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REVIEW

Tumor Microenvironment-Responsive Nanoparticles: Promising Cancer PTT Carriers

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Abstract: The tumor microenvironment (TME) is often characterized by distinctive features such as hypoxia, low pH, the over-expression of extracellular matrix-degrading enzymes, and increased redox reactions. These attributes create a specialized internal environment that promotes tumor cell survival and proliferation, thereby facilitating tumor development, metastasis, and the emergence of drug resistance. These challenging aspects pose significant hurdles to the efficacy of traditional cancer therapies. However, they also offer unique opportunities for the development of responsive nanomedicines that specifically target the TME to improve treatment outcomes for cancer patients when combined with photothermal therapy (PTT). This review provides an overview of the predominant features of the TME and delves into recent advancements in the field of nanomedicine, with a special focus on TME-responsive nanomedicines. Each type of TME-responsive nanomedicine is reviewed for its potential value in drug delivery in combination with PTT and chemotherapy, which may enable effective multimodal antitumor therapy. Finally, the review discusses the challenges and opportunities associated with the use of TME-responsive nanomaterials in PTT, highlighting the potential for these innovative strategies to overcome current therapeutic limitations and improve patient outcomes.

Keywords: tumor microenvironment, photothermal therapy, cancer therapy, nanoparticle

Introduction

Cancer remains one of three leading causes of death worldwide,[1] particularly since many patients are diagnosed with advanced, metastatic disease, which is still considered to be incurable.[2] Over the past decade or so, there has been a continuous search for new strategies and methods for tumor treatment, and nanomaterials have gradually been used for the diagnosis and treatment of cancer[3] to reduce systemic toxicity and increase the targeting of tumors and metastatic cancer cells.[4]

In the early stages of nanotechnology development, scientists discovered that some metal nanoparticles, owing to their unique optical properties, possess excellent photothermal conversion abilities.[5] They can exert thermal effects upon irradiation with a laser or another light source.[6] This provides more options and potential applications for photothermal therapy (PTT). Therefore, in recent years, PTT with nanomaterials has become a hot topic in both research and application.[7] With the advancement of nanotechnology, scientists have begun to develop various types of nanomaterials for PTT, such as semiconductor nanocrystals,[8] multiwalled carbon nanotubes,[9] graphene,[10] iron oxide nanoparticles,[11] and nanoparticles based on organic materials.[12] PTT, which converts light energy into heat to kill tumor cells, has attracted widespread attention. Furthermore, there is a new understanding of cancer, which is now considered an evolutionary and ecological process involving continuous, dynamic, and interactive relationships between tumor cells and the tumor microenvironment (TME).[13] Therefore, TME-responsive nanoparticles are promising carriers for cancer PTT, which is an effective tumor treatment modality; the combination of these strategies has advantages such as noninvasive application, strong targeting ability, low systemic toxicity, and fewer side effects.[14]

This review mainly summarizes the TME and discusses the application of TME-responsive nanomaterials in PTT.

Graphical Abstract
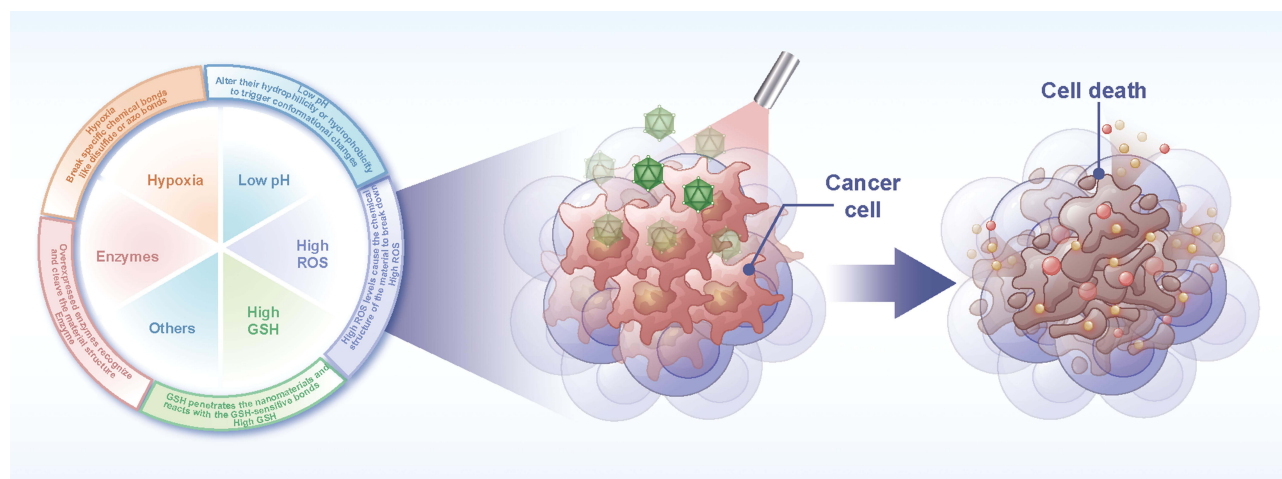
Characteristics of the Tumor Microenvironment

The TME is a crucial component in the process of tumor growth and metastasis.[15] It consists not only of the tumor cells themselves but also of the surrounding nontumor cells, the extracellular matrix (ECM), the vascular system, immune cells, and various cytokines.[16] Within the TME, different components interact with each other in complex ways that affect tumor development and response to treatment.[13] The characteristics of the TME include hypoxia,[17] an acidic pH value (pH 6.0–7.0),[18] the overexpression of certain enzymes,[19] a shift in redox potential toward more reductive conditions,[20] and high ATP levels,[21] among others (Figure 1).

Hypoxia

The TME is hypoxic, where tumor cells often proliferate and expand rapidly, leading to a swift increase in oxygen demand. Hypoxia may also be associated with angiogenesis.[22] Tumor-induced angiogenesis (the formation of new blood vessels) is usually disordered and abnormal. These newly formed vessels are often twisted and immature, and their blood flow may be unstable or insufficient, leading to problems with oxygen delivery and thus preventing sufficient oxygen from reaching the tumor regions.[23] Although hypoxia can damage both normal and cancerous cells, cancer cells are able to adapt, survive and proliferate under hypoxic conditions.[24] Moreover, hypoxia also participates in the regulation of factors such as glycolysis, growth factor signaling, immortality, genetic instability, tissue invasion and metastasis, and apoptosis, among others, enhancing tumor cell resistance to radiotherapy and chemotherapy.[25,26]

Low pH

One of the prominent features of the TME is that its pH value is lower than that of normal tissues (pH 7.2–7.4).[27] This may be attributed to the preference of the tumor tissue for anaerobic respiration and its state of high metabolism, which leads to increased production of lactic acid and other acidic metabolic byproducts, resulting in a local decrease in pH.[28] Additionally, cancer cells normally exhibit rapid proliferation and metabolic activity far exceeding that of normal cells.[29] These conditions increase the demand for energy and metabolic substrates, which could also result in the generation of excessive amounts of acidic metabolic byproducts. Hypoxia can further cause cellular acidosis, which inactivates proton pumps on the cell membrane, impedes the extrusion of protons, and thereby further reduces the pH of the extracellular fluid.[30] The infiltration of inflammatory cells[31] and the activity of immune cells[32] can also affect the local pH value.
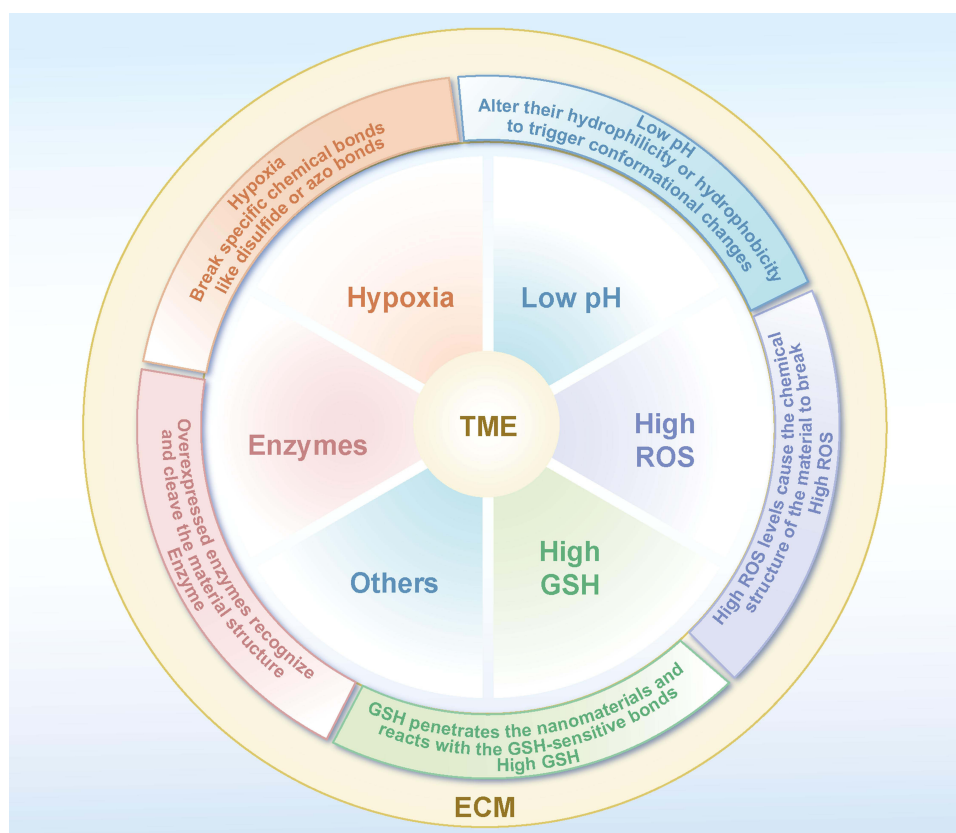
Figure 1 Illustrated Guide to the Features of the TME and Corresponding Response Strategies.

High GSH

Glutathione (GSH), a thiol-containing organic molecule abundantly found in the human body, plays a significant role in facilitating the maintenance of the cellular redox equilibrium and providing antioxidant protection.[32] It maintains the static potential of various cellular organelles and sustains a difference in surface potential.[33] GSH, primarily in the form of small, free sulfonyl groups, is highly reactive at low concentrations. In cancer cells, increased GSH levels are associated with the overexpression of γ-glutamyl cysteine synthetase and γ-glutamyl transferase. These enzymes are key in the GSH biosynthetic pathway, and their active expression in tumor cells leads to a significant increase in the GSH concentration, endowing the tumor cells with a stronger antioxidant capacity and greater potential to eliminate reactive oxygen species (ROS).[34] GSH levels in cells can reach up to four times the normal level, and GSH effectively helps tumor cells evade programmed cell death triggered by ROS.[35] GSH can maintain redox homeostasis, protect cells from oxidative damage, and reduce the toxicity induced by chemotherapy drugs, thereby safeguarding tumor cells from the impacts of most oxidative cancer treatment strategies.[36]

Overexpressed Enzymes

Enzyme overexpression is one of the key characteristics of the TME and may be caused by the upregulation of genes within tumor cells. These cells may harbor mutated proteins that increase the production of enzymes.[37] In particular, oncogenes with the potential to induce cancer may become hyperactive, whereas tumor suppressor genes, which typically regulate cell division, may be inactivated. This results in an imbalance of cellular regulatory mechanisms. These genetic alterations are often the drivers of increased enzyme production.[38] Abnormal expression and dysregulation of enzymes in the human body are the pathological bases of many diseases. Dysregulated enzymes are very valuable tumor diagnostic markers and treatment targets.

Overexpression of matrix metalloproteinases (MMPs) can promote tumor cell migration and invasion by promoting degradation of the ECM; this provides a physical pathway by which tumor cells can more easily penetrate the basement membrane and surrounding tissues, thereby facilitating the invasion and spread of the tumor.[39] Cyclooxygenase-2 (COX-2) is an enzyme that is also overexpressed in many types of tumors, where it participates in the synthesis of prostaglandins. These prostaglandins can promote inflammatory responses and contribute to the growth and apoptosis resistance of tumors.[40]

ROS

In the TME, the level of ROS production is usually high, mainly due to high metabolic activity, oxidative stress, impaired mitochondrial function, and a lack of antioxidant capacity. Tumor cells often exhibit high aerobic glycolysis to meet their demands for rapid growth and proliferation, which results in increased ROS production.[41] Moreover, tumor cells are affected by various stimuli, such as the hypoxic state in the TME and inflammatory responses. These factors can cause oxidative stress, prompting the cells to produce excess ROS to maintain survival.[42] Furthermore, the mitochondrial function of tumor cells may be compromised, leading to leakage in the mitochondrial electron transport chain and increased instability of electrons, thereby promoting ROS generation.[43] Tumor cells also lack a robust antioxidant defense system to effectively clear or neutralize ROS.

ECM

The ECM in the TME undergoes pathological remodeling, which is characterized by abnormal composition and structure, altered physical properties, and dysregulated biochemical functions.[44] This pathological transformation stems from multifactorial interactions: cancer-associated fibroblasts (CAFs)[45] and immune cells actively remodel the ECM by secreting proteases and profibrotic factors,[46] whereas tumor cell genetic mutations drive abnormal ECM protein expression.[47] Hypoxia and acidosis activate collagen-synthesizing enzymes and accelerate ECM degradation, creating a vicious cycle.[48] Additionally, posttranslational modifications of ECM components alter their functionality, promoting immune evasion and therapy resistance.[49] In summary, the aberrant evolution of the tumor-associated ECM arises from bidirectional crosstalk between tumor cells and the microenvironment, ultimately promoting the formation of a protumor fibrotic matrix that profoundly influences tumor progression and therapeutic outcomes.

TME-Responsive Nanoparticles for PTT

Nanoparticles can circulate within the body and eventually accumulate near tumor tissues, where they utilize the unique characteristics of the TME to achieve precise and efficient drug release. This targeted drug delivery enables accurate and effective attacks on tumor cells. In this process, PTT plays a crucial role. When nanoparticles release photosensitizers at the tumor site and are exposed to light, the local temperature rapidly increases. Elevated temperatures can directly kill tumor cells or increase the efficacy of drugs, thereby inhibiting tumor growth (Figure 2).

Photosensitizers can precisely target the tumor microenvironment through nanomaterials to trigger localized heating for PTT and synergize with chemotherapy via a multimodal approach to increase efficacy, achieving TME-responsive drug release for improved therapeutic outcomes.

Hypoxia-Responsive Nanomaterials

Hypoxia-responsive nanomaterials change their structure under low-oxygen conditions by breaking specific chemical bonds such as disulfide[50] or azo bonds,[51] thus causing drug release from the nanoparticles (Figure 3). They can also alter optical properties,[52] such as fluorescence, thereby serving as tools for monitoring the hypoxic state of tumors.[53]

YB1, a particularly attractive genetically modified safe Salmonella Typhimurium strain, shows self-propelling properties to penetrate the hypoxic tumor core while minimizing damage to normal tissue. Chen et al developed a biohybrid/non-biohybrid system, YB1-INPs, by linking indocyanine green (ICG), a fluorescent dye widely used in medical imaging and diagnostics, loaded nanoparticles to YB1 via amide bonds for precise tumor targeting. This system showed specific targeting of hypoxic areas in solid tumors, excellent photothermal conversion, and efficient fluorescence
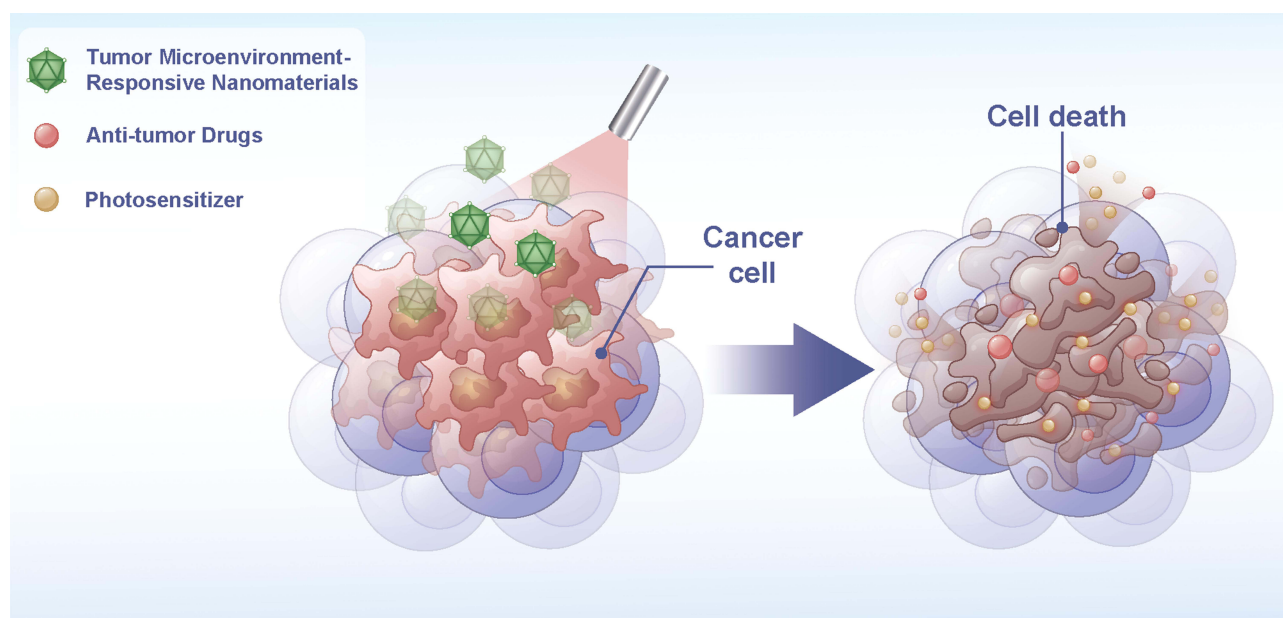
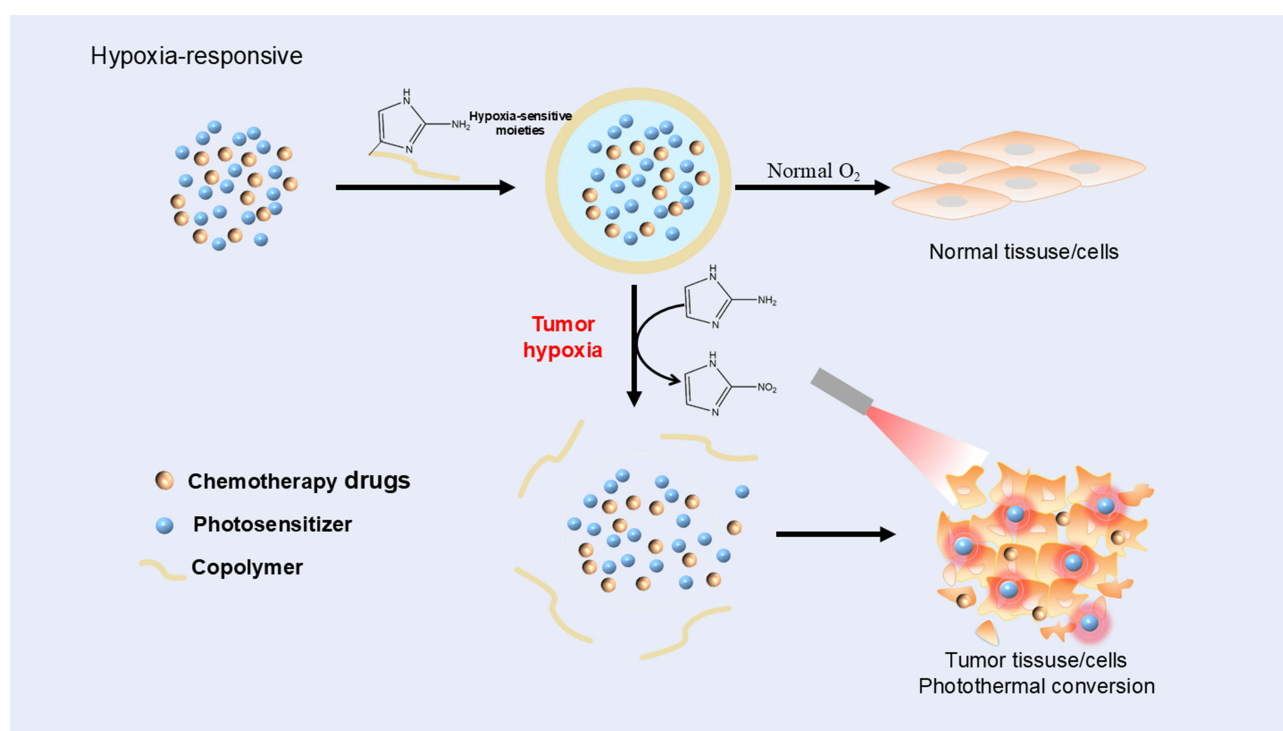**Figure 2** TME-responsive nanodelivery system for multimodal cancer therapy.

Figure 3 A graphical illustration of the mechanism of hypoxia-responsive nanoparticles.

imaging.[54] Following photothermal treatment, YB1-INP bioaccumulation increased 14-fold due to the synergistic effects of disrupting tumor tissue and attracting nutrients.

Shi et al developed a hemoglobin (Hb)-based biomimetic synthesis method to create gadolinium (Gd) nanostructures coloaded with chlorin e6 (Ce6) and oxygen, aiming to alleviate tumor hypoxia and increase the efficacy of PTT under MRI guidance.[55] The Gd@Hb-Ce6-PEG nanoparticles effectively maintained tumor oxygenation, delivered oxygen and Ce6 to tumor tissues, and exhibited excellent tumor-targeted accumulation for precise MRI-guided PTT. Photoacoustic

imaging confirmed their ability to alleviate tumor hypoxia, whereas post-PTT diffusion-weighted imaging quantified their therapeutic efficacy. The biomimetic synthesis of ultrasmall paramagnetic Gd nanostructures using endogenous Hb represents a novel approach for MRI-guided, oxygen-supplying PTT.

Hypoxia-responsive nanotherapeutics offer promise in targeting tumor cells, but challenges in accurately identifying hypoxic regions within tumors can affect their efficacy. Due to tumor heterogeneity., oxygen levels can differ due to factors such as the tumor type and local conditions. This can result in uneven drug distribution across the tumor, causing overmedication in some areas while leaving others with insufficient drug exposure.[56] Overdosing can harm nearby healthy tissue, and underdosing can reduce the efficacy and potentially lead to drug resistance in cancer cells. Advancements in imaging techniques, hypoxia indicators, and nanocarrier design are needed to improve the precision of hypoxia detection and drug delivery, increasing the overall success of nanotherapeutic treatments for cancer.[57]

pH-Responsive Nanomaterials

pH-responsive nanomaterials, which are composed of copolymers[58] or monomers[59] with functional groups, react to environmental pH variations by undergoing protonation or deprotonation. This molecular adjustment alters their hydrophilicity or hydrophobicity, triggering conformational changes that affect their stability and functionality.[60] These properties are crucial for applications such as targeted drug delivery, where drugs are released in response to the acidic pH of tumors, and in biosensing technologies used to monitor pH-related changes[61] (Figure 4).

Polymer nanoparticles were synthesized with a pH-sensitive polyethylene glycol (PEG) coating on their surface and were successfully loaded with the drug ICG. The results demonstrated that these nanoparticles possess excellent drug loading efficiency and pH-triggered drug release properties. Upon exposure to near-infrared (NIR) laser irradiation, the nanoparticles generated a significant photothermal effect, enhancing the thermotherapeutic effect on cancer cells.[62]

Additionally, Wang et al developed a smart polymer drug carrier that delivers docetaxel (DTX) and the photosensitizer IR825 to tumor cells through a pH-responsive charge reversal mechanism, achieving combined chemotherapy and PTT.[63] The polymer nanoparticles are capable of charge reversal in a slightly acidic environment, which enhances their
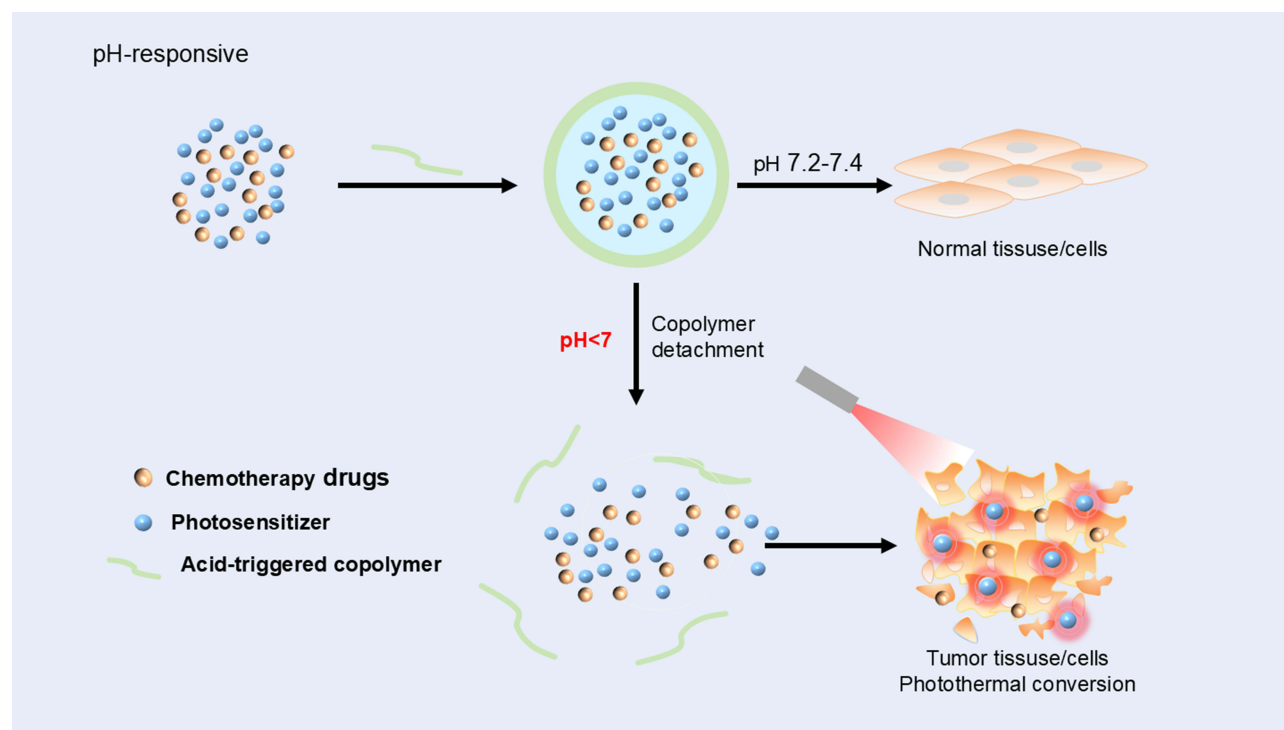

Figure 4 A graphical illustration of the mechanism of pH-responsive nanoparticles.

cellular uptake and drug release. Research results indicate that these polymer nanoparticles increase the efficacy of antitumor therapy in vitro and in vivo with good biocompatibility and safety.

Although the concept of using a decreased pH in the TME to facilitate the action of responsive nanomaterials is innovative, there are still many limitations to its current application. Within the human body, there are numerous other locations where a decrease in pH occurs, not just within the tumor area. Lysosomes, for example, can internalize nanomaterials and cause them to degrade within the body, which might lead to off-target effects and undermine the specificity of the therapy, potentially resulting in undesirable side effects.[64]

Therefore, the development of nanomaterials that can precisely identify and effectively respond to the unique microenvironment of tumors, as well as improve the stability and responsiveness of these materials, are key issues that need to be addressed in current research.

Enzyme-Responsive Nanomaterials

Nanomaterials with specificity for the enzymatic overexpression characteristic of pathologic tissues—predominantly cancerous anomalies as opposed to their normal physiological counterparts—are engineered to exploit this dysregulated expression. These constructs encompass moieties that are reactive to the aberrant enzymatic activity, incorporating peptides,[65] synthetic polymers[66] or alternative small-molecule substrates that undergo enzymatic cleavage or modification.[67] These functionalities act as conjugative linkers tethering therapeutic modalities to the nanomaterial framework, thereby localizing agent deployment until enzymatic mediation occurs. Upon infiltration of the neoplastic milieu, pathological enzyme activity facilitates the severance of these linkers, instigating site-specific liberation of the chemotherapeutic payload (Figure 5). This ensures an augmented concentration gradient within the neoplasm while mitigating the propensity for systemic toxicity.[68]

MMPs

MMPs are a prime example of enzymes that are often overexpressed in tumors.[69] MMPs play a pivotal role in the degradation of the ECM, which is a necessary step for cancer cells to invade neighboring tissues and form metastatic lesions in distant organs. By breaking down the ECM, MMPs facilitate the formation of new blood vessels
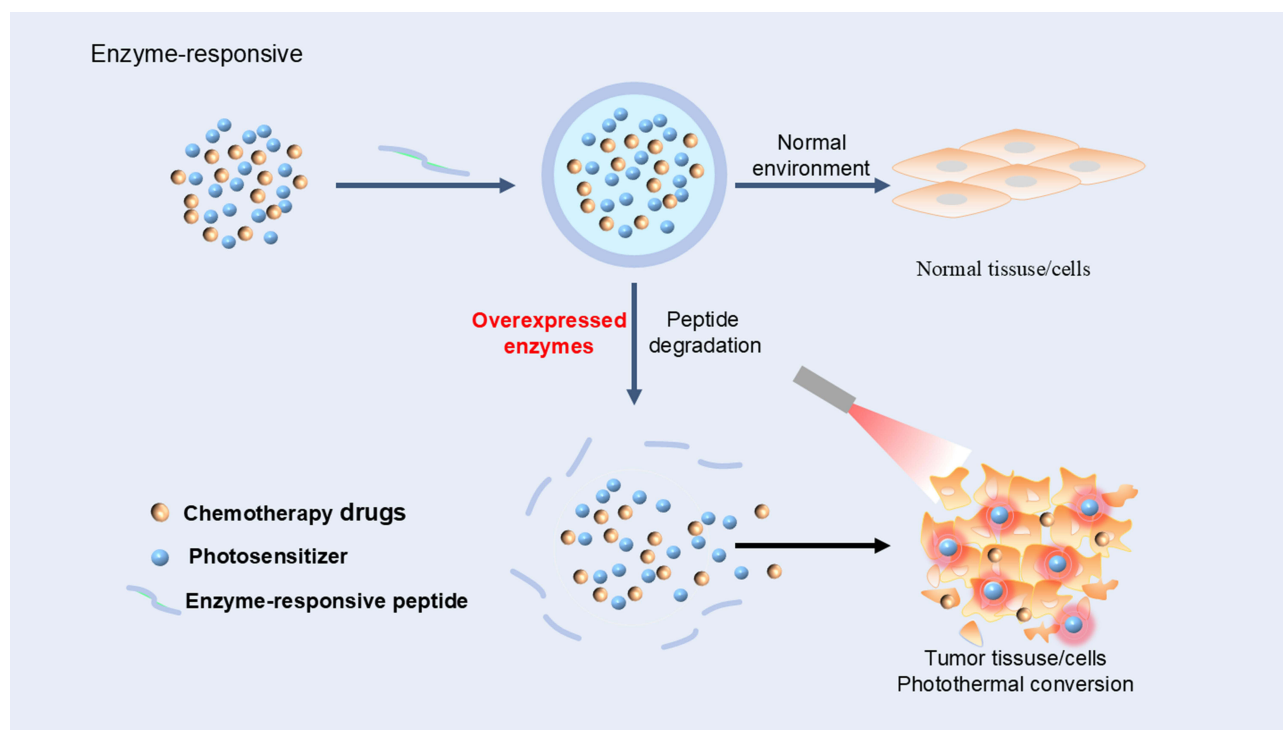

Figure 5 A graphical illustration of the mechanism of enzyme-responsive nanoparticles.

(angiogenesis), thereby supplying the tumor with the necessary oxygen and nutrients for continued growth.[70] Furthermore, MMPs contribute to the modulation of the immune response, as well as signal transduction processes that further increase tumor progression.[71]

MMP-2

An innovative nanocarrier system comprising gold nanorods (AuNRs)-doxorubicin (DOX)/mPEG$_{10K}$-peptide/P(AAm-co -AN) (APP-DOX) has been presented for drug delivery. In this system, the AuNRs act as potent agents for PTT. The APP-DOX nanoparticles are optimally sized to enable targeted localization within tumor tissue following intravenous circulation. High concentrations of MMP-2 in the tumor milieu capture and sever the peptide chains conjugated to the surface of APP-DOX. Concurrently, shedding of the PEG chains results in an increase in the hydrophobic nature of the nanoparticles, leading to their aggregation into larger particles that are retained within the tumor for enhanced accumulation. Under irradiation with an 808 nm NIR laser, the APP-DOX system undergoes a progressive heating process. The generated heat can efficiently ablate tumor cells while triggering a phase transition in the upper critical-solution-temperature (UCST) polymer that facilitates the release of the encapsulated anticancer drug DOX, which then efficiently eradicates cancer cells.[72]

MMP-9

A self-assembled spherical nucleic acid liposome was ingeniously designed by coupling 1,2-diacyl-sn-glycero-3-phos-phoethanolamine (DOPE) with the chemotherapeutic agent DOX and conjugating DOPE with MMP-9 and an immu-nostimulatory CpG oligodeoxynucleotide. This innovative spherical nucleic acid liposome (SNA) was specifically designed for targeted delivery, enabling the efficient cotransport of DOX and CpG directly to tumor sites. Upon reaching the TME, this system leverages the enzymatic activity of MMP-9, which is prevalent in many tumors, to trigger the release of both therapeutic agents.[73]

The strategic release of these drugs not only maximizes their therapeutic efficacy but also limits off-target effects, enhancing safety. Extensive research into the impact of liposomal SNAs on the immune system has revealed significant immunomodulatory benefits. Notably, it amplifies the activation of dendritic cells (DCs), which are critical players in initiating and regulating the immune response. Additionally, it promotes the proliferation of CD8+ and CD4+ T cells both within the tumor and the spleen, which are essential for mounting an effective antitumor response. The culmination of these effects is a pronounced inhibition of tumor growth and a notable extension of survival times in experimental models, highlighting the potential of this approach in advancing cancer treatment paradigms.

HAase

A hyaluronidase-responsive nanoplatform based on oxygen-deficient titanium dioxide (TiO2-x) is used for mild NIR phototherapy. Within the TME, overexpressed hyaluronidase (HAase) can easily lead to dysregulation of hyaluronic acid (HA) levels and the release of Cas9/sgRNA targeting stress alleviation regulators, namely, nuclear factor E2-related factor 2 and heat shock protein 90α, thus reducing the stress tolerance of tumor cells. Under subsequent NIR light irradiation, TiO2-x displays enhanced anticancer effects both in vitro and in vivo.[74]

Importantly, enzymes present at nonpathological sites can also trigger the release of enzyme-responsive nanomedi-cines. Many enzymes abnormally present in tumor sites are also widely found in normal tissues, and enzymes within the same family often have similar substrates, which can cause the release of the drug at nontarget sites. To ensure that enzyme-responsive drugs act only at the pathological site, it is necessary to identify more ideal tumor-specific enzymes. Moreover, the design of enzyme-responsive nanomedicines should focus on the kinetics of enzyme-catalyzed reactions. The time of the enzyme reaction and the extent of the reaction affect both the rate of drug release and the therapeutic effect and can be optimized on the basis of enzyme catalytic kinetics to adjust the dosage used for drug delivery.

Redox-Responsive Nanomaterials

Redox potential is one of the primary physiological differences between tumor and normal tissues and is advantageous for designing redox-reactive nanostructures for the delivery of chemotherapy drugs.[75] The realization of redox-triggered

drug release is primarily based on the presence of redox-sensitive components within the carriers, such as disulfide and selenide bonds. These compounds can maintain stability in the mildly oxidized extracellular space, where there is a relatively low concentration of GSH, yet they become disrupted by the significantly higher concentration of GSH present within cells. Consequently, carriers can deliver their payload intact to target cells and then rapidly disintegrate following endocytosis, thereby triggering the swift and complete release of the loaded drug within the target cells[76] (Figure 6). Redox-reactive nanocarriers achieve nearly zero premature drug release, thus avoiding off-target toxicity associated with free drugs. Thus, these nanocarriers have considerable potential in the development of more effective drug delivery systems with better pharmacokinetics and pharmacodynamics.[77]

ROS-Responsive Nanomaterials

Nanomaterials are designed to contain chemical bonds that can be oxidized or reduced by ROS, such as thioether bonds, aryl thioether bonds, disulfide bonds, and silex bonds. When these nanoparticles are exposed to high concentrations of ROS, they undergo chemical changes leading to the disaggregation or disintegration of the nanomaterial.[78] Active drug molecules can be encapsulated within ROS-responsive nanomaterials.[79] Once these nanocarriers enter cells or tissues with high levels of ROS, they respond to the ROS signals by undergoing structural changes, which in turn lead to the release of the encapsulated drugs.[80]

Zhang et al developed a cluster-bomb-like nanoplatform (CPIM). For the first time, this platform combines variable size and cellular internalization strategies to enhance both passive and active transport. For passive diffusion, to address the high ROS concentration in the TME, the cluster bomb CPIM releases drug-loaded "bomblets" (PAMAM loaded with IR780/1-methyl-D-tryptophan (1-MT), <10 nm) to promote diffusion within the tumor. Additionally, IR780 generates ROS under NIR irradiation and enhances this responsiveness; thus, NIR-triggered autodestruction behavior is induced, which endows CPIM with spatiotemporal regulatory function. In terms of anticancer performance, CPIM enhances both the PDT/PTT activity of IR780 and the indoleamine 2,3-dioxygenase (IDO) pathway inhibition effect of 1-MT, thereby enhancing tumor penetration and achieving desirable phototherapy efficiency.[81]
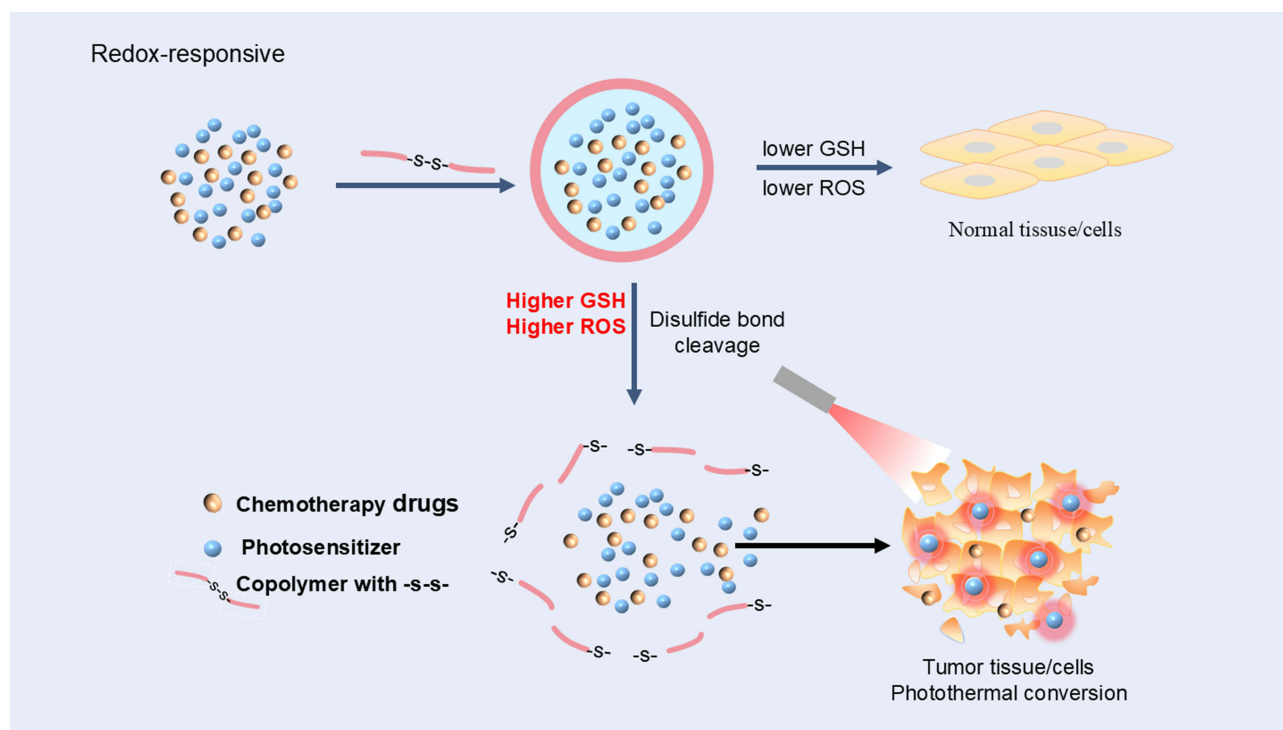

Figure 6 A graphical illustration of the mechanism of redox-responsive nanoparticles.

GSH-Responsive Nanomaterials

GSH-responsive nanomaterials are generated by incorporating GSH-sensitive chemical bonds into the structure of the nanomaterials. These chemical bonds or crosslinkers can be selectively reduced by high concentrations of GSH within cells, leading to structural changes in the nanomaterials. Inside targeted cells, GSH penetrates the nanomaterials and reacts with the GSH-sensitive bonds, which results in structural changes in the nanomaterials and the subsequent release of encapsulated drugs. This release mechanism enables efficient drug delivery targeting tumor cells.[82]

Yang et al discussed a GSH-responsive PTT nanoparticle. The study revealed that the nanoparticle undergoes fluorescence signal restoration in the presence of GSH because GSH can cleave the disulfide bonds within it, leading to the collapse of its hydrophobic core and thus the release of the ultraviolet fluorescence dye DiR and the anticancer drug paclitaxel (PTX). Additionally, the study revealed that the fluorescence signal restoration of DiR is related to the release and therapeutic action of PTX. Therefore, by monitoring the fluorescence signal restoration of DiR, one can track the release and therapeutic efficacy of PTX. These GSH-responsive PTT nanoparticles hold potential for future clinical applications. Furthermore, researchers discovered that the concentration of GSH affects the fluorescence signal restoration of this kind of nanoparticle and its cytotoxicity. Higher concentrations of GSH result in stronger fluorescence signal restoration and greater toxicity to cancer cells. Conversely, lower concentrations of GSH lead to weaker fluorescence signal restoration and reduced toxicity to cancer cells.[63,83]

Zhang et al utilized monodispersed gold nanoparticles (GNPs), which were conjugated to hepatocellular carcinoma cell-specific targeting oligonucleotides (TLS11a) via Au–S bonds. The targeting oligonucleotide featured Ce6 labeling at the 5′ end, which was linked through (GA)10 repetitive bases to Cu(II) to load AQ4N at the 3′ end. In cancer cells, the fluorescence and ROS-generating capabilities of Ce6 were specifically restored by strategic cleavage of the Au–S bond, which was facilitated by elevated levels of intracellular GSH.[84]

Furthermore, the interaction between cellular GSH levels and the efficacy of cancer therapies highlights a significant challenge in oncological treatments. When GSH in cancer cells is depleted, these cells activate their internal GSH synthesis systems. This response serves as a defense mechanism, potentially diminishing the long-term effectiveness of treatments that depend on GSH depletion to impair cancer cell viability.[85] Therefore, therapeutic approaches that integrate multiple strategies, not only targeting GSH depletion but also inhibiting the compensatory synthesis of GSH, may be a more robust solution. Such multifaceted therapies may include oxidative stress-inducing agents or inhibitors of key enzymes in the GSH synthesis pathway, with the goal of disrupting the cellular redox balance thoroughly and preventing cancer cells from adapting to and resisting treatment.

Multimodal Strategies

Due to the complexity of the TME, therapeutic approaches predicated solely on reactive measures are limited by the specificity of pharmaceuticals to singular pathological conditions.[86] However, an integrated pharmacological approach in which multiple agents are modulated in a synergistic manner can induce concomitant biochemical responses, thereby facilitating holistic and efficacious modulation of the TME. This approach effectively mitigates the inherent qualitative heterogeneity and dynamic attributes of the microenvironment. Empirical evidence suggests that the use of multiple modalities that are responsive to different stimuli not only increase precision in neoplastic targeting but also substantially attenuate collateral damage to healthy human tissues.[87] Moreover, the orchestrated release of therapeutic agents from nanoscale delivery systems, triggered by distinct stimuli at respective loci, surpasses the limitations of traditional pharmacotherapy—characterized by suboptimal solubility, pronounced toxicity and compromised stability—culminating in superior drug bioavailability and administration fidelity.[88]

Zheng et al developed a highly biocompatible nanocarrier called BMP NTs, which achieve precise antitumor therapy via a two-stage delivery mechanism. First, BMP NTs utilize the enhanced permeation and retention (EPR) effect and selectively shed their surface cleavable layer under the action of overexpressed MMP-2 in the TME, exposing hydrophobic sections and thereby achieving significantly increased tumor accumulation. Once inside cancer cells, which have an excess of GSH and H_2O_2, BMP NTs undergo a second-stage "unloading process", releasing Mn^{2+} ions and ultrasmall Bi2S3@BSA nanoparticles. The resulting Mn^{2+} can act as a Fenton-like catalyst, continuously catalyzing endogenous

H_2O_2 to produce highly toxic hydroxyl radicals (•OH) for chemodynamic therapy (CDT). The depletion of GSH, in turn, improved the $Mn^{2\pm}H_2O_2$ reaction, further increasing the efficiency of CDT. Moreover, the ultrasmall Bi2S3@BSA endows the BMP NTs with excellent photothermal conversion capability, generating local high temperatures to expedite the internal Fenton reactions within the tumor, thereby achieving effective tumor treatment under the synergistic effect of CDT/PTT. Furthermore, BMP NTs can also perform in situ spontaneous MRI and photoacoustic imaging (PA) for the guidance of precise cancer therapy.[89]

Combining different stimulus-responsive strategies can overcome the drawbacks of single stimulus responses, providing mutual assistance and complementarity. Such integrated, more advanced, and intelligent strategies are the direction of development in tumor therapy and hold immense potential. However, the preparation and therapeutic mechanisms of multi-stimulus-responsive nanodrugs are quite complex, and the absence of a single stimulus might lead to the failure of drug therapy. It is necessary to continuously observe the effects over an extended period under regular medication conditions in live animal models and to assess the efficacy and toxicity when a single stimulus is lacking.[90]

TME-Responsive Nanoparticles for Drug Delivery and Imaging

A novel carrier-free nanoconjugate that functions as a direct-acting antiviral (DAA) agent was created and featured near-infrared activity, synergistic antivascular properties, and pH-responsive photodynamic and photothermal capabilities to increase the effectiveness of cancer therapy.[91] DAA nanoparticles, developed via self-assembly, are biocompatible and have enhanced photodynamic and photothermal effects in acidic tumor environments due to diethylaminophenyl protonation. The antivascular agent 5,6-dimethylxanthenone-4-acetic acid is released by ester bond cleavage in the acidic vesicles of endothelial cells, where it targets vascular endothelial growth factor and disrupts the tumor vasculature. This precise delivery to vascular endothelial cells and tumor lysosomes enables effective tumor elimination in vitro and in vivo, suggesting a promising cancer therapy that combines antivascular effects with dual photodynamic and photo-thermal treatments.

Liu et al developed a new type of targeted polymeric micelle that can sense hypoxia in tumors, thereby activating cytotoxic and immunogenic responses and effectively eradicating advanced breast cancer.[92] These low-activation polymer micelles can also effectively deliver anticancer drugs and photosensitizers to cancer cells, inducing synergistic cytotoxicity and immunogenic cell death through chemotherapy and PTT. In addition, the micelles can activate a systemic antitumor immune response, effectively suppressing tumor recurrence and significantly inhibiting distant metastases.

TME-responsive nanoparticles enable targeted drug delivery and imaging by responding to tumor microenvironment cues such as pH and enzymes. They minimize off-target effects, improve treatment efficacy, and allow real-time monitoring via fluorescence imaging. This approach improves the accuracy of diagnosis, personalized therapy, and cancer treatment.

Conclusion

Responsive nanomaterials have emerged as pivotal carriers in PTT, offering transformative potential in tumor treatment. Their unique advantages stem from their ability to achieve precise targeting[93] and synergistic therapeutic effects.[94] By harnessing TME-specific response mechanisms, these materials enable intelligent, on-demand drug release while significantly increasing photothermal conversion efficiency and prolonging retention at the lesion site.[95] Furthermore, the photothermal effect can indirectly modulate the TME by suppressing stromal components, thereby improving nanomaterial penetration and therapeutic efficacy.[96]

The future of the use of responsive nanomaterials in PTT lies in the following key directions. First, NIR-II-responsive materials need to be developed to increase tissue penetration and therapeutic depth.[97] Second, multimodal synergistic platforms that integrate immune modulation and other therapeutic mechanisms are needed to amplify efficacy while minimizing toxicity.[98] Finally, new personalized nanomedicine strategies, in which material response thresholds are dynamically tailored to patient-specific microenvironmental features,[99] are needed.

Despite these promising attributes, there are several critical challenges in the clinical translation of responsive nanomaterials. Due to tumor heterogeneity, a delicate balance between universality and specificity needs to be achieved in material design, yet current research models often fall short of capturing the complexity of real-world pathologies.[100] Additionally, the photothermal ablation of deep-seated or large tumors remains constrained by limited tissue penetration depth and uneven thermal diffusion, underscoring the urgent need to expand the spectral response range of conventional photothermal agents.[101] Biosafety concerns further complicate their clinical application, as the long-term in vivo metabolic behavior and stability of these materials require comprehensive evaluation.

By addressing these challenges and embracing these innovations, responsive nanomedicines have the potential to bridge the gap between groundbreaking research and transformative clinical applications, ultimately redefining the landscape of tumor therapy.

Author Contributions

Heming Sun: Design, conceptualization, writing, and draft; Yuebo Li and Ming Xue: data mining, revision, supervision, and figure preparation; Dingqing Feng: design, review and editing. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no conflicts of interest.

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