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Opinion Article

Targeting Tumor Energy Homeostasis: Disrupting Metabolism to Sensitize Tumors

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DESCRIPTION

The advancement of nanozyme-based strategies in cancer therapy is rapidly redefining conventional treatment modalities. Among these, the concept of using nanozymes to disrupt tumor energy homeostasis and mediate ferroptosis has gained significant traction, especially in enhancing the efficacy of radiotherapy. The strategic coupling of nanozymes with ferroptosis a distinct, iron-dependent form of programmed cell death characterized by lipid peroxidation presents a promising avenue to overcome resistance in radioresistant tumors and achieve high-efficiency therapeutic outcomes. This approach integrates tumor microenvironment manipulation, redox balance interference and metabolic disruption into one coordinated platform.

Nanozymes are nanomaterials with intrinsic enzyme-like catalytic properties, providing advantages such as high stability, tunable activity and ease of surface functionalization. When engineered appropriately, nanozymes can mimic peroxidase, oxidase, catalase and superoxide dismutase activities to generate or scavenge Reactive Oxygen Species (ROS). This catalytic flexibility is particularly significant in the context of radiotherapy, where oxidative stress is the principal mechanism driving tumor cell death. Conventional radiotherapy often fails to achieve complete tumor regression due to hypoxia, low ROS production and adaptive tumor metabolic pathways. Nanozymes that catalyze endogenous substrates such as hydrogen peroxide into hydroxyl radicals or lipid peroxides can bridge this gap by amplifying oxidative stress *in situ*.

What sets nanozyme-mediated ferroptosis apart from other strategies is its intersection with tumor energy metabolism. Tumors often rely on metabolic reprogramming to maintain redox homeostasis and survive under stress. Disrupting this metabolic adaptability is fundamental to sensitizing tumors to radiotherapy. Nanozymes can be designed to interfere with energy production pathways such as glycolysis and oxidative phosphorylation by depleting NADPH, consuming intracellular Glutathione (GSH) and inhibiting key enzymes that detoxify lipid peroxides. As a result, the energy balance in tumor cells collapses, rendering them highly vulnerable to ferroptosis.

This process is further enhanced by iron catalysis. Nanozymes composed of iron-based nanostructures, such as Fe3O4 or metal-organic frameworks doped with iron, can supply catalytic Fe^{2+} that drives Fenton reactions. The localized production of hydroxyl radicals and lipid peroxides leads to uncontrolled oxidative damage, particularly in the presence of polyunsaturated fatty acids in the cellular membrane. Moreover, the radiation-induced ROS synergize with nanozyme-generated ROS, producing a cumulative effect that overwhelms the antioxidant defense of cancer cells. Importantly, ferroptosis circumvents traditional apoptosis-resistance mechanisms, making it suitable for targeting malignancies with high genetic variability and therapy evasion capacity.

Despite these advantages, there are still challenges and nuances that warrant critical attention. One issue is the potential off-target toxicity, especially considering the systemic catalytic activity of nanozymes. Unlike natural enzymes, nanozymes do not always have the same substrate specificity, which may lead to unintended reactions in non-tumor tissues. Another concern is the delivery efficiency and tumor specificity of nanozyme systems. To fully leverage their potential, nanozymes must be integrated with tumor-targeting moieties or stimuli-responsive delivery platforms that ensure selective accumulation and activation in the tumor microenvironment. This becomes even more critical when considering the variable levels of hydrogen peroxide and GSH in different tumor types, which directly affect nanozyme activity.

Moreover, the heterogeneity of tumor metabolism poses a challenge in designing universal nanozyme therapies. Not all tumors rely on the same metabolic pathways and their response to energy disruption can vary. Personalized medicine approaches, potentially guided by metabolic profiling and imaging techniques, may be required to identify patients who would benefit the most from nanozyme-based ferroptosis therapy. The

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integration of nanozymes with imaging agents could further allow real-time monitoring of biodistribution, catalytic activity and therapeutic response.

In conclusion, nanozyme-mediated disruption of tumor energy homeostasis to induce ferroptosis represents a novel and compelling strategy to augment radiotherapy efficacy. By exploiting the catalytic potential of engineered nanomaterials and targeting the metabolic vulnerabilities of cancer cells, this approach holds promise for treating resistant and aggressive tumors. However, careful optimization of delivery, specificity and safety remains crucial for successful translation. Continued interdisciplinary research combining nanotechnology, oncology and systems biology is likely to unlock the full potential of this strategy in the coming years.