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Stimuli-Responsive Nanomedicine for Overcoming Multidrug Resistance in Solid Tumors

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ABSTRACT

Multidrug resistance (MDR) remains one of the most formidable barriers to successful chemotherapy in solid tumors, accounting for the failure of many otherwise potent anticancer agents. MDR arises from a complex interplay of cellular, molecular, and microenvironmental mechanisms, including drug efflux transporter overexpression, altered drug metabolism, enhanced DNA repair, evasion of apoptosis, and tumor microenvironment–mediated protection. Conventional approaches to overcome MDR, such as dose escalation or combination chemotherapy, often exacerbate systemic toxicity without achieving durable responses. Stimuli-responsive nanomedicine has emerged as a highly promising strategy to address these limitations by enabling spatially and temporally controlled drug delivery in response to tumor-specific internal or external cues. These nanocarriers are engineered to respond to physicochemical stimuli such as pH, redox potential, enzymes, hypoxia, and reactive oxygen species, or to externally applied triggers including light, heat, ultrasound, and magnetic fields. By selectively releasing therapeutic payloads at the tumor site or within resistant cancer cells, stimuli-responsive nanomedicine enhances intracellular drug accumulation, bypasses efflux mechanisms, and re-sensitizes tumors to chemotherapy. This review provides a comprehensive and critical analysis of the biological basis of MDR in solid tumors, the design principles of stimuli-responsive nanomedicine, and their applications in overcoming drug resistance. Current challenges and future perspectives for clinical translation are also discussed.

Keywords: multidrug resistance; stimuli-responsive nanomedicine; solid tumors; tumor microenvironment; precision drug delivery

INTRODUCTION

Multidrug resistance (MDR) is a multifaceted phenomenon that severely limits the efficacy of chemotherapy in solid tumors[1–3]. It is defined as the ability of cancer cells to develop cross-resistance to a broad spectrum of structurally and functionally unrelated anticancer drugs. MDR may be intrinsic, existing prior to treatment, or acquired following repeated exposure to chemotherapeutic agents[3]. Regardless of origin, MDR is responsible for tumor recurrence, metastasis, and poor patient prognosis across many cancer types, including breast, lung, colorectal, pancreatic, and ovarian cancers [4].

One of the most extensively studied mechanisms of MDR is the overexpression of ATP-binding cassette (ABC) transporters, such as P-glycoprotein (P-gp/ABCB1), multidrug resistance–associated proteins (MRPs), and breast cancer resistance protein (BCRP)[5, 6]. These transporters actively efflux chemotherapeutic drugs out of cancer cells, reducing intracellular drug concentrations below cytotoxic thresholds. In parallel, cancer cells may downregulate drug uptake transporters, further limiting intracellular drug accumulation. Together, these processes dramatically impair the effectiveness of conventional chemotherapy[7, 8].

Beyond drug transport, MDR is reinforced by alterations in drug metabolism and detoxification pathways. Increased expression of phase I and phase II metabolic enzymes enables rapid drug inactivation, while elevated glutathione and antioxidant systems neutralize drug-induced oxidative stress[9, 10]. Additionally, resistant

tumor cells often exhibit enhanced DNA repair capacity, allowing them to survive genotoxic insults from alkylating agents and topoisomerase inhibitors. Dysregulation of apoptosis pathways, including upregulation of anti-apoptotic proteins such as BCL-2 and survivin, further enables cancer cell survival despite drug exposure[11, 12].

The tumor microenvironment (TME) plays a critical and often underappreciated role in MDR. Hypoxia, acidic pH, high interstitial fluid pressure, and dense extracellular matrix collectively limit drug penetration and create protective niches for resistant cancer cell subpopulations. Hypoxia-inducible factors (HIFs) not only promote angiogenesis and metabolic adaptation but also directly regulate MDR-related genes, including those encoding efflux transporters[13, 14]. Stromal cells, immune cells, and cancer-associated fibroblasts further contribute to resistance by secreting cytokines, growth factors, and extracellular vesicles that support survival signaling and drug tolerance.

Despite decades of research, pharmacological inhibition of individual MDR mechanisms has achieved limited clinical success. Efflux pump inhibitors, for example, often lack specificity and cause unacceptable toxicity due to inhibition of physiological transporters in normal tissues[15]. Similarly, systemic combination therapies frequently result in cumulative toxicity without fully suppressing resistance. These challenges underscore the need for innovative therapeutic strategies that can selectively target resistant tumor cells while sparing healthy tissues. In this context, nanomedicine and particularly stimuli-responsive nanomedicine offer a paradigm shift by integrating drug delivery with tumor-selective activation, thereby addressing the biological complexity of MDR in solid tumors[16, 17].

2. Design Principles of Stimuli-Responsive Nanomedicine

Stimuli-responsive nanomedicine is based on the rational design of nanoscale drug delivery systems that undergo physicochemical or structural changes in response to specific stimuli. These changes may include nanoparticle disassembly, drug release, charge reversal, or activation of therapeutic function. The overarching goal is to ensure that drugs remain stable and inactive during systemic circulation while becoming selectively activated at the tumor site or within cancer cells[18–20].

At the core of these systems are nanocarriers such as polymeric nanoparticles, liposomes, micelles, dendrimers, inorganic nanoparticles, and hybrid nanostructures. Responsiveness is engineered through the incorporation of stimulus-sensitive linkers, coatings, or functional groups[21, 22]. Internal stimuli exploit intrinsic differences between tumors and normal tissues, including acidic extracellular pH, elevated intracellular glutathione levels, overexpressed enzymes, hypoxia, and high reactive oxygen species (ROS). External stimuli, in contrast, rely on externally applied triggers such as light, heat, ultrasound, or magnetic fields to induce localized drug release[23].

A critical design consideration is balancing stability and responsiveness. Nanocarriers must be sufficiently stable in the bloodstream to avoid premature drug leakage and rapid clearance, yet sensitive enough to respond efficiently to tumor-specific cues. Size, surface charge, and hydrophilicity strongly influence circulation time, biodistribution, and cellular uptake. Surface functionalization with polyethylene glycol or targeting ligands can further enhance tumor accumulation and cellular internalization[24, 25].

Importantly, stimuli-responsive nanomedicine allows integration of multiple functions within a single platform. For example, nanocarriers can simultaneously incorporate targeting ligands, imaging agents, and combination therapeutics[26, 27]. This multifunctionality is particularly advantageous for overcoming MDR, as it enables co-delivery of chemotherapeutic drugs with efflux pump inhibitors, gene-silencing agents, or apoptosis sensitizers in a coordinated and tumor-specific manner.

3. pH- and Redox-Responsive Nanomedicine for MDR Reversal

pH- and redox-responsive nanomedicine represents one of the most extensively investigated approaches for overcoming MDR in solid tumors. Tumors typically exhibit a slightly acidic extracellular environment due to high glycolytic activity and lactic acid accumulation, while intracellular compartments such as endosomes and lysosomes are even more acidic[28]. pH-responsive nanocarriers exploit this gradient by incorporating acid-labile bonds that trigger drug release under acidic conditions.

Such systems enhance intracellular drug availability by releasing payloads after endocytosis, thereby bypassing efflux pumps localized at the plasma membrane. Additionally, charge-reversal nanoparticles that become positively charged in acidic environments show enhanced interaction with negatively charged cellular membranes, improving cellular uptake in resistant cancer cells[29]. Redox-responsive nanomedicine exploits the markedly elevated glutathione concentrations in cancer cells compared with normal tissues. Disulfide bonds are commonly used as redox-sensitive linkers that remain stable extracellularly but are cleaved intracellularly, triggering rapid drug release[30]. This strategy is particularly effective for delivering hydrophobic chemotherapeutics or nucleic acids directly into the cytosol, minimizing efflux and degradation. Together, pH- and redox-responsive systems provide complementary mechanisms to selectively overcome MDR at the cellular level.

4. Enzyme- and Hypoxia-Responsive Nanomedicine in Resistant Tumors

Multidrug resistance (MDR) remains one of the most formidable obstacles in cancer therapy, frequently arising from a combination of altered drug transport, metabolic adaptation, and microenvironmental protection[31, 32]. Enzyme-responsive nanomedicine exploits the aberrant enzymatic landscape of drug-resistant tumors to

achieve selective and localized drug release. Many resistant tumors overexpress proteolytic and metabolic enzymes, including matrix metalloproteinases (MMPs), cathepsins, and phospholipases, which are involved in extracellular matrix remodeling, invasion, and survival signaling[31]. Nanocarriers engineered with enzyme-cleavable peptides or polymeric linkers remain structurally stable in normal tissues but undergo degradation or structural rearrangement in enzyme-rich tumor microenvironments, enabling site-specific payload release.

MMP-responsive nanoparticles are among the most extensively studied systems in this category. These nanocarriers incorporate peptide substrates that are selectively cleaved by tumor-associated MMPs, triggering drug release or nanoparticle disassembly within invasive tumor regions. Similarly, cathepsin-responsive nanomedicines leverage the elevated lysosomal protease activity in resistant cancer cells to facilitate intracellular drug activation[33]. By confining therapeutic release to enzyme-rich niches, these systems enhance tumor specificity while minimizing systemic toxicity and damage to healthy tissues.

Hypoxia-responsive nanomedicine addresses another hallmark of resistant tumors: oxygen deprivation. Hypoxic regions arise from aberrant vascularization and are strongly associated with MDR, immune evasion, and aggressive tumor behavior[34]. These regions are typically poorly accessible to conventional drugs and exhibit reduced sensitivity to radiotherapy and chemotherapy. Nanocarriers incorporating hypoxia-sensitive moieties such as nitroimidazole derivatives, azobenzene linkers, or hypoxia-cleavable polymers can be selectively activated under low oxygen conditions. Upon exposure to hypoxia, these moieties undergo reduction or bond cleavage, resulting in localized drug release within resistant tumor zones[34].

Targeting hypoxic niches is particularly important because these regions often serve as reservoirs for cancer stem-like cells and therapy-resistant subpopulations. By delivering cytotoxic agents or sensitizers directly to hypoxic areas, hypoxia-responsive nanomedicine disrupts a critical source of tumor relapse[35]. Moreover, alleviation of hypoxia-associated signaling can partially normalize the tumor microenvironment, enhancing the effectiveness of subsequent therapies. Together, enzyme- and hypoxia-responsive nanomedicine represents a rational strategy to overcome MDR by exploiting intrinsic biochemical vulnerabilities of resistant tumors.

5. External Stimuli-Responsive Nanomedicine: Light, Heat, and Ultrasound

Externally triggered nanomedicine offers unparalleled spatiotemporal control over drug activation, enabling clinicians to precisely regulate when and where therapeutic agents are released. Light-responsive nanoparticles are among the most extensively explored systems in this category[36]. These nanocarriers incorporate photo-cleavable linkers or photosensitive materials that respond to specific wavelengths of light. Upon irradiation, structural changes or bond cleavage trigger rapid drug release. Light-responsive systems are particularly suitable for superficial tumors or lesions accessible via endoscopic or optical fiber-based techniques[36].

In addition to controlled drug release, light-activated nanomedicine can induce photothermal or photodynamic effects. Photothermal nanoparticles convert light energy into localized heat, disrupting cellular membranes and impairing efflux pump function, a key mechanism of MDR. Photodynamic therapy generates reactive oxygen species that damage intracellular structures and sensitize cancer cells to chemotherapy[37, 38]. These combined effects enhance intracellular drug accumulation and reduce resistance.

Thermo-responsive nanocarriers represent another powerful external stimulus-based approach. These systems are designed to release drugs upon exposure to mild hyperthermia, typically in the range of 40–45°C[39]. Hyperthermia can be generated using focused ultrasound, magnetic fields, or infrared irradiation. Thermo-responsive nanomedicine benefits from the dual effects of enhanced drug release and improved tumor perfusion, which increases nanoparticle accumulation and penetration[39]. Ultrasound-responsive nanomedicine further expands the therapeutic toolbox by leveraging mechanical and acoustic effects. Ultrasound can induce cavitation, temporarily increasing cell membrane permeability and enhancing drug uptake. Nanocarriers engineered to respond to ultrasound waves can release their payloads in response to acoustic pressure, enabling deep tissue penetration and noninvasive activation[40]. These features make ultrasound-responsive systems particularly attractive for treating deep-seated tumors.

Collectively, externally stimuli-responsive nanomedicine provides clinicians with real-time control over therapy, offering a dynamic and adaptable strategy to overcome MDR.

6. Combinatorial Stimuli-Responsive Strategies and Clinical Translation

Given the multifactorial nature of MDR, combinatorial stimuli-responsive nanomedicine has emerged as a highly promising strategy. These advanced systems are engineered to respond to multiple endogenous and exogenous stimuli, either sequentially or simultaneously, ensuring robust and selective activation within resistant tumors[41]. For example, nanoparticles may be designed to exploit acidic pH for tumor accumulation, enzymatic activity for extracellular activation, and redox conditions for intracellular drug release. Such multistage responsiveness maximizes therapeutic precision while minimizing off-target effects[41].

Combinatorial systems also enable synchronized delivery of multiple therapeutic agents, such as chemotherapeutics, MDR modulators, and sensitizers. By co-encapsulating these agents within a single nanostructure, coordinated pathway inhibition can be achieved, reducing the likelihood of resistance development. This level of integration is difficult to achieve with conventional drug combinations administered systemically[42, 43].

Despite encouraging preclinical outcomes, clinical translation of stimuli-responsive nanomedicine faces significant challenges. Manufacturing scalability, reproducibility, and long-term stability must be rigorously

addressed to meet regulatory standards[44]. Additionally, comprehensive safety evaluations are required to assess potential toxicity, immunogenicity, and off-target effects. Regulatory frameworks for complex, multifunctional nanomedicines are still evolving, necessitating standardized characterization and validation protocols.

Nevertheless, advances in materials science, imaging, and precision oncology are steadily bridging the gap between laboratory innovation and clinical application. As these challenges are overcome, combinatorial stimuli-responsive nanomedicine holds substantial promise for transforming the management of drug-resistant cancers.

7. Conclusion and Future Perspectives

Stimuli-responsive nanomedicine represents a powerful and versatile strategy for overcoming multidrug resistance in solid tumors. By integrating tumor-specific responsiveness with advanced drug delivery design, these systems enhance intracellular drug accumulation, bypass resistance mechanisms, and minimize systemic toxicity. While significant challenges remain in clinical translation, continued progress in nanomaterial engineering, tumor biology, and patient stratification is rapidly advancing the field. Future success will depend on rational, mechanism-driven design and close integration with clinical oncology.

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