Dual sensitization enables synergistic photodynamic therapy and radiotherapy for breast cancer

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ABSTRACT

Radiotherapy (RT) and photodynamic therapy (PDT) for breast cancer are limited by tumor hypoxia and suboptimal photosensitizer performance.We developed folate-modified copper-doped carbon dots (FC) and loaded them with 5-aminolevulinic acid (ALA) to yield FCA, a nanoplatform that executes cascade nanozyme activities to remodel the tumor microenvironment: decomposing H_2O_2 to relieve hypoxia, generating hydroxyl radicals and singlet oxygen ($^1O_2$), and depleting glutathione (GSH). This priming enabled efficient ALA-to-protoporphyrin IX (PpIX) conversion, which subsequently amplified reactive oxygen species (ROS) generation. The elevated oxidative stress then synergized with RT to accumulate DNA double-strand breaks and trigger cell-cycle arrest. Consequently, FCA-PDT-RT reduced 4T1 cell viability to 20.09% and induced 83.82% apoptosis-outcomes mechanistically linked to NRF2-KEAP1-HMOX1 pathway activation. Despite compensatory upregulation of antioxidant genes (HMOX1, GCLM), intracellular GSH and adenosine triphosphate (ATP) were severely depleted, establishing a metabolic crisis wherein synthesis could not match consumption. This redox/energy collapse drove the pronounced cytotoxicity observed. In an orthotopic 4T1 model, FCA-PDT-RT achieved superior tumor control at only 12 Gy, which correlated with increased $CD3^+/CD8^+$ T-cell infiltration and suppressed angiogenesis, while maintaining favorable safety. FCA thus enables synergistic PDT-RT through sequential microenvironment remodeling, oxidative amplification, and metabolic exhaustion, offering a dose-sparing strategy with translational promise for breast cancer therapy.

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INTRODUCTION

Breast cancer is a leading cause of cancer mortality, with radiotherapy (RT) widely applied for postoperative adjuvant treatment to suppress local recurrence. However, tumor radioresistance driven by robust DNA repair and antioxidant TME compromises RT efficacy, resulting in treatment failure and adverse toxicities, highlighting the need for effective dose-sparing sensitization approaches. Photodynamic therapy (PDT) exerts precise tumor cytotoxicity via ROS but is limited by poor photosensitizer accumulation and TME ROS scavenging. PDT-RT combination presents synergistic effects by amplifying oxidative DNA damage, offering a promising strategy to improve therapeutic outcomes while lowering radiation dose. Herein, we constructed a folate-modified copper-doped carbon dot nanoplatform loaded with 5-aminolevulinic acid (FCA). FCA enables tumor-targeted photosensitizer delivery and TME redox remodeling via cascade nanozyme reactions, relieving hypoxia and antioxidant defense. This work aims to achieve synergistic PDT-RT sensitization and low-dose radiotherapy for efficient breast cancer treatment.

RESULTS

➢ **Nanoplatform fabrication and TME modulation**

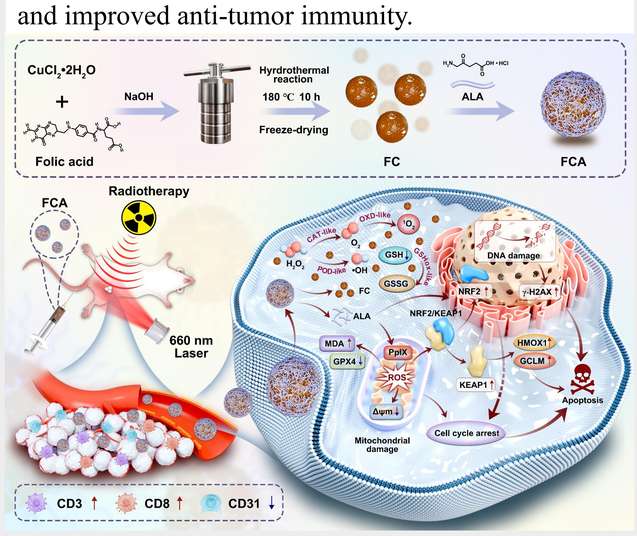
Uniform, stable FCA nanodots with high ALA loading and copper active sites were successfully synthesized. FCA exhibits cascade enzyme-mimetic activities to generate oxygen, amplify ROS and deplete GSH, effectively reversing hypoxic and reductive TME to overcome PDT-RT resistance.

➢ **In vitro synergistic therapeutic mechanism**

FCA achieves targeted tumor uptake and intracellular PpIX enrichment. Optimized FCA-based PDT-RT dramatically elevates oxidative stress, causing lipid peroxidation and mitochondrial damage. It impairs DNA repair, induces replication stress and mitochondrial apoptosis, and suppresses breast cancer proliferation by breaking tumor antioxidant compensation.

In vivo anti-tumor efficacy and biosafety

FCA possesses favorable biocompatibility and tumor targeting. Under fixed radiation dose, FCA-assisted PDT-RT suppresses tumor growth via oxidative injury and improved anti-tumor immunity.



Scheme 1 Schematic illustration of the multifunctional nanoplatform FCA for synergistic sensitization in combined therapy.

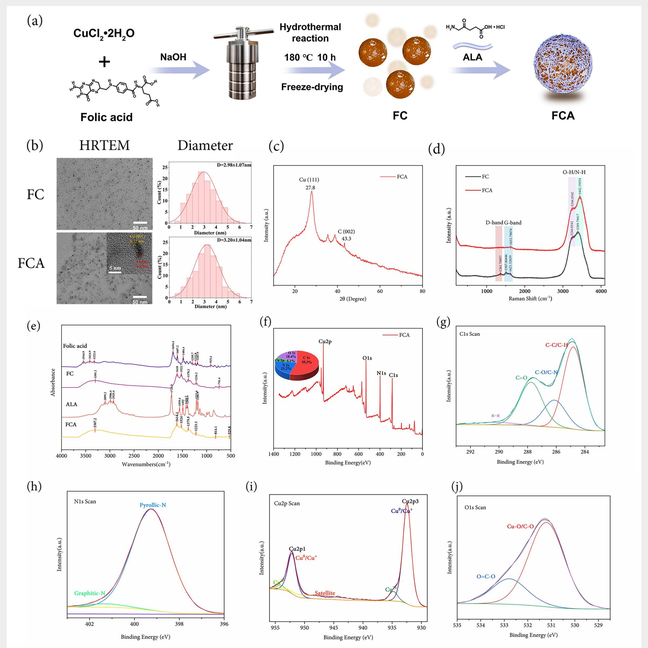


Figure 1 Construction and characterization of the multifunctional FCA nanoplatform.

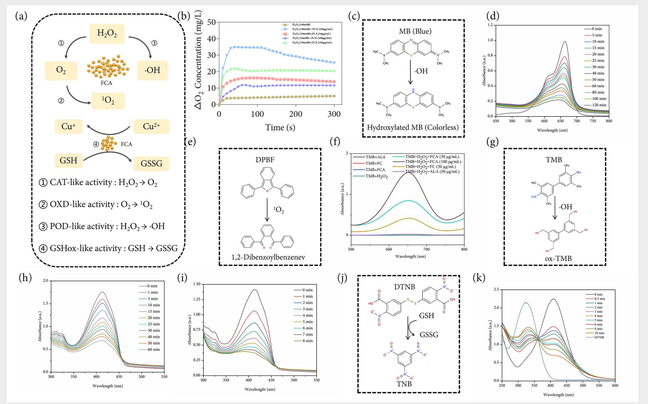


Figure 2 Evaluation of multi-enzyme mimetic catalytic activities of FCA.

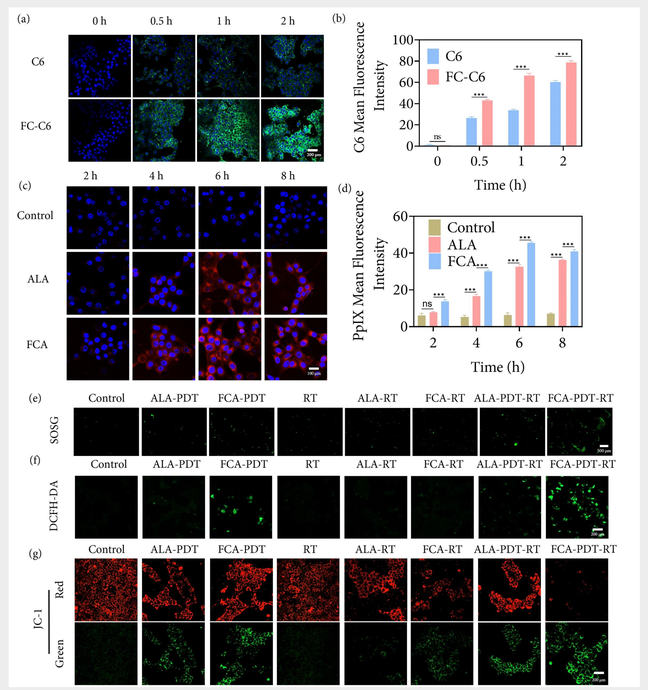


Figure 3 In vitro photodynamic-radiotherapy synergy and oxidative stress enhancement.

DISCUSSION

➢ **Core innovation and synergistic mechanism**

This work develops a multifunctional FCA nanoplatform to address two critical bottlenecks of clinical PDT-RT: tumor hypoxia and ROS scavenging.

By integrating targeted photosensitizer delivery and TME redox remodeling, FCA synergizes PDT-induced mitochondrial injury and RT-triggered DNA damage for superior anti-tumor efficacy.

➢ **Clinical translational value**

FCA-induced sustained redox stress disrupts tumor metabolism and DNA repair, promoting tumor apoptosis and remodeling immune microenvironment. With good biosafety and dose-sparing advantages, FCA provides a novel and translational multimodal sensitization strategy for breast cancer therapy.

➢ **Study limitations and future prospects**

This study is limited to single cell line and mouse model, lacking large-animal and tumor subtype validation, with unclear long-term in vivo metabolic and immune mechanisms. Future work will advance translational research to promote clinical application of the PDT-RT synergistic strategy.

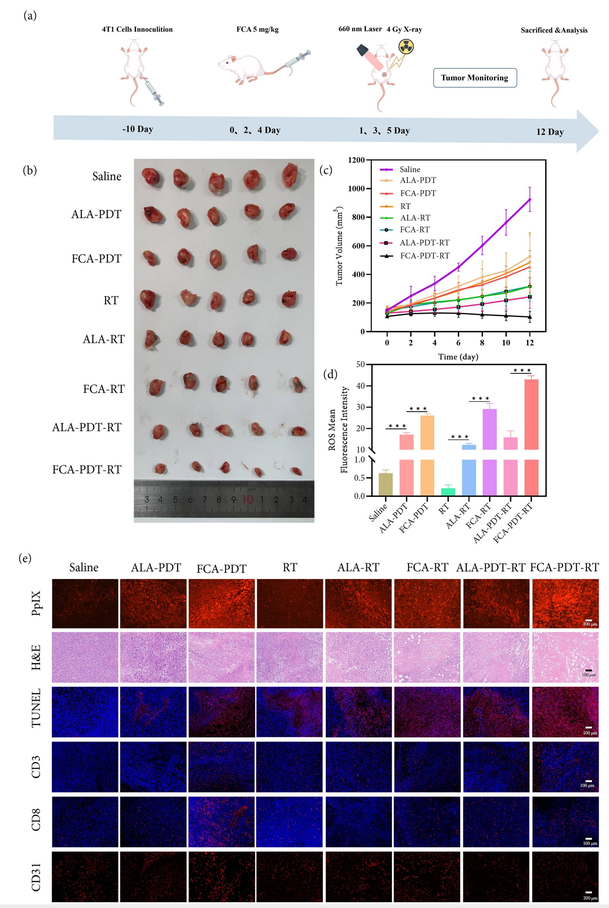


Figure 4 Antitumor efficacy and mechanistic analyses of different treatment strategies in 4T1 tumor-bearing mice.

CONCLUSION

This study developed a biocompatible, tumor-targeted FCA nanoplatform with high ALA loading for synergistic PDT-RT therapy. FCA remodels tumor redox microenvironments via multi-enzyme activity to relieve hypoxia, amplify ROS and deplete GSH, overcoming breast cancer therapeutic resistance. The combined treatment induces oxidative, DNA and mitochondrial damage to trigger robust tumor apoptosis. In vivo, FCA improves tumor accumulation and anti-tumor immunity, enabling safe, dose-sparing tumor suppression. This work offers a translational nanoplatform for precise breast cancer radiophotodynamic therapy.