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Tumor microenvironment responsive nanotherapeutics in cancer treatment: obstacles, opportunities and future prospects

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Highlights:

- Systematic overview of single and multi-TME responsive nanomedicines for tumor-specific drug release.
- Critical challenges in drug release, drug delivery, formulation manufacturing and evaluation, and preclinical animal models are discussed.
- Future optimization strategies and development trends are proposed.

Abstract: Cancer remains one of the most severe global health challenges. The emergence of nanomedicines has opened new avenues for targeted tumor therapy, with over 15 types currently in clinical use. Although nanomedicines improve drug accumulation through the enhanced permeability and retention effect, challenges such as inefficient and nonspecific drug release limit their therapeutic efficacy. Due to abnormal proliferation and metabolic disorders, the tumor microenvironment (TME) exhibits significant differences from normal tissues, including low pH, hypoxia, and enzyme overexpression. These specific endogenous signals provide opportunities to achieve tumor-specific drug release and enhance the therapeutic effect of cancer treatment. Consequently, TME-responsive nanomedicines have garnered significant attention from researchers. This review systematically summarizes the latest advancements in TME-responsive nanomedicines in recent years. Furthermore, we discuss several emerging challenges and prospects of TME-responsive nanomedicines, aiming to provide novel insights and significant breakthroughs in this field.

Keywords: cancer treatment; nanomedicine; precise release; tumor microenvironment responsive

1. Introduction

Cancer remains one of the most formidable global health crises [1,2]. According to the latest Global Cancer Statistics data, approximately 20 million new cancer cases were diagnosed worldwide in 2022, with 9.7 million deaths [3]. It is estimated that more than 35 million new cases will occur annually by 2050 [4]. Conventional therapies have made some progress, yet there are also significant drawbacks. For instance, incomplete surgical resection frequently leads to tumor recurrence, while chemotherapy often induces severe systemic toxicity due to nonspecific drug distribution. Hence, there is an urgent need to develop a novel tumor treatment strategy [5,6].

Over the past three decades, nanomedicines have significantly advanced tumor-targeted drug delivery [7]. The nanomedicines significantly enhanced the blood stability of drugs. Moreover, the drug accumulation in tumors is enhanced via Enhanced Permeability and Retention (EPR) by the nanocarriers [8,9]. The surface of nanomedicines can be functionalized for modification to further enhance their tumor-targeting efficiency. Since Doxil® approval as the first Food and Drug Administration (FDA)-approved cancer nanomedicine in 1995, more than 15 nanomedicines (e.g., Apealea®, Abraxane®) have been incorporated into routine clinical use [10]. At present, over 80 novel candidates are being evaluated in clinical trials [11]. However, the difficult and non-specific release of the drugs leads to their limited therapeutic effect [12]. It highlights the critical need for more precise and tumor-specific drug release platforms.

The tumor microenvironment (TME) constitutes a complex ecosystem composed of tumor cells, stromal cells, immune cells, blood vessels, extracellular matrix (ECM) [13], and various soluble mediators, which exhibits distinctly different pathological features from normal tissues, mainly characterized by low pH, elevated glutathione (GSH) and reactive oxygen species (ROS) levels, hypoxia, overexpression of enzyme and adenosine triphosphate (ATP) [14]. These specific pathological features of TME mainly arise from the uncontrolled proliferation of malignant cells and the consequent metabolic disorders [15–17]. These endogenous biological signals provide an opportunity for the design of tumor-specific responsive drug-release nano platforms (Figure 1). Such smart carriers can remain drug stable during systemic circulation, while upon exposure to specific stimuli of the TME, they will undergo specific structural transformations such as hydrolysis, bond cleavage, charge reversal, or disassembly to enable specific drug release for improving therapeutic efficacy [18–20]. In recent years, TME-responsive nanomedicines have emerged as a transformative strategy to overcome the limitations of conventional nanocarriers [21].

Here, we systematically summarize the latest advancements of TME-responsive nanomedicines in recent years, including both single-stimulus (pH, GSH, ROS, hypoxia, enzyme, and ATP)-responsive platforms (pH, GSH, ROS, hypoxia, enzyme, and ATP) and multi-signal synergistic systems (Table 1). Also, we critically analyze core barriers hindering clinical translation, and discuss challenges such as tumor heterogeneity, challenges in drug release, difficulties in upstream delivery, obstacles in formulation manufacturing, and a lack of reliable preclinical animal models. In response to these challenges, we propose corresponding optimization strategies. Additionally, by integrating current progress and unmet needs, we outline future development trends for TME-responsive nanomedicines, providing references and ideas for exploring the potential of nanotechnology in cancer treatments.

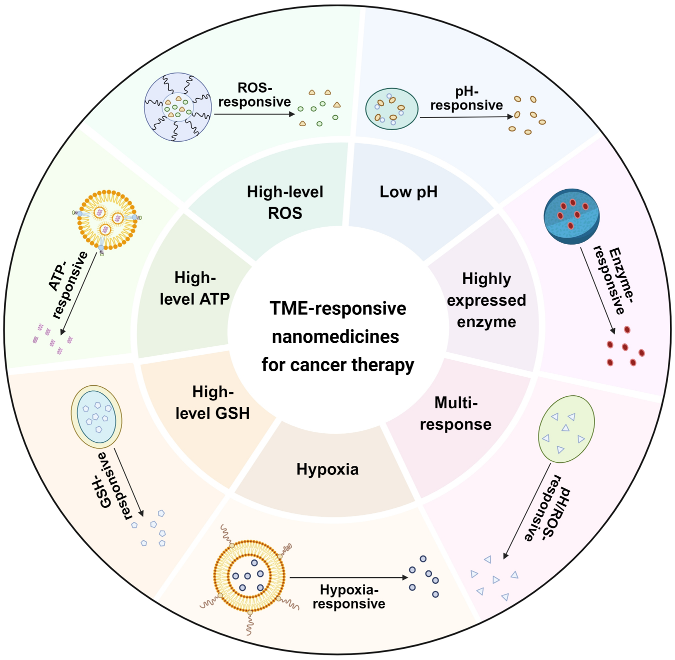

Figure 1. TME-responsive nanomedicines are constructed by leveraging characteristic physiological and biochemical signals within the TME, such as high levels of ROS/ATP/GSH/enzyme, low pH, and hypoxia, thereby achieving precise drug release. Created in BioRender.

2. Single-signal responsive nanomedicines

Single-signal responsive nanomedicines that utilize specific endogenous signals within the TME as drug release switches represent the fundamental form of TME-responsive nanomedicines. Through specific interactions between the responsive groups on the nanocarrier and the TME signals, these systems achieve tumor-selective drug release. We systematically describe the pathological basis, response mechanisms, and representative designs of various single-signal responsive systems from the literature in recent years.

2.1. pH-responsive drug release

The low pH TME is one of the core pathological features of tumors, primarily stemming from abnormal tumor cell metabolism and vascular dysfunction [22,23]. Even under aerobic conditions, tumor cells preferentially undergo glycolysis, producing large amounts of lactic acid [24–27]. The distorted, leaky vascular system within the tumor region and inefficient lymphatic drainage mechanisms impede the timely clearance of lactic acid [28,29], resulting in the pH in the tumor extracellular environment ranging from 6.5 to 6.8 [30], significantly lower than the pH of normal tissues (7.2–7.4) [31–33]. It is worth noting that the pH value of a tumor is spatially heterogeneous. Areas near blood vessels may have a pH close to physiological levels, while the pH in the tumor core, where blood flow is poor, is lower than the range mentioned above. The low pH TME provides a natural triggering mechanism for designing pH-responsive nanomedicines. Building on this, the main design strategies of pH-responsive nanomedicines include: (1) introducing acid-labile covalent bonds, such as hydrazine, acetal, and ketal bonds that undergo acid-catalyzed hydrolysis; (2) the incorporation of protonatable functional groups, which, upon protonation, induce a hydrophilic-to-hydrophobic transition and lead to carrier dissociation; and (3) the use of acid-degradable inorganic materials that dissolve in acidic environments, such as calcium phosphate or calcium peroxide.

For example, Sun *et al.* constructed a pH-responsive PEPCA@SPA/Fe^{3+} nanocarrier for breast cancer treatment [34]. In this system, cinnamaldehyde was linked to the polymer backbone via an acetal bond. Under the acidic TME, the acetal bond broke, causing the PEPCA shell to decompose and release SPA/Fe^{3+}. This formulation demonstrated superior tumor growth inhibition compared to the control group in tumor models. Another example is the pH-responsive polymeric vesicles developed by Albuquerque *et al.* for lymphoma cancer treatment [35]. Within the acidic TME, the poly(2-(diisopropylamino)ethyl methacrylate (PDPA) segments in this carrier underwent protonation, transforming from hydrophobic to hydrophilic and causing the vesicles to depolymerize and release doxorubicin (DOX). In mouse tumor models, these polymeric vesicles significantly inhibited tumor growth compared to free DOX. In addition, Lei *et al.* designed a pH-responsive covalent organic polymer (COP) nanoparticle [36]. In the low pH TME, the COP scaffold degraded and released the drug, achieving a tumor suppression rate of 71.5% in a mouse liver cancer model.

Besides, pH-responsive drug release based on acid-degradable inorganic nanomaterials, including calcium phosphate, calcium peroxide, and hydroxyapatite, occurs as these materials undergo dissolution in acidic TME, leading to structural collapse of the carrier and rapid drug liberation, often accompanied by the release of ions or gaseous byproducts that further amplify therapeutic efficacy [37–39]. For melanoma treatment, Liu *et al.* developed a pH-responsive calcium phosphate nanocarrier (aPD-L1/APCP@CaP) (Figure 2) [40]. Upon exposure to the tumor's low pH microenvironment, the phosphate groups were cleaved, causing the carrier to rapidly dissolve and release medicines, achieving a primary tumor suppression rate exceeding 95%. Building upon this mechanism, An *et al.* developed a pH-responsive nanocarrier (CaNP@cAD-PEG) with CaO_2 as its core system [41]. Upon responding to the acidic TME, Ca^{2+} ions released from CaO_2 decomposition synergistically interacted with the released cAD. In the B16 melanoma model, drug accumulation increased by 4.2-fold compared to the free formulation, significantly enhancing therapeutic efficacy. Besides, Cai *et al.* developed a pH-sensitive nanocapsule ($Cu_2O/Cu_{2-x}Se$/MSA-2) [42]. The low pH TME induced the oxidation and dissolution of Cu_2O, triggering drug release and immune activation. In a bilateral tumor mouse model, this system completely suppressed primary tumors.

Overall, pH-responsive nanocarriers exploit the weakly acidic TME to achieve site-specific drug release through either acid-labile bond cleavage or acid-degradable inorganic materials, providing a robust and versatile strategy for enhancing tumor selectivity and therapeutic efficacy while maintaining systemic stability.

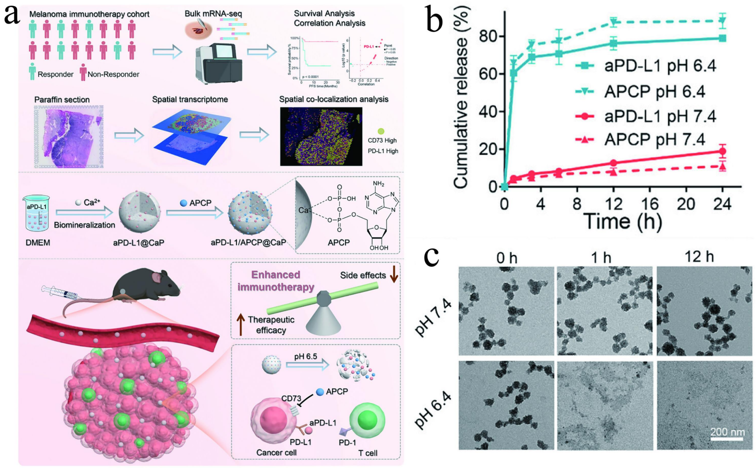

Figure 2. pH-responsive aPD-L1/APCP@CaP nanomedicine enabling efficient drug release for cancer immunotherapy. **(a)** Schematic illustration of the preparation process for aPD-L1/APCP@CaP; **(b)** *In vitro* release profiles of aPD-L1 and APCP under neutral (pH 7.4) and acidic (pH 6.4) conditions; **(c)** TEM images depicting the time-dependent changes in aPD-L1/APCP@CaP nanoparticles under neutral and acidic conditions [40]. Reprinted with permission. Copyright 2024 Wiley-VCH GmbH.

2.2. ROS-responsive drug release

The unique oxidative stress state of the TME, such as a significant increase in ROS levels, provides an opportunity for designing stimuli-responsive drug delivery systems to promote drug release [43,44]. This abnormal accumulation of ROS primarily stems from metabolic disorders in tumor cells and tumor-related inflammation, thereby establishing a unique high redox stress microenvironment locally within the tumor [45–47]. H_2O_2 concentrations in tumor tissues can reach up to 100 μM, approximately five times higher than in normal cells [48]. In addition, the ROS levels in cancer cells are also relatively higher than in normal cells [49]. This significant concentration gradient provides the physicochemical basis for designing ROS-responsive nanocarriers for *in vivo* applications. Under these pathological conditions, researchers designed ROS-responsive nanocarriers that maintain structural stability under normal physiological conditions but degrade upon exposure to high levels of ROS, thereby triggering drug release. Key design strategies include: (1) introducing chemical bonds that can be cleaved by ROS; (2) utilizing ROS-induced physicochemical phase transitions, in which oxidation converts hydrophobic groups into hydrophilic groups, thereby causing the carrier to swell and dissociate.

When designing ROS-responsive carriers, reductive functional groups are frequently incorporated to enable selective drug release under oxidative stress conditions [50]. Sulfide bond–based ROS-responsive systems represent one of the most classical and extensively explored approaches, owing to their clear oxidation-triggered cleavage behavior and high specificity to the tumor redox microenvironment [51,52]. For example, Deng *et al.* proposed an ROS-responsive cationic polymer prodrug nanocarrier (PBAE-S-AZA/C_{pn-11}) for the treatment of triple-negative breast cancer (Figure 3) [53]. Under high ROS conditions, the sulfide bonds within the nanocarrier underwent oxidation, causing dissociation of the poly (β-amino ester)-S-azacytidine (PBAE-S-AZA) complex and releasing CRISPRi gene editing plasmids along with AZA. In disease models, this drug-delivery carrier achieved a tumor inhibition rate of 83.51%. Besides, Han *et al*. developed a ROS-responsive nanoparticle (NP2) for osteosarcoma treatment [54]. High levels of ROS within tumor cells triggered the cleavage of thiol-ketone bonds in the carrier, leading to drug release. In an osteosarcoma patient-derived xenograft (PDX) mouse model, the tumor volume in the NP2-treated group was only 6.9% of that in the saline group, demonstrating significant antitumor efficacy. Building upon this bond-cleavage-based ROS-responsive mechanism, similar strategies have been further extended toward more complex therapeutic functions, particularly tumor immunotherapy. For instance, Wan *et al*. designed a ROS-sensitive nanoparticle system to enhance tumor immunotherapy through the synergistic delivery of siFGL1 and siPD-L1 [55]. The nanocarrier featured a poly-ε-l-lysine backbone grafted with thioketal (TK) and cis-citric acid groups. When exposed to high levels of ROS, the TK bonds within the nanoparticle are cleaved, causing the nanoparticle to disintegrate and release siFGL1 and siPD-L1.

Beyond ROS-induced bond cleavage, more advanced ROS-responsive designs exploit oxidative stress to induce physicochemical transitions of the carrier material itself. Wei *et al*. reported an ROS-responsive nanocarrier (VP/OTS964@NPs) for treating triple-negative breast cancer [56]. When exposed to high levels of ROS, sulfide groups within the carrier oxidized into hydrophilic polysulfone/sulfate compounds, causing the carrier to swell and disintegrate, thereby releasing drugs. In tumor models, it demonstrated superior therapeutic efficacy compared to the control group. In addition, supramolecular structures have also been applied in research on such nanocarriers. Chen *et al*. developed ROS-responsive supramolecular nanoparticles for the treatment of colorectal cancer [57]. A high-ROS microenvironment triggered supramolecular interactions that disrupted the nanoparticles and released the drug payload, achieving a tumor suppression rate of approximately 85% in the CT26 tumor model.

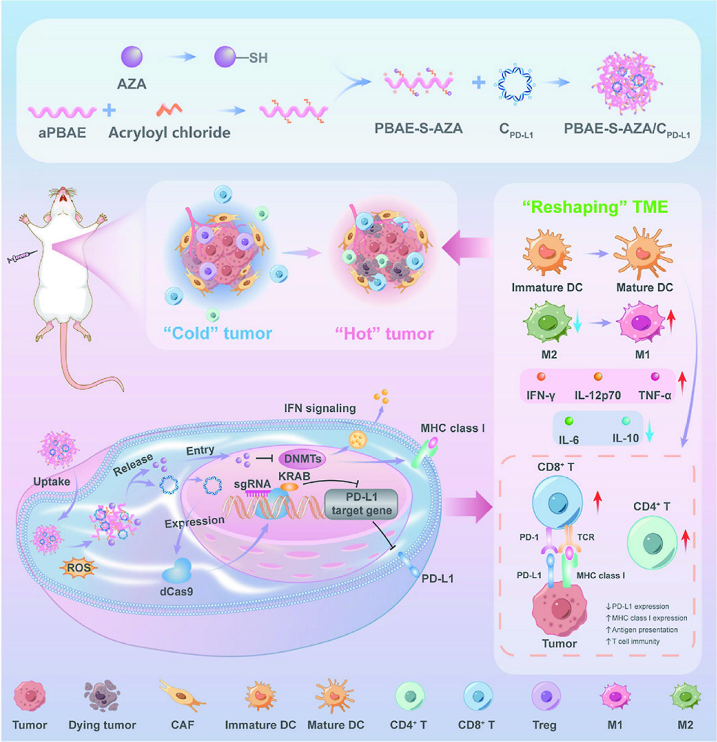

Figure 3. Preparation and ROS-responsive mechanism of PBAE-S-AZA/C_{pn-l1} for cancer therapy via mediating PD-L1 downregulation and tumor microenvironment remodeling [53]. Reprinted with permission. Copyright 2025 Elsevier.

Together, these ROS-responsive drug release strategies, ranging from simple sulfide bond cleavage to advanced ROS-induced material phase transitions, lay a foundation for designing precise drug delivery systems that can specifically release drugs into the tumor-specific microenvironment, thereby enhancing therapeutic efficacy.

2.3. GSH-responsive drug release

To counteract oxidative stress, such as ROS overload, tumor cells accelerate GSH synthesis, leading to elevated GSH levels [58–61]. Intracellular GSH levels in tumor cells can reach 2–10 mM, which is significantly higher than that in normal cells (1–2 mM) [62–65]. This significant difference provides the basis for designing GSH-responsive nanocarriers. The main design strategies for GSH-responsive nanocarriers include: (1) introducing covalent bonds that cleave under reducing conditions, such as disulfide(-S-S-), trisulfide(-S-S-S-), and selenide (-Se-Se-) bonds [66–69]; (2) incorporating disulfide bonds into the polymer backbone or cross-linking structures to induce carrier depolymerization or nanoparticle disintegration; and (3) utilizing supramolecular or metal-coordination interactions that dissociate at high GSH concentrations.

Disulfide bond is a commonly used GSH-responsive group, cleavable to thiol groups in reducing environments. By virtue of this property, disulfide-linked drug carriers can selectively release their therapeutic payload in GSH-enriched tumor tissues [70,71]. For example, Zhang *et al.* developed a GSH-responsive nanoparticle (S-NP-CPT) for colorectal cancer treatment (Figure 4a) [72]. This nanoparticle underwent disulfide bond cleavage in the high GSH environment of tumor cells, releasing CPT. *In vivo* experiments using the CT26 colon cancer model demonstrated that the nanoparticle exhibited significantly enhanced antitumor efficacy, achieving a tumor inhibition rate of 79%. Alternatively, the polymer backbone can be engineered for sensitivity instead of modifying the drug itself. For instance, Xu *et al.* designed GSH-responsive nanoparticles (FA-CMC-GNA NPs) for lung cancer treatment using disulfide-crosslinked thiol-modified carboxymethylcellulose (CMC-SS) as the scaffold (Figure 4b,c) [73]. At tumor sites, high concentrations of GSH cleaved the disulfide bonds, causing the carrier to depolymerize and release gallic acid. In an A549 lung cancer xenograft model, this approach demonstrated outstanding therapeutic efficacy. Beyond covalent chemistry, supramolecular and coordination interactions have also been explored. Tang *et al.* designed a GSH-responsive nanocarrier through the self-assembly of α-cyclodextrin-polyethyleneimine and dextran-sulfonic acid-3-nitrobenzene [74]. The carrier triggered disulfide bond cleavage in high GSH concentrations, releasing the drug Lonidamine (LND) to enhance antitumor efficacy. In addition to disulfide bonds, coordination bonds can also be utilized in designing nanoscale delivery carriers. Cui *et al.* developed a GSH-responsive nanocarrier (IAA NPs) [75]. In the high GSH environment of pancreatic cancer tumor cells, this carrier dissociated via Mn–O coordination bonds to release Fe^{3+} and artemisinin, thereby enhancing drug accumulation at the tumor site and significantly improving pancreatic cancer treatment efficacy, with a tumor inhibition rate exceeding 60%.

These diverse strategies demonstrate the multifunctionality of GSH as a controlled-release trigger. From traditional disulfide bond cleavage to complex supramolecular assembly and coordination-mediated dissociation, various approaches have been provided for designing precise drug delivery systems that can specifically release drugs in high-GSH TME.

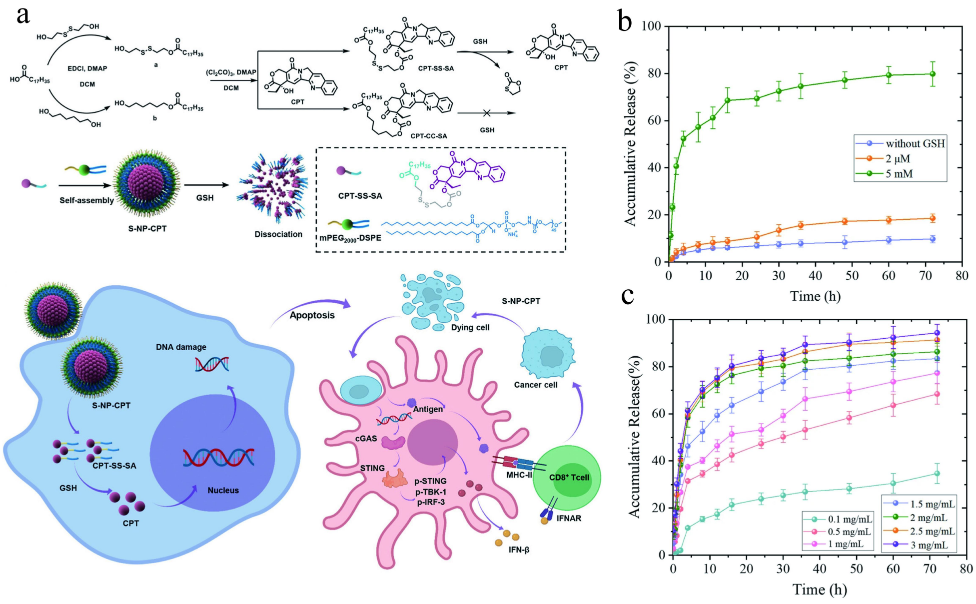

Figure 4. GSH-responsive nanoparticles enable drug release in response to high levels of GSH. **(a)** Synthesis route for GSH-responsive CPT-SS-SA nanomedicine. CPT-SS-SA (containing a disulfide bond that is GSH-responsive) can be co-assembled with PEG-2000-DSPE to form S-NP-CPT [72]. Reprinted with permission. Copyright 2022 Wiley-VCH GmbH; **(b, c)** Cumulative release profiles of FA-CMC-GNA NPs **(b)** under different GSH concentrations and **(c)** with varying FA-CMC-SH concentrations during synthesis [73]. Reprinted with permission. Copyright 2025 Springer Nature.

2.4. Enzyme-responsive drug release

Biocatalysis also provides a trigger mechanism for precise tumor drug release. The TME overexpresses multiple enzymes, which primarily stem from both the secretion by tumor cells themselves and the paracrine effects of tumor-associated stromal cells [76,77]. Compared with normal cells, the activity of some enzymes inside and outside tumor cells is significantly increased [78,79]. Taking matrix metalloproteinases (MMPs) as an example, matrix metalloproteinase-2 (MMP-2) activity increases approximately 8.6-fold in colorectal tumor tissues and approximately 3.8-fold in non-small cell lung cancer [80]. Under the catalysis of tumor-specific enzymes, these peptides undergo cleavage or chemical bonds undergo hydrolysis, triggering the disassembly to achieve specific drug release [81,82]. Key design strategies for nanomedicines engineered to exploit the overexpression of specific enzymes in TME include: (1) incorporating enzyme-cleavable peptide sequences into the nanocarrier, which are specifically cleaved by enzymes overexpressed in tumors; (2) introducing enzyme-sensitive chemical bonds or lipid components that can be cleaved by enzymes, causing the carrier to dissociate and release the drug upon contact with specific enzymes.

Cleavage of specific enzyme-sensitive peptide sequences by tumor-overexpressed enzymes represents a widely adopted strategy to achieve precise and efficient drug release. Among these, MMPs have been extensively exploited to trigger nanocarrier disassembly for on-demand drug release before cellular internalization [83–85]. In one design, Fan *et al.* constructed a nanocarrier (dBET6@CFMPD) through self-assembly (Figure 5a) [86]. Upon reaching the tumor site, the MMP-2 sensitive peptide of the carrier was cleaved, releasing the Ce6-FFRFK fragment and the therapeutic drug dBET6. The Ce6-FFRFK fragment transforms spherical nanoparticles into nanofibers in situ through the action of diphenylalanine, further enhancing nanoparticle retention at tumor sites and drug enrichment effects. In addition, Yen *et al.* developed a gelatinase-responsive delivery system for lung cancer therapy based on an mPEG-PVGLIG-PCL copolymer backbone (Figure 5b) [87]. Within the TME, highly expressed gelatinase specifically cleaved the PVGLIG peptide segment within the carrier, significantly accelerating the release rate of αPD-1 and the TGF-β receptor I inhibitor galunisertib.

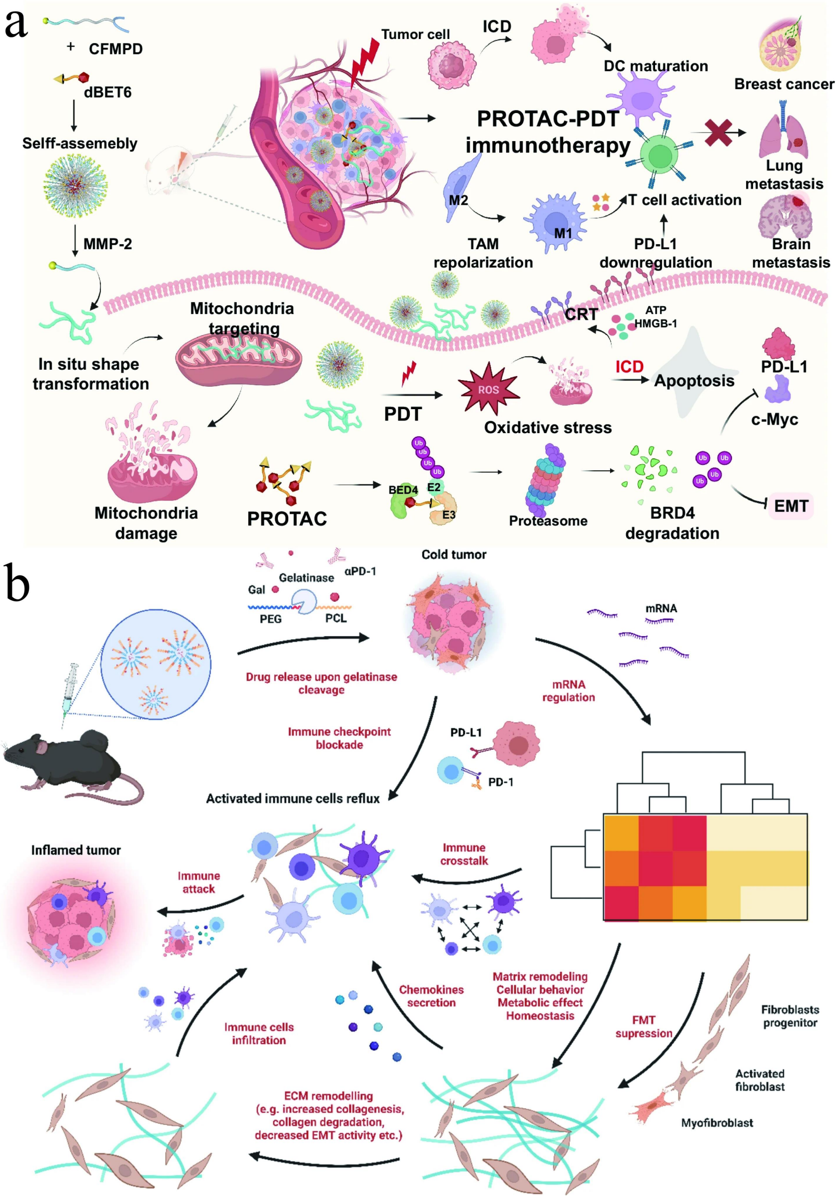

Figure 5. MMP-sensitive nanocarriers for precise drug delivery in cancer. **(a)** Schematic illustration of the composition of the MMP-2-responsive nanomedicines BET6@CFMPD and its therapeutic mechanism on primary breast cancer and brain metastases [86]. Reprinted with permission. Copyright 2024 Springer Nature; **(b)** Schematic illustration of systemic injection of collagenase-responsive GPNPs nanoparticles loaded with αPD-1/galunisertib to enhance tumor immunotherapy by modulating TME [87]. Reprinted with permission. Copyright 2025 Springer Nature.

Beyond extracellular enzyme responsiveness, intracellular enzyme-triggered drug release provides an additional level of precision. Song *et al*. reported a branched glycopolymer nanocarrier (BPGP@CAP) responsive to cathepsin B for synergistic treatment of gastric cancer (Figure 6) [88]. Upon entering cancer cells, the Glycine-Phenylalanine-Leucine-Glycine (GFLG) peptide segment within the polymer structure is cleaved by overexpressed cathepsin B in lysosomes, triggering the release of capecitabine (CAP). In a gastric cancer xenograft model, this carrier demonstrated outstanding efficacy with a tumor inhibition rate of 75.8%. Phospholipase A2 can also serve as a signal to trigger a response in nanoparticles. For example, Yuan *et al*. developed an enzyme-responsive multistage nanoparticle (DMSN@Pla-Lipo) [89]. Under the action of phospholipase A2, which is highly expressed in tumor tissue, the phospholipid bonds are hydrolyzed, causing the liposome membrane to rupture and release the drug. In a colorectal tumor model, 80% of the mice survived for 90 days, a rate significantly higher than that of other groups.

Collectively, enzyme-responsive drug delivery systems exploit the differential expression of tumor-associated enzymes to trigger structural changes of nanocarriers at both extracellular and intracellular levels, resulting in controlled drug release and improved therapeutic efficacy.

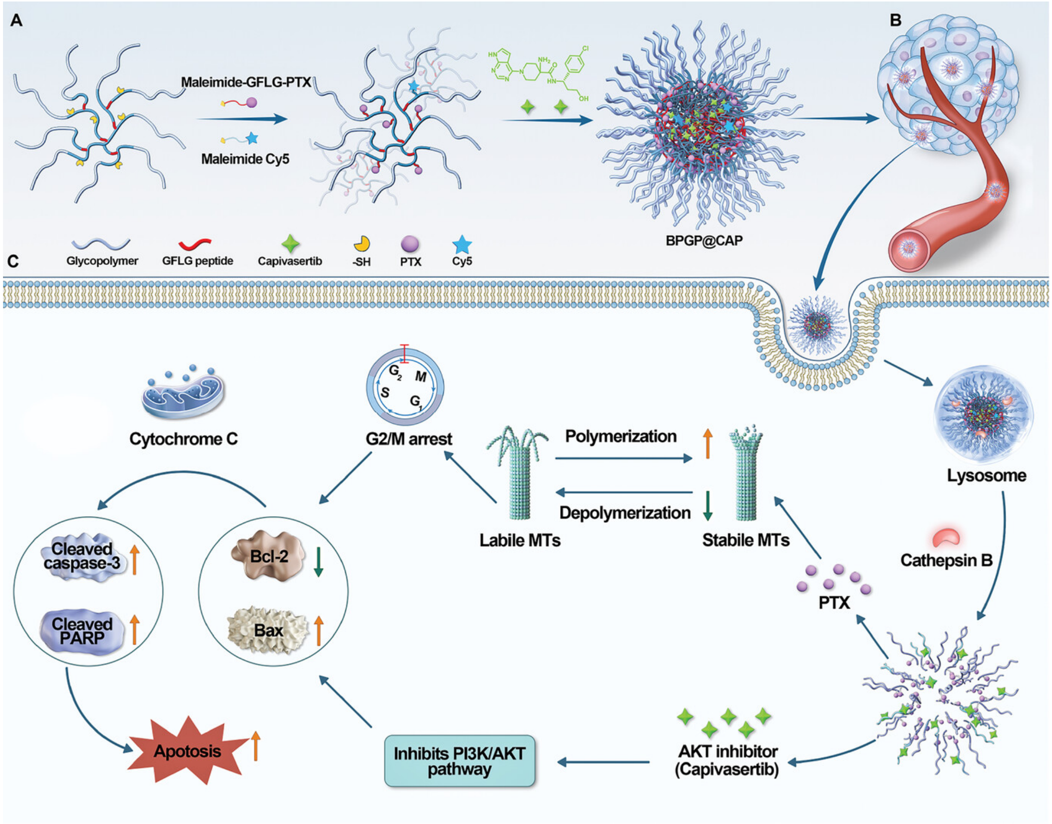

Figure 6. Cathepsin B-responsive BPGP@CAP enables synergistic tumor treatment through the combined chemotherapy and targeted therapy. Schematic illustration of enzyme-responsive branched glycopolymers (BPGP@CAP) for synergistic antitumor therapy. Within tumor cells, overexpressed cathepsin B triggers the specific cleavage of the GFLG peptide segment in the polymer structure, leading to carrier degradation and concomitant drug release. The released PTX and CAP exert synergistic antitumor effects by inducing apoptosis [88]. Reprinted with permission. Copyright 2023 Wiley-VCH GmbH.

2.5. Hypoxia-responsive drug release

Hypoxia caused by the imbalance between rapid tumor cell proliferation and insufficient angiogenesis, coupled with vascular structural disorganization, also constitutes a significant factor for designing TME-responsive nanomedicines [90,91]. The tumor core exhibits low vascular density and poor blood perfusion, leading to significantly reduced oxygen partial pressure (pO_2), typically below 10 mmHg, whereas normal tissue pO_2 is approximately 65 mmHg [92,93]. This stark differential provides the basis for designing nanomedicines that incorporate hypoxia-sensitive functional groups, such as nitroimidazole, azo bonds, triphenylphosphine salts, that undergo reductive cleavage or hydrophilic-hydrophobic reversal under hypoxic conditions, triggering the disassembly of the nanocarrier and drug release [94,95]. Based on this pathological foundation and response mechanism, the primary design strategies for hypoxia-responsive nanocarriers include: (1) introducing hypoxia-sensitive functional groups (such as nitroimidazole; upon reduction, these functional groups undergo a hydrophobic-to-hydrophilic transition, leading to carrier dissociation; (2) incorporating hypoxia-cleavable chemical bonds (such as azo bonds), which undergo reductive cleavage under hypoxic conditions, leading to carrier instability and drug release.

Among hypoxia-responsive functional groups, nitroimidazoles are the most extensively employed due to their reduction potentials closely matching oxygen levels in hypoxic tumor tissues [96]. Upon enzymatic reduction under oxygen-deprived conditions, nitroimidazole moieties undergo hydrophobic-to-hydrophilic conversion, thereby triggering nanocarrier disassembly and drug release [97]. Yang *et al.* reported a hypoxia-responsive nanocarrier (ALA-hMVs) [98]. In hypoxic tumor regions, the nitroimidazole group within the carrier converted to an aminoimidazole group, transforming the nanoparticle structure from hydrophobic to hydrophilic. This induced carrier disassembly and releases δ-aminolevulinic acid (ALA) at a significantly higher rate than under normoxic conditions. Beyond redox-induced polarity reversal, hypoxia-triggered cleavage of azo bonds provides an alternative strategy that directly destabilizes nanocarrier structures. Cai *et al.* prepared hypoxia-responsive nanocarriers (PAD@MS) for colorectal cancer treatment via a one-pot method [99]. Within the hypoxic TME, the azo bonds in the polyethylene glycol-azo-dopamine (PAD) layer of the nanocarriers underwent cleavage, accelerating drug release. Under simulated hypoxic conditions, the drug release rate reached approximately 80% within 8 hours, significantly higher than the release rate in PBS. Besides, Wang *et al.* designed a hypoxia-responsive nanocarrier (SHC4H) (Figure 7) [100]. Under hypoxic conditions, the azo bond of the carrier molecule azocalix [4] arene (AC4A) on the SHC4H surface broke down and was reduced to an amino compound, releasing hydroxychloroquine (HCQ) and a photosensitizer (SMNB). This significantly increased drug concentration at tumor sites and enhanced therapeutic efficacy against multiple hypoxic cancers.

Hypoxia-sensitive azo bond cleavage has also been integrated into more structurally complex nanocarriers. For example, Huang *et al.* developed a hypoxia-responsive covalent organic framework (COF) nanocarrier with a core-shell-surface-modified multilayer composite structure [101]. In hypoxic TME, the azo bonds in the COF membrane broke, releasing drugs to exert their therapeutic effects. In a mouse tumor model, statistics on tumor weight showed that the UAPiGCH+L group had the lowest weight, and the tumor growth curves indicated that tumor growth in this group had essentially ceased, demonstrating a significant tumor growth-inhibition.

Collectively, hypoxia-responsive drug release systems leverage the oxygen-deprived TME to trigger nanocarrier disassembly through redox-induced polarity reversal or hypoxia-sensitive bond cleavage, enabling spatially controlled and tumor-selective drug release.

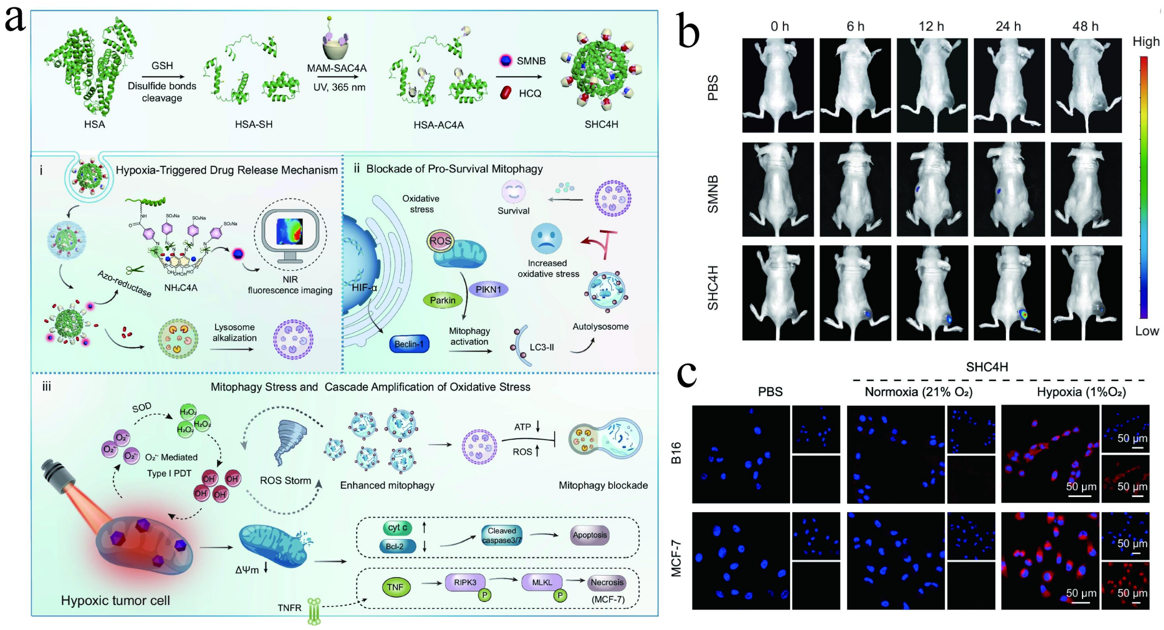

Figure 7. A hypoxia-responsive supramolecular albumin-based nanoparticle designed to treat hypoxic tumors. **(a)** Schematic illustrates of the construction process of SHC4H, which exhibits hypoxia-responsive drug release and fluorescence imaging capabilities; **(b)** *In vivo* fluorescence imaging of B16 tumor-bearing mice at the indicated time points after intravenous injection of PBS, SMNB, and SHC4H; **(c)** Confocal laser scanning microscop images of B16 and MCF-7 cells co-cultured with SHC4H for 12 h under hypoxic or normoxic conditions [100]. Reprinted with permission. Copyright 2025 Springer Nature.

2.6. ATP-responsive drug release

Because of the faster metabolic processes, excess glycolysis, and fast proliferation of cancer cells, the ATP content inside tumor cells is higher than that in normal cells, and the ATP concentration outside tumor cells is even 1000 times higher than that in normal tissues [102,103]. Its high concentration characteristic provides a specific target for designing ATP-responsive nanocarriers. Based on the pathological characteristic of elevated ATP levels, the core design principle of this type of responsive nanomaterial is to introduce ATP-specific recognition units, such as aptamers and metal ion coordination complexes. The specific binding of ATP to these recognition units triggers conformational changes or disintegration of the nanocarrier, thereby achieving drug release [104].

Among these strategies, small-molecule recognition units such as phenylboronic acid (PBA) represent a relatively simple and well-defined approach for ATP-triggered nanocarrier disassembly. For example, Xiong *et al.* used microfluidic technology to prepare an ATP-responsive lipid nanoparticle (LNP-P/siMITF) for melanoma treatment [103]. After being taken up by tumor cells, LNP-P/siMITF specifically binds to PBA under high ATP concentrations, reducing the nanoparticle's positive charge density and accelerating the release of siRNA. In the B16F10 melanoma model, the tumor suppression rate in the LNP-P/siMITF group reached 76.8%, more than double that of the other groups. Beyond conventional nanocarriers, ATP-responsive mechanisms have also been integrated into biohybrid systems to achieve amplified therapeutic outcomes. Yang prepared ATP-responsive manganese-loaded bacterial materials (E. coli@PDMC-PEG and VNP20009@PDMC-PEG) [105]. The PBA in the PDMC nanocoating of these materials reacted with ATP in the TME, causing the coating to rupture and degrade, thereby triggering the release of Mn^{2+} and exposing the bacteria. The bacteria continuously secrete eDNA, and Mn^{2+} synergizes with eDNA to exert an antitumor effect. ATP-triggered coordination dissociation is also utilized in the design of such nanomedicines. Nan *et al.* prepared ATP-responsive iron-doped carbon dot liposome nanoparticles (FeCDs/GOx) [106]. High concentrations of ATP triggered the release of iron ions from the carbon dots, along with glucose oxidase (GOx), achieving a tumor suppression rate of approximately 80% in a 4T1 tumor-bearing nude mouse model.

Collectively, ATP-responsive drug delivery systems exploit elevated intracellular ATP levels in the tumor microenvironment to trigger nanocarrier disassembly via ATP-aptamer binding, competitive coordination, or ATP-driven structural transformation, thereby enabling tumor-selective payload release and enhanced therapeutic efficacy.

3. Multi-responsive drug release

Single-signal responsive systems, while offering advantages such as simplified design and lower cost, still face some challenges. The tumor heterogeneity leads to uneven distribution of TME signals, and inflammatory sites may harbor isolated abnormal signals, triggering insufficient drug release at the tumor site [20,108]. Multi-responsive nanomedicines integrate two or more endogenous TME signals. The key design strategies for multi-responsive nanocarrier delivery systems include: (1) cascade-responsive systems: one stimulus triggers structural changes in the carrier, thereby exposing or activating a second responsive unit; (2) dual/multi-stimuli "AND-gate" systems: Drug release is triggered only when multiple stimuli are present simultaneously.

Among these, cascade-type dual-signal systems represent the most intuitive design. Following this design principle, Yang *et al.* developed a pH/cathepsin B-responsive polymer-conjugated PROTAC nanocarrier (PSRNs) for the treatment of colorectal cancer (Figure 8a) [108]. In a weakly acidic TME, PSRNs partially depolymerize to expose the GFLG peptide chain; upon entering the cell, GFLG is cleaved by cathepsin B, releasing the PROTAC. In an HCT116 colorectal cancer xenograft model, PSRNs achieved a tumor suppression rate of 89.2%, significantly higher than that of other groups. Besides, Cai *et al.* reported a pH/ROS dual-responsive nanocarrier for the treatment of lung cancer [109]. Under slightly acidic extracellular conditions, the nanocarrier shell degraded, exposing selenium-selenium bonds. Upon entering the cell, high concentrations of ROS triggered the cleavage of the Se–Se bonds and the release of the drug. Under combined stimulation with pH 6.5 and H_2O_2 (100 μM), the release rates of ART and siARH2 were significantly higher than those under single-stimulation conditions, highlighting the effectiveness of dual-signal regulation. Similarly, Huang *et al.* developed a pH/GSH dual-responsive nanocarrier (GDTF) for breast cancer therapy (Figure 8b) [110]. In the weakly acidic TME, the surface coating dissociated to expose DPSNs, while elevated intracellular GSH levels cleaved disulfide bonds within the carrier, resulting in GA release. Under combined pH 6.5 and GSH (5 mM) conditions, GA release reached 87.4% within 48 h, whereas release under single-stimulus conditions remained below 18%. For another example, Meng *et al.* developed a pH/ATP dual-responsive nanocarrier (Met/RSL3@ZIF90@Fe-TA) designed for the treatment of breast cancer [111]. In the slightly acidic TME, this nanocarrier first induced dissociation of the Fe–TA shell, exposing the ZIF-90 core. Upon entering the cell, high concentrations of intracellular ATP strongly coordinate with Zn^{2+} ions, destabilizing the ZIF-90 framework and thereby triggering drug release.

To further address the complexity and heterogeneity of solid tumors, multi-responsive nanocarriers integrating three or more stimuli have been developed. A typical example can be found in that Shu *et al.* reported a pH/ROS/MMP-2 triple-responsive nanoparticle formulation (PEG-M-PPMT NPs) [112]. In TME, MMP-2-mediated PEG detachment enhanced tumor penetration, while acidic conditions and ROS induced nanoparticle swelling. *In vitro* studies showed that under triple-stimulation conditions, the release rate of SRF reached 74.3% after 72 h, whereas under physiological conditions, it was less than 35%. The core advantage of the multi-signal synergistic responsive system lies in its exceptional tumor specificity. Through multi-signal validation, it significantly reduces off-target toxicity while adapting to complex and heterogeneous TME [113,114].

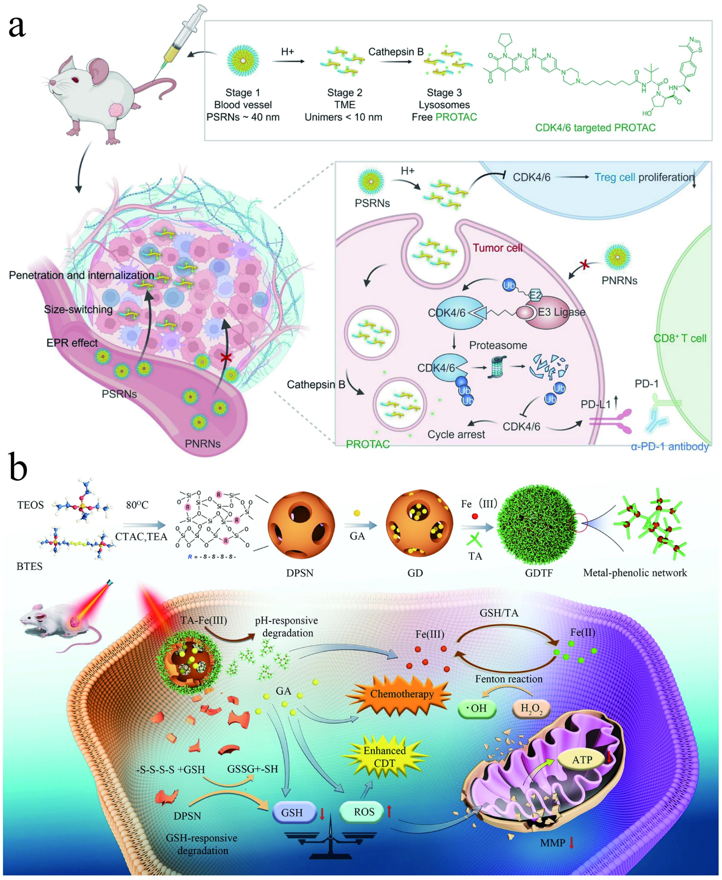

Figure 8. Multi-responsive nanomedicines for precise drug release in cancer. **(a)** Schematic illustration of the structure and the pH/cathepsin B response process of PSRNs following intravenous administration [108]. Reprinted with permission. Copyright 2024 Springer Nature; **(b)** Preparation and treatment mechanism of GDTF with pH/GSH dual-responsive drug release properties. Reprinted with permission [110]. Copyright 2024 Springer Nature.

Table 1. Representative examples of TME-responsive nanomedicines and their applications in cancer therapy.

Signals	Response environment	Molecular basis	Nanocarriers	Drugs	Tumors	Reference
Weakly acid	pH 6.5	acetal bond	polymer-encapsulated nanoparticles	SPA/Fe^{3+}	breast cancer	[34]
	pH 6.8	amine	polymersome	DOX	lymphoma tumor	[35]
	pH 6.5	CaP	CaP nanoparticles	aPD-L1, APCP	liver cancer	[40]
	pH 6.5	CaO_2	calcium-based nanoparticles	cAD	melanoma	[41]
ROS (H_2O_2) (in vitro)	10 Mm	thioether bond	polymer nanoparticles	AZA	TNBC	[53]
	5 mM	TK	polymeric self-assembled nanoparticles	siFGL1, siPD-L1	TNBC	[55]
	10–100 mM	thioether bond	nucleic acid-drug conjugate polymer nanoparticles	VP, OTS964	TNBC	[56]
	0.1–1 mM	amide bond	supramolecular nanoparticles	Luminol	breast cancer	[115]
	10 mM	$S\text{-}CH_2\text{-}CH_2\text{-}O$	organic nanoparticles	SN38-CA	lung cancer	[116]
	5/10 mM	TK	carrier-free prodrug self-assembled nanoparticle	CisPt (IV) prodrug, Syro	osteosarcoma	[54]
	1 mM	thioether linkage	micelles	PTX, anti-PD-L1 peptide	breast cancer	[117]
	1 mM	TA-CA linkers	micellar	PTX, CA	breast cancer	[118]
GSH	10 mM	-S-S-	host–guest self-assembled nanoparticles	CPT	colorectal cancer, ovarian cancer	[72]
	5 mM	-S-S-	polysaccharide-based polymeric nanoparticles	GNA	lung cancer	[73]
	10 mM	-S-S-	self-assembled prodrug nanoparticles	LND	colon cancer	[74]
	5–10 mM	metal-organic coordination bond	self-assembled polymeric nanoreactor	AS, αPD-L1	pancreatic cancer	[75]
	5–10 mM	S-S	self-assembled antibody-drug conjugate nanomedicines	PROTAC MS28	epidermal carcinoma, esophageal cancer	[119]
	10 mM	-S-S-	supramolecular nanoparticles	MTX	cervical cancer, colorectal cancer, lung cancer, breast cancer	[120]
	10 mM, 20 mM	metal–ligand coordination bond	MOF metal framework	Dalpiciclib, Fluzoparib	osteosarcoma	[121]
Enzyme	MMP-2	peptide bond	self-assembled lipid–peptide hybrid nanoparticles	dBET6	breast cancer	[86]
	MMP-2	peptide bond	polymeric nanoparticles	αPD-1, Gal	gastric cancer	[87]
	cathepsin B	peptide bond	branched glycopolymer-based self-assembled nanoparticles	PTX, CAP	lung cancer	[88]
	ALP	phosphoester bond	polymeric self-assembled nanoparticles	DOX	HCC	[122]
	HDAC	lactic acid-glycolic acid ester bond	polymeric nanoparticles	PANO	HCC	[123]
Hypoxic	hypoxic	2-nitroimidazolyl	nanovesicle	ALA, MFNs	melanoma	[98]
		azo bond	nanoscale coordination polymer	MTO, SAS	colorectal cancer	[99]

Table 1. *Cont.*

Signals	Response environment	Molecular basis	Nanocarriers	Drugs	Tumors	Reference
Hypoxic	hypoxic	azo bond	COF nanoparticles	GA Au-Pd islands	breast cancer	[101]
		azo bond	protein-based nanoparticles	HCQ	hypoxic tumor	[100]
ATP	1 mM	borate bond	lipid nanoparticles	MITF siRNA	melanoma	[103]
	0.1–0.4 mM	coordinate bonds in Mn-TCPP complexes	manganese-based biohybrid nanomaterial	Mn^{2+}, VNP20009	melanoma liver cancer	[105]
Dual-signal	pH/Enzyme	GFLG tetrapeptide chain	polymer–PROTAC conjugated nanoparticles	CDK4/6 targeted PROTAC	colorectal cancer	[109]
	pH/ROS	Se-Se, N = C	polymeric responsive nanoparticles	siARH2, ART	LUAD	[110]
	pH/GSH	-S-S-S-S-	hybrid nanoparticles	GA	breast cancer	[111]
	pH/ATP	Fe-TA coordination, imidazole-zinc coordination structure	MOF-based hybrid nanoplatform	Met, RSL3	breast cancer	[112]
	pH/GSH	electrostatic attraction, non-covalent hydrophobic interactions, and coordinate bonds	bionic nanoparticles	TMZ	glioma	[124]
	pH/GSH	Mn-O	hollow MnO_2 nanoparticles	DOX, ISL, Cas9/sg-PTPN2	breast tumor	[125]
	miR-21/Enzyme	APE1, base pairing	self-assembled polymer nanocarriers	DOX, ASO	colorectal cancer	[126]
	pH/GSH	Mn-O	polymer–inorganic hybrid nanoparticles	DOX	colorectal cancer	[127]
	pH/GSH	metal-ligand coordination bond	MOF metal framework	DHA, CORM-401	colorectal cancer	[128]
	pH/GSH	schiff base, -S-S-	nanogel	DNAzyme, siRNA, ASO	cervical cancer	[129]
	GSH/ROS	-S-S-	self-assembled organic nanoparticles	DHA	liver cancer	[130]
Three-signal	pH/ROS/ MMP-2	MMP-2 cleavable peptide segment, -S-, tertiary amino structure	nanoparticles	SRF	non-Small cell lung cancer	[113]

4. Key challenges and prospects for TME-responsive nanomedicines

TME-responsive nanomedicines have demonstrated significant advantages in preclinical cancer research. However, their clinical translation remains extremely limited. This predicament primarily stems from several factors: barriers to TME-responsive drug release, systemic delivery obstacles, challenges in formulation manufacturing and evaluation, and limitations of conventional preclinical models. In-depth analysis of these barriers and exploration of optimization strategies are crucial for advancing the clinical application of TME-responsive nanomedicines.

4.1. Challenges in TME-responsive drug release

The uneven distribution and dynamic changes of TME signals can affect the efficiency of TME-responsive drug release [131]. For example, the location of the tumor affects the TME signal strength. Vascularized areas have normal oxygenation, while the core area is under a perfused and hypoxic state [132], leading to the activation of hypoxia-responsive nanomedicines only in the core regions and insufficient drug release at the peripheral regions. Furthermore, TME signals differ at different stages of tumor development. Compared to early-stage tumors, late-stage tumors typically exhibit relatively lower extracellular pH and higher intracellular GSH levels [133]. These factors lead to differences in TME response signals, thus directly affecting the release efficiency and therapeutic effect of TME-responsive nanomedicines. To adapt to distinct TME characteristics across different regions and achieve effective drug release within heterogeneous tumors, multi-responsive nanocarriers integrating multiple TME-response signals can be developed to reduce the dependence on a single signal [134,135]. Carriers with dynamic response capabilities can be designed, which can adjust drug release rates in response to changes in TME signals [136]. In addition, three-dimensional tumor models constructed using organ-on-a-chip and microfluidic technologies can serve as important supplementary tools to assist in replicating complex *in vivo* processes such as drug tissue distribution, thereby better assessing the adaptability of TME-responsive nanocarriers in heterogeneous tumors [137,138].

In addition to tumor heterogeneity, the inherent limitations in the performance of nanocarriers can also directly impact their response sensitivity and drug release efficiency [139]. For instance, disulfide bonds exhibit low affinity for TME signals like GSH and ROS, requiring relatively high signal to trigger effective responses. Besides, the carrier's structure, such as core-shell structures or crosslinked networks, usually results in slow drug release [140]. When designing TME-responsive nanomedicines, nanocarriers with lower response thresholds or integrated signal amplification modules may improve the TME-responsive drug release [141,142]. Also, the construction of lightweight shells or low-crosslinking structures may be effective by shortening signal diffusion pathways [143].

4.2. Systemic delivery barriers of nanomedicines

In addition to the tumor heterogeneity and inherent characteristics of the nanomedicines affecting TME-responsive drug release, there are some obstacles in nanomedicine delivery, which severely limit their clinical translation. Although the enhanced EPR effect is a key mechanism for tumor accumulation of nanomedicines, there are some limitations of EPR in clinical settings. Recent studies have shown that EPR is highly heterogeneous in human tumors, often less pronounced than in mouse models [11,144] and strongly influenced by tumor type, anatomical location, stromal pressure, vascular permeability, and prior treatments [8,9]. Furthermore, nanomedicines face multiple delivery barriers upon entering systemic circulation. The protein corona formed by plasma protein adsorption alters their physicochemical properties, thereby affecting tumor targeting [145,146]. Meanwhile, immune recognition and clearance further decrease the effective dose reaching tumor tissues [147]. Even if nanomedicines accumulate at the tumor periphery, dense ECM and high interstitial pressure hinder deep penetration [148,149]. Together, these obstacles impair delivery efficiency and therapeutic outcomes.

TME-triggered drug release alone does not address upstream delivery barriers such as tumor penetration and intratumoral distribution. Therefore, some strategies that are combined with TME-responsive systems can be used to improve the delivery efficiency of nanomedicines. For instance, designing charge or size-switchable nanoparticles can prolong blood circulation and enhance tissue permeability by dynamically adjusting their physicochemical properties *in vivo* [136]. In addition, degrading or remodeling the dense ECM can facilitate nanoparticle diffusion within tumor tissues [150]. Cell-based systems can also help nanomedicines bypass multiple physiological delivery barriers [151]. Therefore, rational optimization of delivery designs, combined with TME-responsive strategies, is important for nanomedicines to achieve effective tumor treatment.

4.3. Formulation manufacturing and evaluation

In addition, the manufacturing of nanomedicines still faces many core challenges, including the difficulty in achieving a uniform large-scale supply of raw materials, the potential *in vivo* toxicity induced by residual solvents, and the unstable quality of nanomedicines due to large-scale production. In addition, the complex design and preparation process of nanostructures lead to unsatisfactory inter-batch reproducibility and fluctuations in efficacy and safety [152–154]. Therefore, key indicators, including particle size distribution, polydispersity index, encapsulation efficiency, and drug release profile, should be strictly monitored to ensure product quality stability through standardized process control.

Beyond standardized preparation, a systematic and comprehensive *in vivo* evaluation system should be established to further accelerate the clinical translation of nanomedicines. For example, the pharmacokinetic behavior and biodistribution characteristics of nanomedicines *in vivo* can be characterized using fluorescence or radiolabeling techniques [155]. The depolymerization process and stimulus-responsive release *in vivo* of nanomedicines can be monitored in real time using activatable fluorescent probes and Förster resonance energy transfer systems [156,157]. Immunotoxicity is also an important monitoring component, which can be assessed by detecting complement activation and cytokine release levels [158,159]. Simultaneously, the metabolic clearance pathways of nanomedicines and their accumulation in various organs should be systematically studied to reduce the potential risk of chronic toxicity [160,161].

4.4. Lack of reliable preclinical animal models

While mouse tumor models are widely used to evaluate *in vivo* therapeutic efficacy, their TME differs substantially from humans in pH gradients, hypoxia, immune composition, and metabolic profiles. Therefore, advanced preclinical models that better recapitulate human tumor features should be employed, including humanized mice, PDX models, and organ-on-a-chip systems. Humanized mice can reconstruct the human immune system and reproduce the human tumor immune microenvironment, thus enabling more accurate assessment of the *in vivo* behavior of nanomedicines [162]. PDX models, which implant patient tumor tissues into immunodeficient mice, provide a more reliable evaluation of tumor distribution, penetration, and efficacy [163]. Organ-on-a-chip models based on human cells also simulate the TME more realistically, thus exhibiting obvious advantages over conventional mouse models [164,165].

5. Conclusion

In summary, this review systematically summarizes the research progress of TME-responsive nanomedicines in recent years, addressing the limited efficacy of tumor treatment due to ineffective and nonspecific drug release. These nanomedicines are mainly divided into single-signal and multi-signal synergistically responsive nanomedicines. Despite progress in controlled drug release, clinical translation remains hampered by factors such as release challenges mediated by tumor heterogeneity and nanocarrier-intrinsic factors, difficulties in upstream delivery, and a lack of reliable preclinical animal models. In the future, these obstacles can be addressed by developing multi-signal and highly response nanomedicines to counteract heterogeneity and enhance responsiveness, engineering charge-switchable or size-tunable platforms to overcome delivery barriers, establishing standardized manufacturing and quality control systems, and employing advanced preclinical models. In summary, with the rapid development of interdisciplinary sciences, TME-responsive nanomedicines hold great promise for achieving substantial breakthroughs in precision cancer therapy.

Data availability statement

No supplementary or additional data were generated in this study.

Declaration of generative AI and AI-assisted technologies

During the preparation of this manuscript, the authors used generative AI tools only to improve language and readability. Specifically, the authors only used artificial intelligence tools such as ChatGPT for idea development and language polishing throughout the manuscript to improve its readability. The authors take full responsibility for all content and the accuracy of the manuscript.

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Authors' contribution

Conceptualization, Q.W. and M.S.; literature search, Q.W., M.S. and Z.Z.; data collection, Q.W., M.S., Y.H. and Z.L.; writing—original draft preparation, Q.W. and M.S.; writing—review and revision, Q.W., M.S., J.L., X.S. and J.S.; supervision, X.Z., X.S. and J.S.; project administration, X.Z. and J.S. funding acquisition, J.L., X.Z. and J.S.; All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

Jinjin Shi holds the position of Editorial Board Members for *Advanced Cancer Research* and has not peer reviewed or made any editorial decisions for this paper.

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