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Stimuli-Responsive Nanocarriers for Controlled Drug Release in Tumor Microenvironments

Mwende Wairimu G.

School of Natural and Applied Sciences Kampala International University Uganda

ABSTRACT

The tumor microenvironment (TME) presents unique physiological and biochemical characteristics distinct from those of normal tissues, such as acidic pH, elevated levels of glutathione (GSH), hypoxia, and overexpressed enzymes. These features offer an opportunity for the development of intelligent drug delivery systems that can selectively respond to such stimuli to enhance therapeutic efficacy while minimizing off-target effects. Stimuli-responsive nanocarriers have emerged as promising platforms for the controlled and targeted release of anticancer agents. These nanocarriers are engineered to undergo structural or chemical changes in response to internal (e.g., pH, redox potential, enzymes) or external (e.g., light, temperature, magnetic field) stimuli, leading to site-specific drug release within the tumor milieu. This review discusses the rationale behind stimuli-responsive drug delivery, design strategies of various nanocarrier systems, recent advances in the field, and their therapeutic applications. Additionally, the article highlights the challenges that remain in translating these innovative platforms from bench to bedside and offers perspectives for future research directions in precision oncology.

Keywords: Stimuli-responsive nanocarriers, tumor microenvironment, controlled drug release, smart drug delivery systems, cancer nanomedicine

INTRODUCTION

Cancer remains a formidable global health challenge, ranking among the leading causes of death worldwide[1–4]. According to the World Health Organization, cancer accounted for nearly 10 million deaths in 2020, and the number continues to rise as populations age and environmental factors evolve[5–8]. Conventional cancer therapies, including surgery, radiation, and chemotherapy, have improved survival rates in various cancers, yet they suffer from significant limitations[9–12]. Chemotherapy, the mainstay for many malignancies, is particularly plagued by a lack of selectivity, resulting in systemic toxicity, off-target effects, and diminished quality of life for patients. The need for more precise, safer, and effective therapeutic modalities has fueled the exploration of innovative technologies, particularly in the field of nanomedicine[2, 13–15].

Nanomedicine, the application of nanotechnology in medicine, has emerged as a promising frontier in cancer therapy. It offers the capability to design nanoscale drug delivery systems that can encapsulate chemotherapeutic agents, protect them from premature degradation, and deliver them selectively to tumor sites[16–19]. These nanocarriers, ranging from liposomes and dendrimers to polymeric nanoparticles and micelles, improve drug solubility, pharmacokinetics, and biodistribution while minimizing systemic side effects.

Among the most innovative advancements within this realm are stimuli-responsive nanocarriers, also referred to as “smart” or “intelligent” drug delivery systems. These specialized carriers are engineered to respond to specific internal or external stimuli, enabling them to release their therapeutic payloads only under certain conditions[20–22]. This feature enhances the selectivity of treatment, allowing for high drug concentrations in tumors while minimizing exposure to healthy tissues. This targeted release mechanism not only boosts therapeutic efficacy but also significantly reduces adverse effects commonly associated with traditional chemotherapy.

One of the most compelling applications of these stimuli-responsive systems is their exploitation of the tumor microenvironment (TME)—a complex, dynamic, and aberrant ecosystem that surrounds cancer cells[23–26]. Unlike normal tissues, the TME is characterized by specific physiological and biochemical abnormalities such as an acidic extracellular pH, hypoxia (low oxygen levels), elevated oxidative stress, and the overexpression of certain enzymes and reducing agents. These unique characteristics are largely a result of the abnormal metabolism and rapid proliferation of cancer cells[27–29]. They provide a rich set of cues that can be harnessed

to activate smart nanocarriers selectively at the tumor site. For instance, the acidic pH in the TME can be utilized to trigger the disintegration of pH-sensitive carriers, while redox-sensitive nanoparticles may release drugs in response to the high concentrations of intracellular glutathione found in cancer cells[17, 30–32]. Similarly, enzyme-sensitive systems can be degraded by tumor-specific proteases such as matrix metalloproteinases (MMPs), leading to site-specific drug release. External stimuli such as light, ultrasound, temperature, and magnetic fields can also be used to activate nanocarriers in a spatially and temporally controlled manner[33]. This review aims to provide a comprehensive overview of stimuli-responsive nanocarriers in the context of cancer therapy. It will delve into the specific types of internal and external stimuli that can be exploited, the various materials and design strategies used to create these carriers, and the advantages and challenges associated with their clinical translation. A particular emphasis will be placed on how the pathological hallmarks of the TME can be used as therapeutic targets to enhance drug delivery and therapeutic outcomes. By harnessing the unique properties of the tumor milieu, stimuli-responsive nanocarriers represent a significant step forward in the quest for more effective, precise, and patient-friendly cancer treatments.

2. The Tumor Microenvironment as a Therapeutic Target

The tumor microenvironment (TME) is increasingly recognized as a pivotal player in the initiation, progression, and therapeutic resistance of cancer. Far from being a passive backdrop, the TME actively shapes tumor biology and significantly influences the efficacy of anticancer treatments[28, 29, 34, 35]. It comprises a complex network of various cellular and non-cellular components, including cancer cells, fibroblasts, immune cells, endothelial cells, pericytes, the extracellular matrix (ECM), and a milieu of cytokines, chemokines, and growth factors. This intricate system fosters a supportive niche that facilitates tumor survival, immune evasion, angiogenesis, and metastasis [36].

A critical insight in modern oncology is the realization that the TME is markedly different from the microenvironment of healthy tissues. These differences can be exploited therapeutically, particularly in the context of stimuli-responsive nanocarriers, which are designed to respond to specific biochemical or physiological abnormalities in the TME[10, 32, 33]. One of the most well-characterized features of the TME is its acidic pH. Due to the Warburg effect, cancer cells rely heavily on glycolysis for energy production, even in the presence of oxygen. This metabolic reprogramming leads to excessive lactic acid production, resulting in an extracellular pH as low as 6.5–6.9 in tumors, compared to a physiological pH of ~7.4 in normal tissues. This pH gradient can be utilized to trigger the release of drugs from pH-sensitive nanocarriers, such as those containing acid-labile linkers or polymers that swell or degrade in acidic conditions[37–39].

Another hallmark of the TME is hypoxia, which arises from the rapid proliferation of cancer cells outpacing the development of adequate vasculature. Hypoxic regions within tumors contribute to drug resistance, genetic instability, and an aggressive phenotype[40]. Hypoxia-responsive nanocarriers, often functionalized with hypoxia-sensitive moieties such as nitroimidazoles or azobenzene derivatives, are designed to release their cargo in low-oxygen environments, improving drug delivery to otherwise hard-to-reach hypoxic zones[40].

The TME is also characterized by an altered redox balance, particularly elevated levels of glutathione (GSH) in tumor cells. GSH acts as a key antioxidant, and its intracellular concentration can be up to 1000 times higher than in the extracellular space[41]. Redox-responsive nanoparticles typically contain disulfide bonds that are cleaved in the presence of high GSH, enabling the release of encapsulated drugs specifically inside tumor cells. Moreover, certain proteolytic enzymes are overexpressed in the TME. Enzymes such as matrix metalloproteinases (MMPs), cathepsins, and phospholipases are secreted by cancer and stromal cells to remodel the ECM, facilitate invasion, and promote angiogenesis. Nanocarriers that are sensitive to these enzymes can be designed with peptide linkers or coatings that are degraded upon enzyme recognition, triggering drug release[42].

Collectively, these TME-specific triggers provide a foundation for designing intelligent drug delivery systems that minimize off-target effects and maximize therapeutic efficacy. By selectively activating nanocarriers in the tumor site, one can enhance local drug concentration, reduce systemic toxicity, and overcome physiological barriers that limit traditional therapies[17, 42–44]. However, leveraging the TME for therapy is not without challenges. The heterogeneity of tumors means that not all regions within a tumor may exhibit the same degree of acidity, hypoxia, or enzyme activity. Therefore, multifunctional nanocarriers that can respond to multiple stimuli or possess hierarchical responsiveness are being explored to increase reliability and robustness.

The TME is a dynamic and exploitable target in cancer therapy. Stimuli-responsive nanocarriers represent a promising strategy to harness these unique microenvironmental features for controlled and site-specific drug delivery. As our understanding of the TME deepens, it will open up new avenues for the design of ever-more sophisticated therapeutic platforms[33, 45, 46].

3. Types of Stimuli-Responsive Nanocarriers

3.1 pH-Responsive Nanocarriers: pH-responsive nanocarriers are smart delivery systems designed to leverage the acidic microenvironment typically found in solid tumors. Unlike normal tissues with a near-neutral pH (~7.4), the extracellular pH in tumor tissues tends to be more acidic (typically pH 6.5–6.8) due to anaerobic glycolysis and poor perfusion[42, 47]. Additionally, intracellular compartments such as endosomes and

lysosomes are even more acidic (pH 5.0–6.0), providing multiple opportunities for pH-triggered drug release. These nanocarriers are constructed using pH-sensitive polymers or acid-labile linkers. Materials like poly(L-histidine), poly(β-amino esters), or polyaniline are engineered to remain stable at physiological pH but become protonated or hydrolyzed in acidic conditions, leading to swelling, disintegration, or cleavage of the nanocarrier[48]. Acid-sensitive linkers such as hydrazone, cis-aconityl, or acetal bonds are frequently used to conjugate drugs to nanocarriers or within polymer matrices. Upon reaching the acidic tumor milieu or within endo/lysosomal vesicles, these linkers degrade, triggering the controlled and localized release of the therapeutic agent[48]. This mechanism minimizes premature drug leakage during circulation and enhances drug accumulation at the tumor site. pH-responsive systems have shown promise in improving the therapeutic index of chemotherapeutic agents like doxorubicin, paclitaxel, and cisplatin. Additionally, they can be combined with targeting ligands for active targeting.[48] One challenge remains the heterogeneity of tumor acidity, which may impact the release profile. However, with fine-tuned material properties and smart design, pH-responsive nanocarriers represent a promising avenue for site-specific drug delivery in cancer therapy.

***3.2* Redox-Responsive Nanocarriers:** Redox-responsive nanocarriers are engineered to exploit the substantial redox gradient between extracellular and intracellular environments, particularly in cancer cells[32]. Tumor cells typically exhibit elevated levels of reducing agents such as glutathione (GSH), which can be up to 1000 times higher intracellularly (2–10 mM) than in the extracellular matrix or bloodstream (2–20 μM). This intracellular redox difference serves as a potent stimulus for targeted drug release. Redox-sensitive systems often incorporate disulfide bonds (-S-S-) within their backbones, side chains, or as cleavable linkers between the nanocarrier and the therapeutic payload.[32] Upon cellular uptake, the high GSH concentration in cancer cells cleaves the disulfide linkages, destabilizing the carrier and releasing the drug in a controlled manner. Common redox-responsive designs include disulfide-crosslinked micelles, vesicles, and dendrimers[49]. Polymers such as PEG-SS-PLA (polyethylene glycol–disulfide–polylactic acid) or disulfide-containing poly(amido amine) dendrimers are typical examples. These carriers maintain high stability during systemic circulation but disassemble efficiently once inside tumor cells. This approach minimizes off-target toxicity and enhances intracellular drug concentration. Redox-responsive systems are particularly useful for delivering chemotherapeutics, gene therapy agents, or siRNA[50]. Moreover, dual-responsive systems combining redox sensitivity with other stimuli like pH or enzyme activity are under active investigation to improve specificity and drug release kinetics. Limitations include variations in GSH levels among different tumor types and potential premature drug release in inflammatory environments. Nonetheless, redox-responsive nanocarriers hold strong potential in cancer nanomedicine due to their precision in intracellular drug release.

***3.3* Enzyme-Responsive Nanocarriers:** Enzyme-responsive nanocarriers are innovative systems that leverage the abnormal enzymatic activity associated with tumor progression, metastasis, and invasion. These nanocarriers are typically engineered to degrade or activate in the presence of specific enzymes that are overexpressed in tumor tissues, such as matrix metalloproteinases (MMPs), cathepsins, and phospholipases[51]. MMPs, particularly MMP-2 and MMP-9, are highly expressed in the tumor extracellular matrix and play a pivotal role in matrix remodeling and tumor metastasis. Nanocarriers are designed with enzyme-sensitive peptides or linkers, such as Gly-Pro-Leu-Gly-Ile-Ala-Gly-Gln (GPLGIAGQ), that serve as substrates for enzymatic cleavage. These components are integrated into the nanoparticle shell, core, or as a gatekeeping mechanism that blocks the drug payload[51]. Upon exposure to the target enzyme, the carrier undergoes structural changes or disassembly, enabling site-specific drug release. For example, liposomes or micelles containing MMP-cleavable shells allow for tumor-specific activation while remaining inert in healthy tissues. This enhances therapeutic efficacy and reduces systemic toxicity[51]. Enzyme-responsive carriers have been successfully employed for the delivery of doxorubicin, paclitaxel, and siRNA. Furthermore, dual-targeted systems incorporating both enzyme-responsive motifs and active targeting ligands (e.g., folate or antibodies) have shown synergistic improvements in tumor selectivity. One challenge is the intertumoral and intratumoral heterogeneity in enzyme expression, which can impact drug release efficiency. However, with advancements in enzyme profiling and responsive material design, enzyme-responsive nanocarriers represent a highly specific and effective strategy for personalized cancer therapy.

***3.4* Hypoxia-Responsive Nanocarriers:** Hypoxia-responsive nanocarriers are specialized systems designed to respond to the low oxygen levels found within the tumor microenvironment, a condition often associated with aggressive tumor growth and resistance to therapy[52]. Hypoxia results from the rapid proliferation of tumor cells outpacing their blood supply, leading to regions with oxygen levels significantly lower than those in healthy tissues. This hallmark of solid tumors provides an opportunity for selective drug release using hypoxia-sensitive materials[52]. Commonly used hypoxia-responsive moieties include azobenzene, nitroimidazole, and quinone-based compounds. These groups undergo bioreductive reactions mediated by hypoxia-inducible reductases, such as nitroreductase or azoreductase, leading to bond cleavage or structural transformation that destabilizes the nanocarrier and releases the therapeutic payload. For instance, nanoparticles incorporating 2-nitroimidazole can be selectively reduced in hypoxic zones, triggering drug release while sparing normoxic tissues. These systems are particularly advantageous for targeting poorly vascularized tumor cores where conventional therapies often fail to reach. Hypoxia-responsive nanocarriers have been developed for

chemotherapy, photodynamic therapy, and gene delivery applications[53]. Additionally, some systems are designed to become fluorescent or photoactive under hypoxic conditions, aiding in tumor imaging and theranostics. One limitation is the spatial and temporal heterogeneity of tumor hypoxia, which may affect the uniformity of drug release. Strategies to overcome this include combining hypoxia-responsiveness with other stimuli (e.g., pH or redox) or using oxygen-depleting agents to enhance hypoxic conditions. Despite these challenges, hypoxia-responsive nanocarriers represent a cutting-edge approach for achieving deep tumor penetration and selective therapy.

***3.5* Externally Triggered Nanocarriers:** Externally triggered nanocarriers offer precise spatiotemporal control over drug release by responding to physical stimuli applied from outside the body. These systems are particularly advantageous because the external triggers—such as light, heat, ultrasound, and magnetic fields can be applied non-invasively and selectively to the tumor region, minimizing off-target effects[54]. Light-responsive nanocarriers, especially those activated by near-infrared (NIR) light, are widely studied due to their ability to penetrate deep tissues. Materials like gold nanorods, carbon nanotubes, and indocyanine green (ICG) absorb NIR light and convert it into heat (photothermal effect), causing nanocarrier disruption and drug release. Thermo-responsive polymers such as poly(N-isopropylacrylamide) (PNIPAM) undergo phase transitions at specific temperatures, enabling controlled drug discharge under localized heating[54]. Ultrasound-triggered carriers often utilize microbubbles or nanodroplets that cavitate or rupture under focused ultrasound waves, enhancing drug release and tissue permeability. Magnetic field-responsive carriers incorporate magnetic nanoparticles (e.g., iron oxide) that can generate localized hyperthermia when exposed to an alternating magnetic field or be guided magnetically to the tumor site. Some systems combine imaging and therapy (theranostics), enabling real-time monitoring of drug delivery. Externally triggered systems are highly versatile and can be adapted for multi-modal therapies, including photodynamic and gene therapy[54]. However, challenges include ensuring uniform stimulus application and avoiding damage to surrounding tissues. With advances in device technology and nanocarrier engineering, externally triggered systems represent a powerful platform for achieving on-demand and site-specific drug delivery in cancer treatment.

4. Recent Advances and Clinical Potential

Recent years have witnessed significant progress in the design and functionalization of stimuli-responsive nanocarriers. Multifunctional platforms that respond to multiple stimuli—such as dual pH and redox-responsive micelles—have been developed to enhance selectivity and overcome tumor heterogeneity[55]. Nanocarriers co-loaded with imaging agents and therapeutics facilitate theranostics, enabling real-time tracking and treatment monitoring. Some formulations, such as pH-responsive liposomes and enzyme-triggered nanoparticles, have shown promising preclinical results and are advancing toward clinical trials[55].

Despite these advancements, only a few stimuli-responsive nanocarriers have reached clinical evaluation due to challenges in large-scale synthesis, stability, immunogenicity, and regulatory hurdles. Nevertheless, the combination of advanced materials science and a deeper understanding of tumor biology continues to drive innovation in this space.

5. Challenges and Future Directions

While the promise of stimuli-responsive nanocarriers is immense, several challenges continue to hinder their full clinical realization. One of the most pressing issues is biocompatibility and safety. Although many of these nanocarriers are engineered to degrade within the body, their long-term toxicity and biodegradation profiles are not yet fully understood. Prolonged accumulation in non-target tissues or the induction of immune responses could pose risks to patients, necessitating comprehensive toxicological studies. Another major hurdle is scale-up and reproducibility. While laboratory-scale synthesis can yield uniform and effective nanocarriers, scaling up production for industrial or clinical use often leads to variability in particle size, drug loading efficiency, and functionalization. Ensuring consistent quality and functionality across batches remains a significant barrier to commercialization.

Tumor heterogeneity adds another layer of complexity. The tumor microenvironment (TME) varies significantly between different tumor types and even among different regions within the same tumor. This variability affects the responsiveness of stimuli-sensitive nanocarriers, potentially reducing their efficacy in heterogeneous clinical settings. Furthermore, regulatory approval presents a formidable challenge. The intricate compositions and mechanisms of these nanocarriers demand thorough evaluation and validation by regulatory agencies, which often results in prolonged review periods and increased costs.

Future research should focus on integrating artificial intelligence and machine learning to enable personalized nanomedicine design tailored to individual patient profiles. Enhanced in vivo imaging and real-time tracking systems will be essential for monitoring distribution and activation. Moreover, the development of universal, modular platforms capable of responding to multiple tumor stimuli could offer more adaptable and broadly applicable solutions. Collaborative efforts involving academia, industry, and regulatory bodies are vital to overcoming these barriers and accelerating clinical translation.

6. Conclusion

Stimuli-responsive nanocarriers represent a transformative approach in cancer therapy, offering site-specific drug delivery and enhanced therapeutic outcomes. By capitalizing on the unique features of the tumor

microenvironment, these smart systems hold the potential to revolutionize cancer treatment. Continued innovation in material design, coupled with rigorous clinical validation, will be essential to fully harness their potential and bring these advanced therapeutics to the clinic.

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