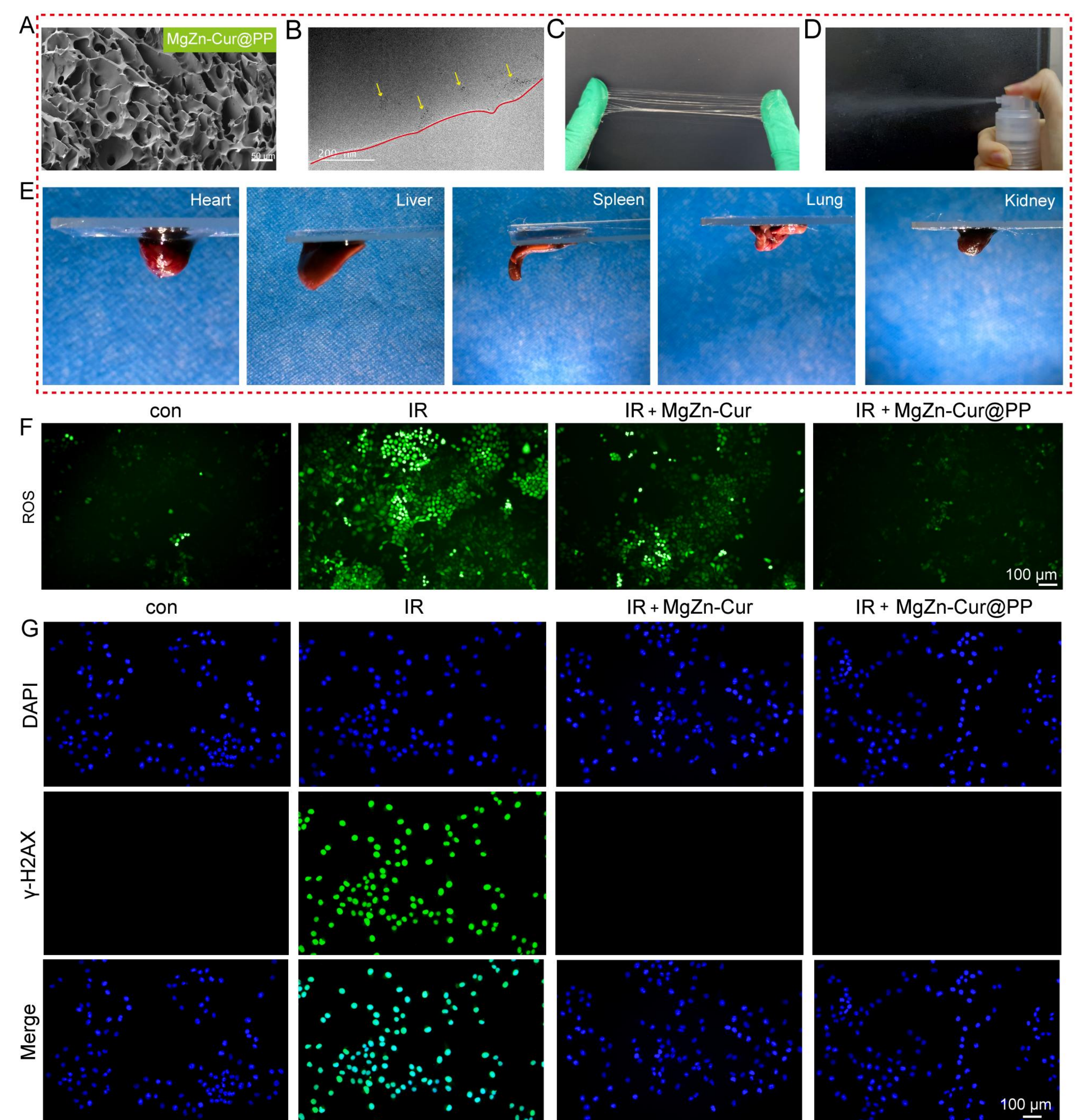


Fig 2.(A-B) SEM and TEM images of the MgZn-Cur@PP hydrogel spray; the yellow arrows indicate Mg and Zn ions; (C-D) spray and in-situ gelation performance; (E) adhesion performance of MgZn-Cur@PP hydrogel to different organ tissues of rats; (F) detection of cell ROS levels in different treatment groups; (G) γ -H2AX immunofluorescence detection of DNA damage levels.

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This work was supported by the National Natural Science Foundation of China (32201102) and the Science and Technology Commission of Shanghai Municipality (BJKJ2024001)]