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COMMENTARY

Sonic priming and biomimetic synergy: A paradigm shift in solid tumor therapy

KEY WORDS

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Ferroptosis;
Tumor therapy

The synergistic combinations of nanomedicine and medical devices represent a transformative approach in modern oncology, offering extraordinary opportunities to overcome the limitations of conventional cancer therapies. In this issue of *Acta Pharmaceutica Sinica B*, Xu et al.[1] conducted an outstanding study demonstrating that platelet-biomimetic liposomes (PLip) loaded with gambogic acid (GA) can synergize with high-intensity focused ultrasound (HIFU) to induce ferroptosis in basal-like breast cancer models. This work not only advances the development of a novel therapeutic strategy, but also highlights the immense potential of combining nanoscale drug delivery systems with precision medical devices for treating solid tumors.

The convergence of drug delivery systems and medical devices exemplifies the next generation of precision medicine. By seamlessly integrating both chemical and physical modalities, therapeutic outcomes are enhanced beyond the sum of their individual effects. This commentary seeks to contextualize the significance of Xu et al.'s findings within the broader landscape of cancer nanomedicine and highlight the emerging paradigm of device-nanomedicine synergy in oncology.

1. The challenge of solid tumor therapy

Solid tumors have formidable challenges to effective drug delivery, including abnormal vasculature, dense extracellular matrix, high interstitial fluid pressure, and immunosuppressive microenvironment. These physical and biological barriers collectively hinder the distribution and penetration of drugs inside tumors, seriously limiting their efficacy. Although nanomedicine brings hope to tumor drug delivery, its clinical translation has been hampered by modest tumor accumulation (only 0.7% of injected dose) and heterogeneous distribution inside tumors[2]. Additionally, the enhanced permeability and retention (EPR) effect of nanomedicines, demonstrates considerable inter-patient and inter-tumor variability, necessitating novel strategies to enhance drug delivery efficiency. Besides, the tumor microenvironment (TME) actively evolves to resist therapy, with cancer-associated fibroblasts generating dense extracellular matrix, immunosuppressive cells creating a hostile immune landscape, and hypoxic regions limiting the efficacy of oxygen-dependent therapies. To overcome these challenges, innovative multifunctional therapeutic strategies that can simultaneously regulate the TME, enhance nanomedicine accumulation and penetration, and exert powerful cytotoxic effects are still urgently required.

1.1. *HIFU: beyond thermal ablation*

HIFU has emerged as a non-invasive therapeutic modality with FDA approval for prostate cancer treatment and ongoing clinical trials for various cancers including breast, liver, and pancreatic cancers[3]. HIFU is traditionally employed for thermal ablation (60−85 °C), but growing evidence reveals that HIFU has diverse biological effects besides simple tissue destruction. Firstly, HIFU irradiation generates reactive oxygen species (ROS), disrupts biological barriers, enhances vascular permeability, and induces tumor ferroptosis[4]. Secondly, the mechanical effects of HIFU, including cavitation and acoustic streaming, physically remodel the TME by disrupting dense ECM and increasing the interstitial space[5]. Thirdly, HIFU opens biological barriers transiently, providing a therapeutic window during which nanomedicine accumulation and penetration can be significantly enhanced. Critically, HIFU upregulates CD44 expression on tumor cells through activation of NF-κB and STAT3 signaling pathways,

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creating a molecular target for specific drug delivery[6]. Xu et al. reported that HIFU treatment upregulated CD44 expression on 4T1 tumor cells by 1.43-fold, thereby facilitating enhanced PLip accumulation through P-selectin−CD44 interaction[1]. Crucially, the study's bioinformatics analysis uncovered a more complex "multiplexed" targeting signature, identifying the upregulation of multiple genes (*SELPLG*, *LGALS3*, *CLEC-2*, and *PVR*) involved in platelet-biomimetic recruitment. This finding shifts the paradigm of nanomedicine, moving from passive delivery toward the use of physical stimuli to actively engineer receptive targeting environments within the tumor.

1.2. Biomimetic nanomedicine: harnessing nature's wisdom

The platelet membrane fusing strategy employed by Xu et al. exemplifies the biomimetic approach to nanomedicine design, which aims to copy the favorable biological properties of natural cells while maintaining the versatility of synthetic nanocarriers. Platelets naturally exhibit intrinsic tumor-homing capabilities mediated by P-selectin and other adhesion molecules[7]. By fusing liposomes with platelet membranes, the resulting PLip inherits the favorable biological properties while maintaining the drug-loading capacity of synthetic liposomes. The interaction between platelet membrane P-selectin and CD44 overexpressed in various tumors including TNBC represents a critical targeting mechanism. This interaction is further strengthened as HIFU treatment upregulates CD44 expression on tumor cells. Xu et al. demonstrated that HIFU treatment increased PLip uptake by 3.76-fold compared to conventional liposomes, establishing a mechanistic basis for the observed synergy[1]. The enhanced uptake was specifically blocked by anti-CD44 antibodies, confirming the P-selectin−CD44 interaction as the primary targeting mechanism.

2. Ferroptosis: exploiting a vulnerability in cancer cells

Ferroptosis, an iron-dependent form of regulated cell death characterized by lipid peroxidation, has gained significant attention as a therapeutic target in cancer[8]. Unlike apoptosis, ferroptosis is primarily mediated by ROS-induced damage to polyunsaturated fatty acids in cellular membranes, leading to loss of membrane integrity and cell death. Cancer cells, commonly with high metabolic activity, iron dependence, and compromised antioxidant defenses, exhibit intrinsic vulnerability to ferroptosis induction[9]. Analysis of ferroptosis-related gene expression in breast cancer subtypes revealed that basal-like breast cancer shows distinct expression patterns: downregulation of *ACSL4* (a ferroptosis driver) but also downregulation of ferroptosis suppressors including *SLC7A11*, *GPX4*, and *AIFM2*[1]. This complex expression profile suggests that basal-like breast cancer may be sensitive to ferroptosis induction under specific conditions. Xu et al. identifies thioredoxin (TXN) and myeloid cell leukemia-1 (MCL1) as potential strategic targets for ferroptosis induction in basal-like breast cancer. TXN maintains cellular redox balance by reducing oxidized proteins, while MCL1, traditionally associated with apoptosis regulation, impacts ROS generation through modulation of *NOX4* activity[10]. TXN is upregulated in all subtypes of breast cancer, indicating its importance in maintaining the redox homeostasis of cancer cells[1]. MCL1 shows a positive correlation with 15 ferroptosis-related genes, suggesting its broader role in regulating ferroptosis susceptibility. Gambogic acid, a natural compound with dual inhibitory activity against both TXN and MCL1, is identified as an potent ferroptosis inducer that disrupts multiple antioxidant defense mechanisms simultaneously[1]. Molecular docking simulations confirmed the binding of GA to both TXN and MCL1 proteins, providing a structural basis for its dual-targeting mechanism.

3. Synergistic mechanism: ROS amplification loop and lipid peroxidation

The converging of HIFU and PLip generates a powerful ROS amplification cascade that overcomes the compensatory mechanisms employed by tumors to resist single-modality therapies. HIFU irradiation creates a high ROS environment, which has dual functions: triggering ROS-responsive drug release from PLip and priming tumor cells for ferroptosis susceptibility[1]. The phospholipid bilayer of biomimetic liposomes containing unsaturated fatty acid chains responds to high ROS concentrations and undergoes structural changes that facilitate drug release. The released GA further inhibits TXN and MCL1, disrupting cellular antioxidant defenses and promoting lipid peroxidation. This creates a positive feedback loop where ROS generation leads to drug release, resulting in further ROS accumulation through inhibition of antioxidant enzymes/proteins. The combination therapy resulted in a 2.64-fold increase in intracellular ROS and a 1.50-fold increase in lipid peroxidation (LPO) compared to control[1], ultimately leading to ferroptotic cell death. More importantly, the combination therapy achieved remarkable tumor suppression (97.5% inhibition) with 40% of treated animals free of tumors, significantly outperforming either HIFU or PLip monotherapy[1]. This synergistic efficacy underscores the potential of rationally designed combination therapies that exploit complementary mechanisms of action. Bioinformatics analysis revealed that the combination therapy upregulated key ferroptosis genes including *HSPB1* (2.3-fold), *HMOX1* (3.1-fold), and *SLC7A11* (4.11-fold)[1], which further confirmed the activation of ferroptosis pathways.

4. Clinical translation considerations

Despite encouraging preclinical findings, several considerations require attention for clinical translation of the HIFU + PLip combination therapy. Firstly, although the safety profile of HIFU + PLip combination therapy appears favorable, with no significant hepatotoxicity, nephrotoxicity, or hematological abnormalities observed in treated mice[1], the long-term effects of ferroptosis induction, particularly regarding immune cell function, require careful evaluation. Ferroptotic cells have been shown to release damage-associated molecular patterns (DAMPs) that can stimulate immune responses[11]. The balance between antitumor immunity and potential autoimmune effects needs to be carefully assessed. Secondly, considering that the heterogeneity of ferroptosis susceptibility across different tumor types and individual patients represents a critical factor for clinical success, biomarkers predictive of ferroptosis response, such as *ACSL4* expression, *GPX4* activity, and intracellular iron levels, will be essential for patient stratification[12]. Xu et al.'s finding that TXN and MCL1 are upregulated in basal-like breast cancer suggests that these proteins could serve as predictive biomarkers for GA-based ferroptosis therapy[1]. Tumors with high TXN/MCL1 expression may be particularly susceptible to this combination therapy, while tumors with low expression may require alternative strategies. Thirdly, the timing and sequencing of HIFU irradiation relative to nanomedicine administration may significantly impact therapeutic outcomes. Xu et al. administered PLip 2 h after HIFU treatment, based on the observation that CD44 upregulation peaks at

this time point[1]. However, optimal timing may vary depending on tumor type, size, and location. The HIFU parameter also requires careful optimization to balance therapeutic efficacy with safety. Excessive HIFU energy can cause tissue damage, while insufficient energy may not adequately enhance nanomedicine delivery or induce ROS generation.

5. Future perspectives

Several exciting directions emerge from the work of Xu et al., each with the potential to further advance the field of device-drug synergy in cancer therapy. Firstly, the biomimetic platform can be extended beyond platelet membranes to macrophage, neutrophil, or T-cell membranes, which enable active targeting to inflammatory tumor microenvironments and intrinsic immune modulation *via* native tumor-homing receptors and engineered immunostimulatory signals. Secondly, the ROS amplification strategy can be strengthened by incorporating additional ROS-generating or antioxidant-inhibiting components into the nanoplatform. For instance, iron oxide nanoparticles can provide Fenton reaction substrates, generating hydroxyl radicals in the presence of H_2O_2. The combination of GA-mediated TXN/MCL1 inhibition with iron-catalyzed ROS generation could create a potent ferroptosis-inducing system. Thirdly, gene silencing of key ferroptosis suppressors such as *GPX4* with siRNA can sensitize tumors to ferroptosis induction. Co-delivery of GA and siRNA targeting these genes could achieve synergistic ferroptosis induction at lower drug doses. Finally, the combination of HIFU-enhanced nanomedicine with immune checkpoint inhibitors represents a particularly promising avenue. HIFU/GA-induced ferroptosis releases tumor-associated antigens and DAMPs, potentially priming antitumor immunity that can be amplified by PD-1/PD-L1 or CTLA-4 blockade. In addition, HIFU and ferroptosis induction can modulate the immunosuppressive TME, repolarizing M2 macrophages to M1 phenotype and increasing $CD8^+$ T cell infiltration[4,13]. These changes create a more favorable environment for immunotherapy.

6. Conclusion

Notably, in Xu's study, this HIFU-biomimetic nanomedicine strategy represents a pivotal advancement in device−nanomedicine combined cancer therapy. By integrating physical barrier disruption, ROS elevation, and targeted molecular regulation, this work establishes a blueprint for the rational design of synergistic cancer therapies. As precision medicine evolves, such nanotechnology−device integrated approaches will be critical to overcoming therapy resistance. Clinical translation will require optimized treatment parameters, predictive biomarkers, and rigorous safety validation; nonetheless, the robust preclinical evidence strongly supports further development. Extending this strategy to other tumor types and therapeutic scenarios will ultimately bridge nanomedicine innovation to clinical benefit, marking a paradigm shift towards precise, synergistic, and mechanism-driven cancer treatment.

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Conflicts of interest

The author declares no conflict of interest.

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