

Tumor Microenvironment-Responsive Nanomedicine: Targeting Hypoxia, Acidity, and ECM for Smart Drug Release

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ABSTRACT

The tumor microenvironment (TME) plays a pivotal role in cancer progression, therapeutic resistance, and metastasis. Characterized by hypoxia, acidic pH, and a dense extracellular matrix (ECM), the TME creates a unique niche that conventional therapies struggle to penetrate. Nanomedicine has emerged as a promising platform to overcome these barriers by designing smart, stimuli-responsive drug delivery systems that selectively respond to TME-specific cues. This review provides a comprehensive overview of tumor microenvironment-responsive nanomedicines, with a focus on their ability to exploit hypoxia, acidity, and ECM abnormalities for targeted and controlled drug release. We explore the design principles, recent advances, and therapeutic benefits of such systems, highlighting their role in enhancing drug bioavailability, minimizing off-target toxicity, and improving clinical outcomes. Furthermore, we discuss translational challenges and future directions to realize the full potential of these nanocarriers in personalized cancer therapy.

Keywords: Tumor microenvironment; Hypoxia-responsive nanomedicine; pH-sensitive drug delivery; ECM-targeted nanoparticles; Smart drug release systems

INTRODUCTION

Cancer continues to be one of the most significant global health burdens, responsible for millions of deaths annually[1–4]. Despite major advances in early detection, surgery, chemotherapy, radiation, and immunotherapy, the overall efficacy of conventional cancer therapies remains limited. This limitation largely stems from the inability of traditional treatments to effectively target and overcome the complexities inherent within the tumor microenvironment (TME)[5–8]. The TME is not merely a passive bystander but a highly active, dynamic, and heterogeneous milieu composed of malignant cells, cancer-associated fibroblasts, immune cells, endothelial cells, pericytes, abnormal vasculature, and a dense extracellular matrix (ECM). These components interact through various signaling pathways and biochemical mechanisms to create a supportive niche for tumor growth, immune evasion, metastasis, and therapeutic resistance[9–12].

Three key physiological abnormalities characterize the TME: hypoxia, acidity, and ECM remodeling[13, 14]. Hypoxia arises due to a mismatch between the rapid proliferation of tumor cells and the insufficient supply of oxygen from the disorganized and leaky tumor vasculature. Acidic pH results from enhanced glycolytic metabolism (Warburg effect), which generates lactic acid and proton accumulation in the extracellular milieu[15]. ECM remodeling, driven by overexpression of matrix metalloproteinases (MMPs) and altered collagen deposition, further contributes to increased tissue stiffness, interstitial pressure, and impaired drug penetration. These hallmarks not only drive malignant progression but also significantly reduce the effectiveness of systemic treatments by creating physical and biochemical barriers to drug delivery[15, 16].

To circumvent these challenges, nanomedicine has emerged as a promising paradigm in oncology. Nanomedicine leverages the principles of nanotechnology to develop drug delivery systems typically in the size range of 10 to 200 nanometers that can preferentially accumulate in tumor tissues through passive (enhanced permeability and retention, EPR effect) and active targeting mechanisms[16]. More recently, the field has evolved to engineer TME-responsive smart nanocarriers that are capable of responding to specific cues within the TME for controlled and localized drug release. These responsive systems can sense changes in oxygen

levels, pH, enzymatic activity, redox status, and mechanical properties of the tumor stroma, and are designed to remain inert during circulation but activate upon encountering tumor-specific stimuli[17–19].

Hypoxia-responsive nanocarriers, for example, exploit the reduced oxygen environment to trigger the cleavage of specific linkers or activation of prodrugs[20]. pH-sensitive systems are tailored to respond to the mildly acidic pH (6.5–6.8) of the tumor interstitium, releasing their cargo selectively within tumor tissues. Similarly, ECM-responsive nanomedicines utilize enzyme-cleavable peptides or ligands to target overexpressed proteases like MMPs, enabling selective degradation of barriers or matrix components that hinder drug diffusion[20].

These smart systems offer several advantages over conventional therapies. They allow for spatiotemporal control of drug release, which minimizes off-target toxicity and enhances drug accumulation at the tumor site[21]. Moreover, by tailoring the physicochemical properties of nanocarriers such as size, charge, surface modification, and ligand attachment, researchers can enhance penetration into tumor cores, improve circulation half-life, and enable real-time imaging through the integration of contrast agents[21, 22].

Despite their promise, TME-responsive nanomedicines face challenges related to inter- and intra-tumoral heterogeneity, immune clearance, manufacturing scalability, and regulatory approval[23]. Nonetheless, preclinical and early-phase clinical trials have shown encouraging results, and ongoing research is focused on optimizing their design, understanding biological interactions, and developing combination therapies that synergize nanomedicine with immunotherapy, radiotherapy, or gene editing technologies[23].

This review comprehensively explores how nanomedicine platforms engineered to respond to hypoxia, acidity, and ECM dynamics are transforming the landscape of cancer treatment. We will detail the design principles, mechanisms of action, preclinical/clinical evidence, and future directions of these advanced therapeutic systems, emphasizing their role in achieving **precision oncology**.

2. Hypoxia-Responsive Nanomedicine

Hypoxia, or reduced oxygen availability, is a defining feature of the tumor microenvironment (TME), especially in solid tumors[15, 16, 20]. It arises from the rapid proliferation of cancer cells outpacing their blood supply and is exacerbated by structurally and functionally abnormal tumor vasculature. Hypoxia promotes tumor aggressiveness, immune evasion, epithelial-to-mesenchymal transition (EMT), angiogenesis, and resistance to therapies such as radiation and certain chemotherapeutics. As such, it represents both a therapeutic challenge and a unique opportunity for stimuli-responsive drug delivery[24–26]. Hypoxia-responsive nanomedicine capitalizes on this feature by engineering nanosystems that are activated or destabilized under low oxygen conditions, thereby enabling selective drug release within hypoxic tumor zone[20]s. These nanocarriers are typically composed of polymers, liposomes, dendrimers, or inorganic materials functionalized with hypoxia-sensitive linkers or moieties. The most commonly used hypoxia-responsive components include azobenzene groups, nitroimidazole derivatives, quinones, and hypoxia-activated prodrugs (HAPs)[27, 28]. One widely studied mechanism involves bioreduction of nitroaromatic compounds under hypoxic conditions by intracellular nitroreductases[29]. For instance, nitroimidazole-functionalized nanoparticles can undergo reduction in oxygen-deficient tissues, leading to the cleavage of bonds or structural changes that result in drug release. Similarly, azobenzene linkers, stable under normoxia, can be cleaved in hypoxia to disassemble the nanocarrier and release the therapeutic payload[29].

A notable example is the use of tirapazamine (TPZ), a hypoxia-activated cytotoxin that becomes highly toxic upon one-electron reduction in hypoxic conditions. Encapsulation of TPZ within liposomes or polymeric nanoparticles has demonstrated improved accumulation in hypoxic tumor cores and enhanced cytotoxicity in multiple cancer models[30]. In addition to therapeutic agents, hypoxia-responsive nanoparticles can be co-loaded with diagnostic probes (e.g., fluorescent dyes, MRI contrast agents) to enable theranostic applications simultaneous imaging and treatment. Moreover, hypoxia-responsive nanomedicines can synergize with other therapies. For instance, combining these nanocarriers with anti-angiogenic agents can further reduce tumor oxygenation, creating a positive feedback loop that enhances drug activation[30]. Similarly, their integration with immune checkpoint inhibitors may counteract hypoxia-induced immunosuppression by selectively killing cells in immune-cold, hypoxic tumor regions[31, 32].

Design considerations for hypoxia-responsive nanocarriers include particle stability in circulation, trigger sensitivity, drug loading efficiency, and biodistribution[20]. Surface functionalization with PEG (polyethylene glycol) can prolong systemic circulation and reduce clearance by the reticuloendothelial system. Active targeting ligands (e.g., folate, transferrin, RGD peptides) may be added to improve uptake by tumor cells expressing specific receptors[33].

Despite these advantages, several challenges remain. The spatial and temporal heterogeneity of hypoxia within tumors complicates uniform drug activation. Some tumor regions may be normoxic or intermittently hypoxic, leading to inconsistent therapeutic effects[34]. Furthermore, the variability in expression of hypoxia-inducible factors (HIFs) and hypoxia-associated enzymes can affect the efficacy of bioreductive systems. Safety profiles and long-term toxicity of these novel materials also require rigorous evaluation in clinical settings[35]. Nevertheless, hypoxia-responsive nanomedicine holds immense promise for precision-targeted cancer therapy.

As our understanding of hypoxic signaling pathways deepens and new biocompatible materials are developed, future nanoplatfoms may feature multiplexed responsiveness targeting not only hypoxia but also acidity, redox

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conditions, or enzymatic activity for enhanced specificity[36, 37]. Ultimately, these systems could be pivotal in addressing therapeutic resistance and improving outcomes in patients with aggressive, hypoxic tumors.

3. pH-Responsive Nanomedicine

One of the hallmark features of the tumor microenvironment (TME) is its acidic extracellular pH, typically ranging from 6.0 to 6.8, compared to the normal physiological pH of around 7.4[38]. This acidic milieu arises due to the Warburg effect, wherein cancer cells preferentially rely on aerobic glycolysis for energy production even in the presence of oxygen. This metabolic reprogramming results in excessive production of lactic acid and protons, which are secreted into the extracellular space[39]. Compounding this effect, poor vascular perfusion and hypoxia in the TME impede proton clearance, further contributing to acidification. This pH gradient provides a unique biochemical trigger that can be exploited for selective and controlled drug release using pH-responsive nanomedicine.

pH-responsive nanomedicines are engineered to remain stable under physiological conditions but undergo structural changes, such as swelling, dissociation, or cleavage, in response to acidic conditions within the tumor. These changes can be harnessed to release encapsulated therapeutic agents specifically within the tumor site, sparing healthy tissues and thereby minimizing systemic toxicity. A variety of pH-sensitive materials and chemical linkers have been employed in the design of such systems[40].

Common acid-labile linkers used in pH-sensitive nanomedicines include hydrazone, cis-aconityl, imine, acetal, and orthoester bonds. These linkers degrade in acidic conditions to release the drug payload. For example, doxorubicin (DOX), a widely used chemotherapeutic, has been conjugated to carriers such as liposomes or dendrimers via hydrazone bonds[41]. These conjugates remain stable in blood circulation but rapidly release DOX in the acidic tumor microenvironment. Such systems are exemplified by hydrazone-linked DOX liposomes, which have demonstrated increased tumor accumulation and enhanced therapeutic efficacy in preclinical models[42]. Additionally, polymeric micelles, composed of amphiphilic block copolymers, can self-assemble into nanosized structures with hydrophobic cores and hydrophilic shells. When functionalized with pH-sensitive components, these micelles disassemble at low pH, facilitating the release of encapsulated drugs directly within acidic tumor compartments[43–45]. For instance, micelles composed of poly(ethylene glycol)-b-poly(L-histidine) exploit the protonation of histidine residues at acidic pH to destabilize the micelle structure and release the payload.

Furthermore, pH-cleavable coatings and surface-modified nanoparticles represent another strategy. For instance, mesoporous silica nanoparticles coated with pH-sensitive polymers (such as poly(acrylic acid) or polydopamine) can degrade or swell under acidic conditions, allowing drug diffusion[46, 47]. Some nanoparticles use proton-sponge effects, where polymers with tertiary amine groups (e.g., polyethyleneimine) become protonated in acidic environments, leading to osmotic swelling and membrane rupture, facilitating endosomal escape and cytoplasmic drug release.

Despite the promise of pH-responsive nanomedicine, challenges remain. The heterogeneity of tumor pH, which can vary between different tumor types and even among regions within the same tumor, complicates the design of universally effective pH-sensitive systems. Consequently, there is a need for tunable nanocarriers that can respond to narrow and customizable pH windows[48]. Moreover, precise control over release kinetics and ensuring stability during circulation are critical for maximizing therapeutic outcomes. To address these limitations, recent advances focus on dual- or multi-responsive systems that integrate pH-responsiveness with other TME features, such as hypoxia or enzymatic activity, for synergistic and staged drug release[48]. Additionally, pH-activated imaging probes can be co-delivered to allow real-time visualization of drug release and tumor acidity, enhancing personalized therapy and treatment monitoring. In sum, pH-responsive nanomedicines offer a powerful and targeted approach to cancer therapy by leveraging the acidic nature of the tumor microenvironment[49]. Through careful selection of acid-labile linkers, responsive polymers, and smart carrier designs, these systems can achieve controlled drug release, improved tumor penetration, and reduced off-target effects. Continued research into pH heterogeneity and nanomaterial engineering will be key to unlocking the full clinical potential of this strategy.

4. ECM-Targeted Nanomedicine

The extracellular matrix (ECM) of tumors plays a crucial role in both tumor progression and therapeutic resistance. Unlike the ECM in normal tissues, the tumor ECM is often dense, fibrotic, and disorganized, with a composition rich in collagen, fibronectin, hyaluronic acid, and proteoglycans[50]. This abnormal ECM not only serves as a structural scaffold but also acts as a physical and biochemical barrier that impedes drug penetration and nanoparticle diffusion. Hence, effective drug delivery must overcome or exploit the ECM to ensure therapeutic agents reach tumor cells efficiently[50].

ECM-targeted nanomedicine strategies are designed to either navigate through the ECM or actively remodel it to facilitate drug transport[50, 51]. One common strategy involves surface functionalization of nanocarriers with peptides or ligands that bind to ECM components. For instance, arginine-glycine-aspartic acid (RGD) peptides bind to integrins (particularly $\alpha\beta3$ and $\alpha\beta5$), which are overexpressed on tumor cells and endothelial cells, enabling targeted delivery to ECM-rich tumor regions[52]. Nanoparticles decorated with RGD peptides have shown enhanced tumor accumulation and deeper penetration.

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Another approach leverages enzyme-responsive nanocarriers that are activated by tumor-specific proteases[53]. Matrix metalloproteinases (MMPs), particularly MMP-2 and MMP-9, are commonly upregulated in many cancers and are associated with ECM degradation during tumor invasion and metastasis. Nanoparticles equipped with MMP-cleavable peptide linkers can release drugs or undergo structural transformation upon encountering these enzymes. This allows for site-specific activation of therapeutics within the tumor microenvironment[54].

Further, nanocarriers can be co-delivered or coated with ECM-degrading enzymes such as hyaluronidase, collagenase, or chondroitinase, which actively digest ECM components. For example, hyaluronidase-coated liposomes or nanoparticles degrade hyaluronic acid in the tumor stroma, decreasing interstitial fluid pressure and enhancing the penetration of co-administered drugs[54]. This strategy has been particularly useful in desmoplastic tumors like pancreatic ductal adenocarcinoma, where ECM density severely limits drug delivery. Additionally, ECM stiffness and mechanical properties have emerged as potential triggers for responsive nanomedicine[55]. Tumor ECM is often stiffer than normal tissue, and this biomechanical property can be used as a stimulus to design mechanosensitive carriers. For example, materials that undergo conformational changes or release cargo under specific mechanical stresses may selectively activate within the tumor ECM[55]. Some nanomedicines also incorporate responsive imaging agents or biosensors that detect ECM remodeling. These systems allow real-time monitoring of ECM degradation, drug release, and therapeutic response, aiding in theranostics and personalized treatment planning. Importantly, ECM-targeted nanomedicine strategies can be synergistically combined with other TME-responsive mechanisms, such as pH- or hypoxia-responsiveness, to develop multi-stage delivery systems. For example, a nanoparticle may first degrade the ECM to penetrate deeply, then release its drug payload in response to acidic pH or hypoxic signals within the tumor core. This sequential strategy ensures both efficient accumulation and targeted drug activation, improving therapeutic outcomes[36]. However, challenges in ECM-targeted therapy include potential off-target ECM degradation, which can harm normal tissue integrity, and variable ECM composition across different tumor types and patients. Therefore, strategies must be tumor-specific and tightly regulated to minimize collateral damage. The ECM represents both a barrier and a target in tumor drug delivery. ECM-targeted nanomedicines hold immense potential in overcoming delivery obstacles by either traversing or remodeling the matrix[56]. Through peptide targeting, enzyme responsiveness, and mechanical sensitivity, these systems can significantly enhance nanoparticle penetration, improve drug efficacy, and serve as part of multifunctional therapeutic platforms for solid tumors.

5. Combination Strategies and Theranostics

The tumor microenvironment (TME) is a multifactorial and dynamic system characterized by heterogeneous acidity, hypoxia, dense extracellular matrix (ECM), and abnormal vasculature[24, 49]. These complexities pose significant barriers to effective drug delivery, therapeutic efficacy, and real-time treatment monitoring. As single-stimulus responsive systems may be insufficient to address such diverse features, researchers have turned to combination strategies that integrate multiple TME-responsive triggers, notably pH, hypoxia, and ECM remodeling, into a single nanocarrier[57]. Simultaneously, the development of theranostic platforms, which combine therapeutic and diagnostic functionalities, offers real-time visualization, precision delivery, and individualized therapy adjustments.

Combination-responsive nanomedicine is designed to sequentially or simultaneously respond to multiple stimuli in the TME. For instance, a nanoparticle may initially penetrate the ECM via enzymatic degradation or ECM-binding peptides, subsequently release its therapeutic payload in response to acidic pH, and finally activate or intensify drug release under hypoxic conditions within the tumor core. These multistage delivery systems provide several advantages: they enhance intratumoral penetration, improve spatial and temporal control of drug release, and increase therapeutic specificity while reducing off-target toxicity[57].

A representative example is a hybrid nanoparticle system engineered with an outer shell sensitive to MMPs for ECM degradation, an intermediate layer that dissolves in acidic pH, and a core responsive to hypoxia for drug activation[58]. The outer MMP-cleavable layer allows the nanoparticle to penetrate the dense ECM. Upon reaching the acidic tumor extracellular matrix, the second layer dissolves, exposing a hypoxia-sensitive prodrug or therapeutic gene that becomes active only in the low-oxygen tumor core[58]. This stepwise activation enables drugs to reach and be released specifically at the most therapeutically relevant regions of the tumor.

Moreover, multifunctional nanocarriers can be engineered to deliver combinational therapeutics such as chemotherapeutics, immune modulators, siRNA, and photosensitizers, enabling synergistic treatments[59]. For example, pH-responsive liposomes co-loaded with a chemotherapeutic drug and a hypoxia-activated prodrug can simultaneously target proliferative and hypoxic tumor regions, which are typically resistant to monotherapies. Similarly, ECM-penetrating nanoparticles carrying immune checkpoint inhibitors and anti-angiogenic agents can modulate both the immune response and tumor vasculature, enhancing therapeutic outcomes[60].

While such complex systems offer superior targeting and efficacy, their successful clinical translation depends on real-time monitoring and precise control, which is where theranostics play a critical role. Theranostic nanomedicines integrate imaging agents—such as near-infrared (NIR) fluorophores, magnetic resonance

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imaging (MRI) contrast agents, or radioactive tracers—into the nanocarrier[17, 32, 61]. These agents allow visualization of nanoparticle biodistribution, drug release, and therapeutic response through non-invasive imaging techniques.

For instance, MRI-visible iron oxide nanoparticles functionalized with pH- or hypoxia-sensitive linkers enable clinicians to track drug accumulation and release in real time[62]. Similarly, fluorescent or photoacoustic imaging probes responsive to enzyme activity or ECM remodeling provide dynamic insight into the tumor microarchitecture and drug penetration. These features can guide personalized therapy, ensuring optimal drug dosing and treatment timing based on individual tumor physiology.

Beyond diagnostics, theranostic systems also support image-guided therapy, such as photothermal or photodynamic therapy. Nanoparticles loaded with both imaging agents and photosensitizers can be directed to tumors using imaging feedback, then activated with external light or energy sources to induce localized cytotoxicity.

Despite the promise of combination-responsive and theranostic nanomedicines, there are design and translational challenges. First, increasing the number of responsive features can lead to overly complex systems, making scalable manufacturing, quality control, and regulatory approval difficult[62]. Second, maintaining stability in circulation while ensuring timely responsiveness to TME stimuli demands finely balanced material properties and structural integrity. Additionally, patient-to-patient variability in TME characteristics requires adaptable and tunable platforms for broad clinical application. To address these issues, recent innovations focus on modular and self-assembling nanoplateforms, which can be easily modified with different responsive elements or imaging labels depending on the therapeutic goal. Moreover, advances in artificial intelligence (AI) and machine learning are being explored to optimize nanocarrier design and predict tumor-specific responses, further enhancing the clinical utility of these systems. In sum, combination strategies that simultaneously target multiple TME features such as ECM, pH, and hypoxia, combined with theranostic capabilities, represent a cutting-edge approach in cancer nanomedicine. These smart platforms not only improve drug delivery and therapeutic precision but also provide real-time feedback for personalized interventions. With continued advancements in material science, imaging technology, and clinical integration, such nanomedicine systems hold great potential to revolutionize cancer diagnosis and therapy.

6. Clinical Translation and Challenges

Despite promising preclinical results, several obstacles hinder the clinical translation of TME-responsive nanomedicines. These include batch-to-batch variability in synthesis, scalability issues, unpredictable pharmacokinetics, and the need for stringent regulatory evaluation. Moreover, the heterogeneity of the TME across different patients and tumor types complicates the generalization of therapeutic responses[63]. Standardized models and robust biomarkers are needed to guide personalized nanomedicine design. Advances in microfluidic tumor models, AI-assisted formulation, and patient-derived xenografts may accelerate the path from bench to bedside[63].

7. Future Perspectives

TME-responsive nanomedicine holds immense promise for next-generation cancer therapy. Future research should focus on: (1) engineering robust, scalable, and reproducible systems; (2) developing intelligent multi-responsive platforms; (3) integrating with immunotherapy and gene editing; and (4) validating efficacy in clinically relevant models. Collaborative efforts between material scientists, oncologists, and bioengineers will be essential to overcome translational barriers. Ultimately, smart nanocarriers tailored to the tumor microenvironment may redefine precision oncology, offering safer and more effective treatments for patients worldwide.

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