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R E V I E W

Smart Nanoplatforms Responding to the Tumor Microenvironment for Precise Drug Delivery in Cancer Therapy

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Abstract: The tumor microenvironment (TME) is a complex and dynamic entity, comprising stromal cells, immune cells, blood vessels and extracellular matrix, which is intimately associated with the occurrence and development of cancers, as well as their therapy. Utilizing the shared characteristics of tumors, such as an acidic environment, enzymes and hypoxia, researchers have developed a promising cancer therapy strategy known as responsive release of nano-loaded drugs, specifically targeted at tumor tissues or cells. In this comprehensive review, we provide an in-depth overview of the current fundamentals and state-of-the-art intelligent strategies of TME-responsive nanoplatforms, which include acidic pH, high GSH levels, high-level adenosine triphosphate, overexpressed enzymes, hypoxia and reductive environment. Additionally, we showcase the latest advancements in TME-responsive nanoparticles. In conclusion, we thoroughly examine the immediate challenges and prospects of TME-responsive nanopharmaceuticals, with the expectation that the progress of these targeted nanoformulations will enable the exploitation, overcoming or modulation of the TME, ultimately leading to significantly more effective cancer therapy.

Keywords: tumor microenvironment, stimulus-responsive, drug delivery, cancer therapy, intelligent biomedicine

Introduction

Malignant tumors are a leading cause of human mortality. In recent years, significant advancements have been made in tumor therapy, thanks to the development of various approaches. Notably, nanotechnology and targeted drug delivery systems have garnered considerable attention due to the favorable characteristics of nanoparticles, such as excellent permeability, enhanced loading capacity and high specificity. Consequently, nanoparticles have become widely adopted as effective carriers for delivering chemotherapeutic drugs, nucleic acids and genes to precise target sites for the treatment of oncological diseases. The tumor microenvironment (TME) plays a pivotal role in tumor development, consisting of tumor cells, tumor stromal cells, the extracellular matrix, as well as various cytokines and chemokines (Figure 1).[1–5] Compared to the normal human internal environment, the TME exhibits distinct biochemical properties, including hypoxia, acidity, strong redox characteristics, abnormal enzyme metabolism, and immunosuppression.[6] Of particular interest in recent research on nano-targeted agents are the weak acidic and strong redox properties, given their significant roles in tumor progression, metastasis and immune evasion.[7] Metabolic differences between cancer cells and normal cells contribute to unique features within the tumor microenvironment, such as hypoxia, angiogenesis, acidosis, hypermetabolism and elevated redox state. Customizing nanomaterials that target the tumor microenvironment based on its specific characteristics holds paramount importance. These tailored nanocarriers can facilitate tumor stimulus-

Graphical Abstract
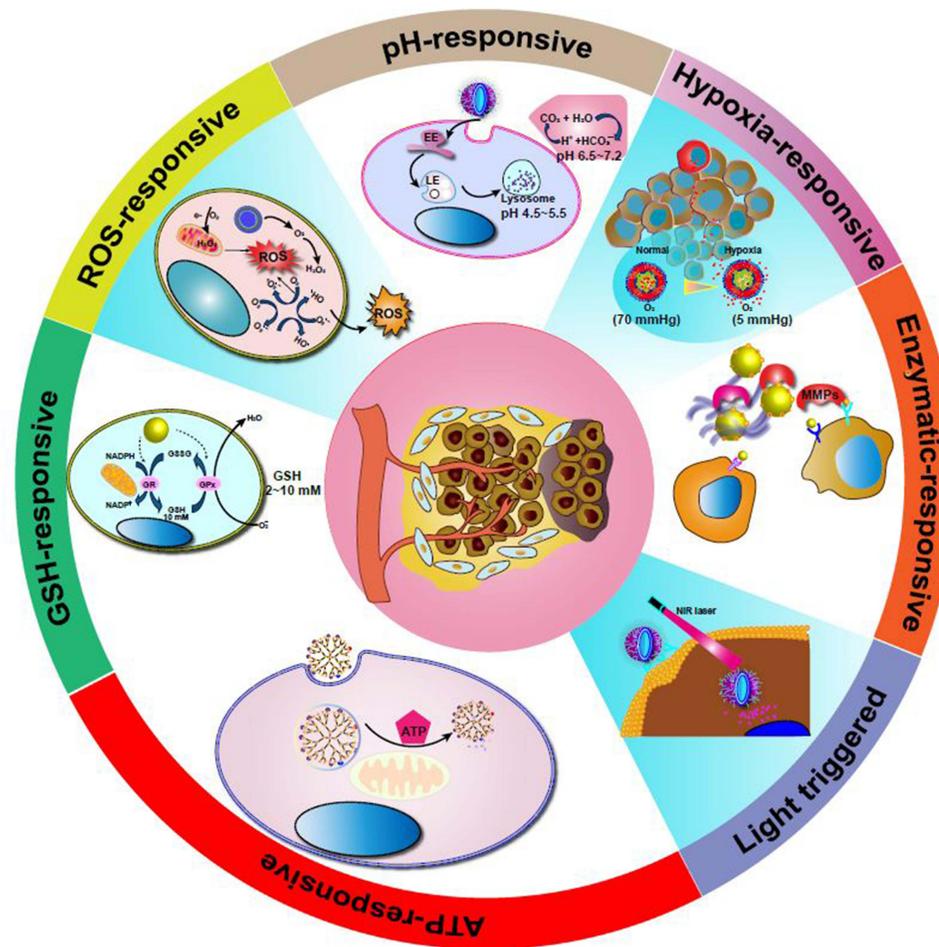
responsive drug delivery through size adjustments, surface charge conversion or other modifications of physicochemical properties. This adaptability ensures that the nanomaterials possess the necessary attributes for efficient accumulation in tumor tissues, penetration into tumor cells, facilitation of endocytosis and ultimately, controlled drug release.

Compared to the conventional clinical use of common nanomaterials like doxorubicin (DOX) liposomes and paclitaxel albumin nanoparticles, tumor microenvironment-responsive nanomaterials offer significant improvements in vivo drug delivery efficiency. They effectively exploit the enhanced permeability and retention effect (EPR), resulting in enhanced therapeutic effects and reduced side effects. As a result, tumor microenvironment-responsive nanomaterials hold immense potential for targeted drug delivery, emerging as a highly effective tool for tumor therapy. This review delves deeply into the realm of tumor microenvironment-responsive nano-delivery systems, with a keen focus on their capacity to respond to or modulate the tumor microenvironment. The study presents three dynamic targeting schemes: size contraction, surface charge conversion and ligand exposure strategies. Furthermore, recent advances in the development of targeted delivery vectors based on the tumor microenvironment were showcased, highlighting various examples of typical multi-stimulus-responsive drug delivery systems (DDSs). The potential applications of tumor microenvironment-responsive NPs in therapeutic industries are emphasized, accompanied by discussions on the feasibility of clinical translation for these nanomaterials. Additionally, the main challenges and potential future developments in this field are outlined. By employing tumor microenvironment-responsive nano-agents, medical professionals can significantly enhance drug delivery to target sites, leading to more effective treatments with fewer side effects. The
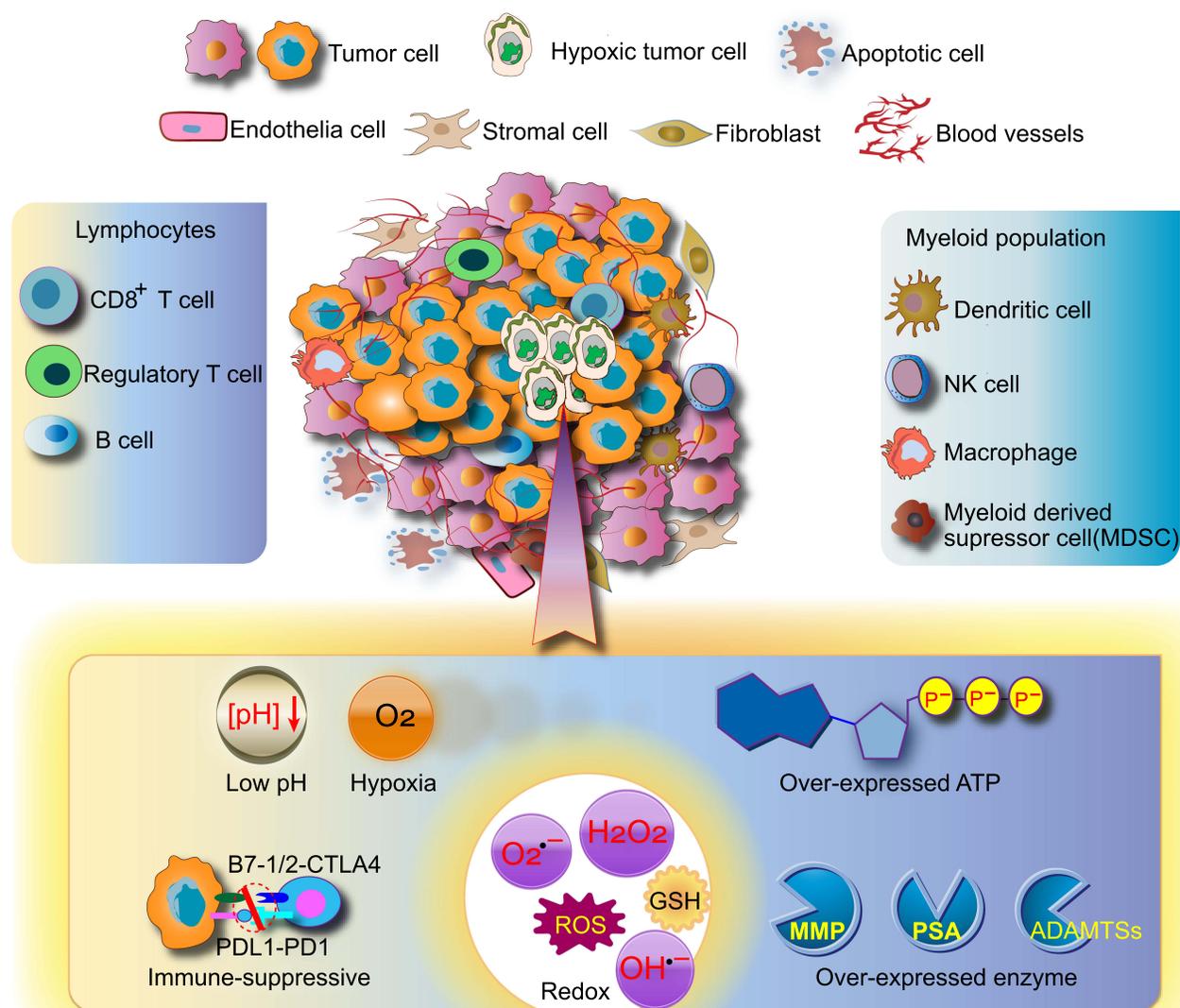
Figure 1 Composition and features of the tumor microenvironment (TME). The TME comprises various components, including endothelial cells, pericytes, immune cells, cancer-associated fibroblasts (CAFs), cancer stem cells (CSCs), extracellular matrix (ECM), blood vessels and other elements present in this complex biological environment. It significantly differs from the normal cellular microenvironment, exhibiting characteristics such as low pH, strong redox potential, overexpressed enzymes, hypoxia and overexpressed ATP level, all of which play crucial roles in tumor development, invasion and metastasis.

ongoing exploration and refinement of these nanomaterials hold promising prospects for advancing cancer therapies in the future. Although there are review papers published on the topic "tumor microenvironment-responsive biomedical nanocomposites", as a research hotspot, nanoplatforms responding to TME for precise drug delivery in cancer therapy have been continuously constructed and updated. Therefore, recent advances should be summarized in time reflecting the latest research achievements of this topic, which serves as the starting point of this review paper updating researchers of the constantly development in this field.

TME-responsive Nanoplatforms

TME-responsive nanodrugs have demonstrated both safety and efficacy in achieving targeted and localized drug release within tumor tissues, leading to improved patient response rates to drug therapy while minimizing associated side effects. Figure 2 illustrates the stimulus-triggered activation of nanoparticles in the tumor microenvironment, enabling rapid drug release at the intended site, enhancing cell binding and internalization, or promoting drug diffusion throughout the tumor
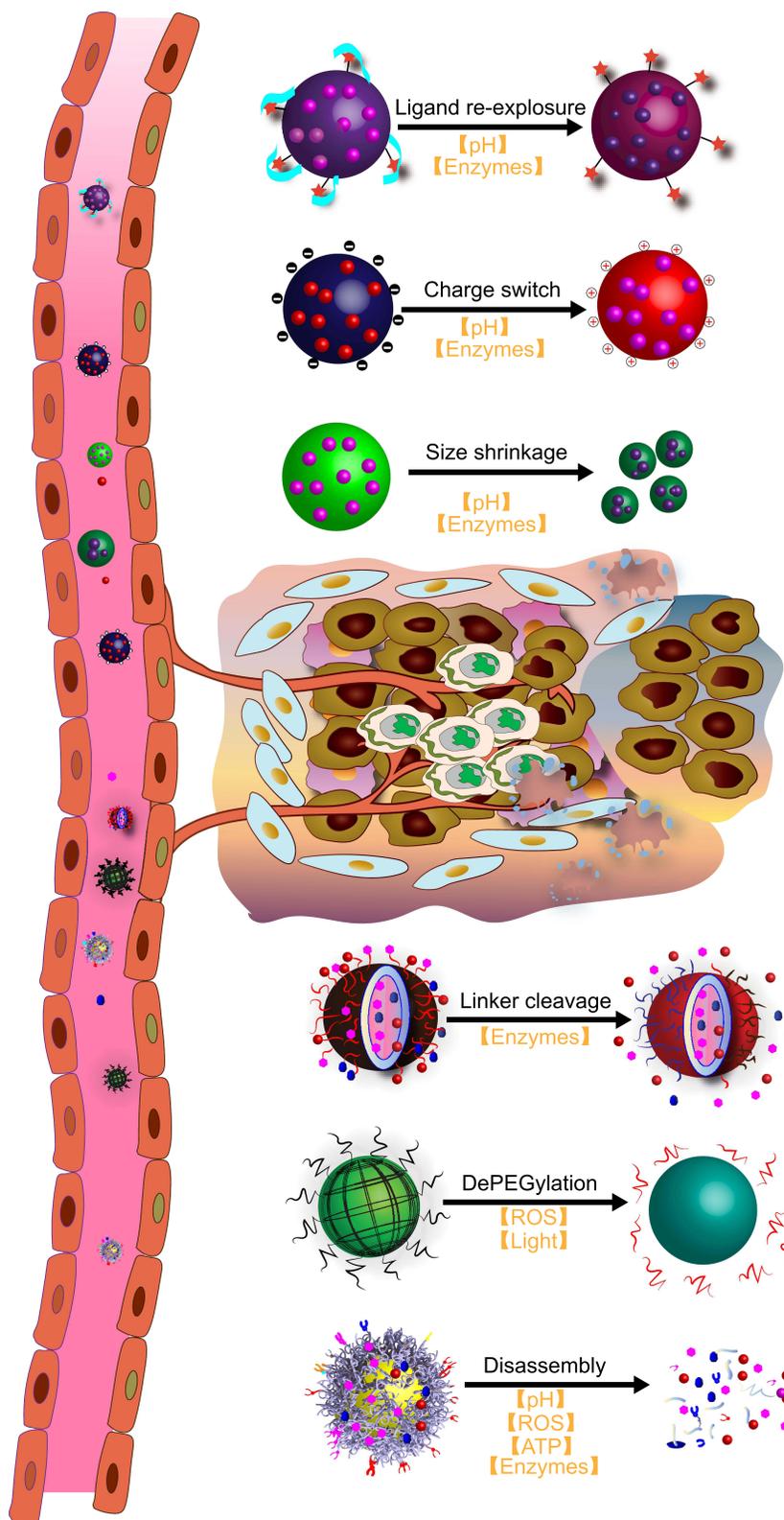
Figure 2 Response models for tumor microenvironment activation. Various response models for tumor microenvironment activation involve nanoparticles that sense the TME and utilize bond cleavage, disassembly, or decapitation mechanisms to promote drug release specifically at the desired sites. This targeted approach improves cell binding and internalization, and enhances drug diffusion and penetration within the tumor tissue.

region. This comprehensive summary encompasses recent breakthroughs in TME-responsive nanodrugs, specifically highlighting their responses to signals within the TME, such as highly reactive oxygen species, weakly acidic and reducing environments, hypoxia, overexpressed enzymes, and high concentrations of adenosine triphosphate.

pH-Responsive Nanoplatforms

The Warburg effect, characterized by increased glucose uptake and aerobic glycolysis in cancer cells leading to elevated lactate production, was first proposed by Warburg in the 1930s.[8] In most solid tumors, the pH of the extracellular tumor microenvironment ranges from 6 to 7, while that of intracellular endosomes and lysosomes falls within the range of 4 to 6.[9,10] Figure 3 showcase that researchers have extensively explored the use of pH-sensitive drug delivery systems, making the tumor microenvironment an ideal platform for such applications, due to these acidic pH conditions.[11]

This review (Table 1) will discuss classic pH-sensitive drug delivery systems separately, based on their triggering mechanisms.[12–20] However, it's important to note that the acidic nature of the pH in solid tumors raises some controversies concerning the efficacy and safety of pH-inducible delivery. As the use of pH-inducible delivery systems expands in both therapeutic and diagnostic fields, there is an urgent need for further exploration of the tumor micro-environment and the development of pH-triggering biorthogonal chemistry.

"Protonated" chemical groups, such as carboxylic acid and amine groups, experience conformational changes due to proton transfer in different pH environments. These pH-dependent conformational changes make these "protonated" chemical groups highly suitable for controlled release systems. There are three main types of pH-sensitive delivery systems based on specific "protonated" chemical structures: biomolecules, inorganic materials and polymers.[34]
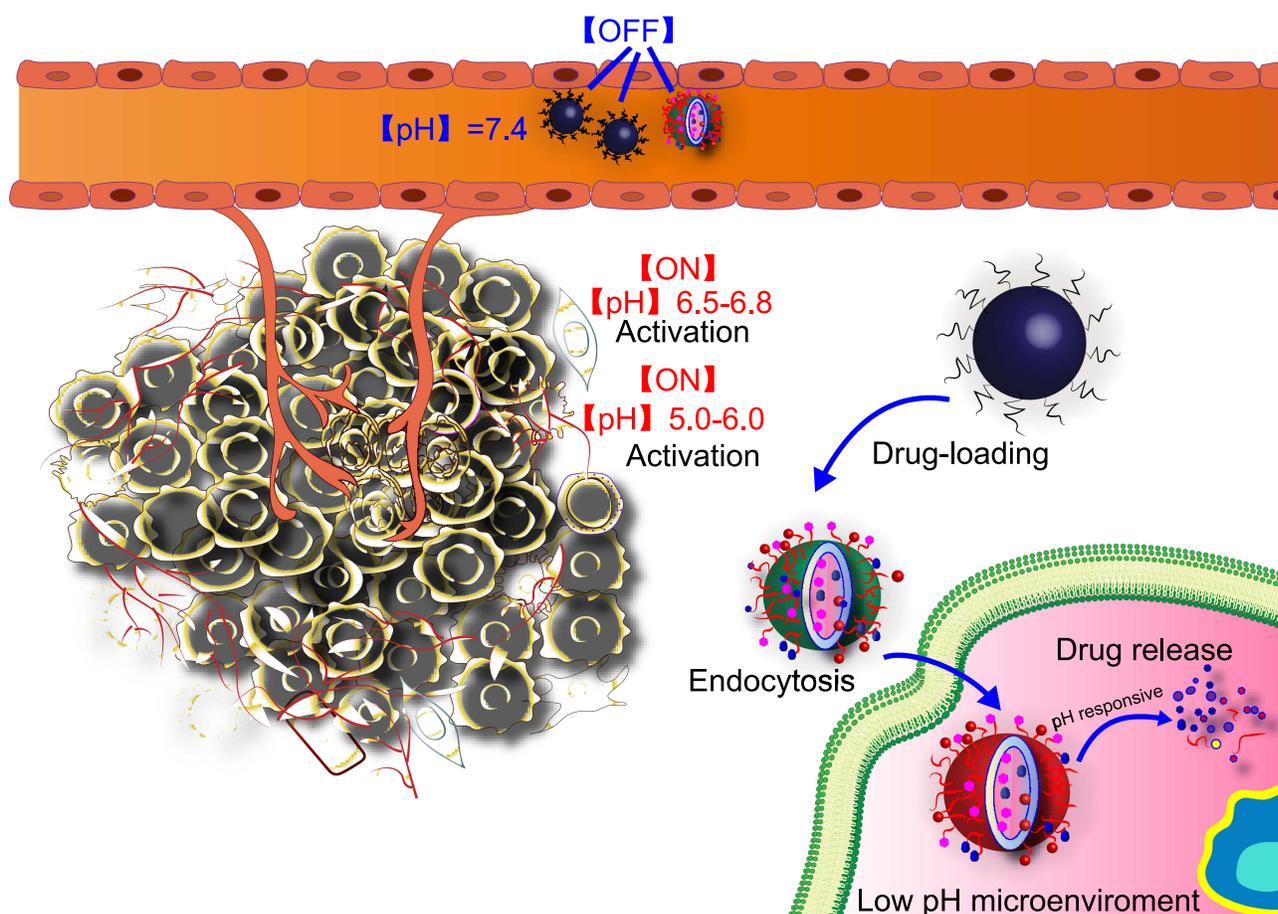
Figure 3 Drug release via pH sensitivity and cumulative drug release profiles. The low intracellular pH (pH 6.0 and 7.0), which is characteristic of the TME, triggers the release of transported drug into late endosomes.

Table 1 Typical Examples of pH-Responsive Nanomedicine for Tumor Therapy

Nanoparticle	Drugs	pH- Responsive Release	Function	Ref.
Micelles	PTX/DOX	Cumulative releases were 75% at pH 6.5, and 95% at pH 5.0	Promote combination chemotherapy for cancer	[12]
Carbon-based nanoparticles	Doxorubicin (DOX)	Accelerate release of DOX at pH 5.0	Controlled drug release	[13]
Polypeptide-modified gold nanoclusters	Photosensitizer chlorin e6 (Ce6)	Cumulative release of DOX at the acid extracellular environment (pH = 6.5)	For imaging-guided cancer therapy	[14]
Gold nanoparticles	DOX	At pH 4.5, the cumulative release of DOX was over 50% after 72 h	Target brain tumor for image and therapy	[15]
Copper chelating coil-comb block copolymer	Resiquimod (R848)	Cumulative release more than 80% of R848 at pH 6.5 or 6.0 after 72 h	High antiangiogenic efficiency	[16]
Micelleplex	siRNA PD-L1	Dissociated at pH = 6.2	Cancer immunotherapy	[17]
Polymeric micelles	Indocyanine green (ICG)	At pH 5.0, the cumulative released IGG in weak acidic environments	For cancer imaging and phototherapy	[18]
Gold nanoparticles (AuNPs)	CytC /ssDNA	At pH 5.5, the sustain release of CytC was 41.2%	Photothermal cancer therapy	[19]
Liposome	DOX	At pH 5.3 the release of DOX more than five times at pH 7.4	Improve drug resistance	[20]
Calcium carbonate	Doxorubicin	Burst drug release was observed under acidic conditions of pH 6.5 and 5.5	Cancer chemotherapy	[21]
MnO_2 nanosheets	Doxorubicin	Released very fast in pH 4.6	2D multifunctional nanomaterials.	[22]
Upconverting nanoparticles	Doxorubicin	Faster drug release at pH 5.0	Imaging-guided cancer therapy	[23]
Polymeric nanoparticle	Doxorubicin	Remarkable drug release at pH = 5.0	Tumor therapy and near infrared (NIR) imaging	[24]
Polymeric micelle	Doxorubicin	Higher uptake efficiency at pH 6.6	Biodegradable drug carriers for target delivery to acidic tumor areas	[25]
Zwitterionic material	Photothermal gold nanocage (AuNC)	Enhanced cell uptake efficiency in acidic pH (≤ 6.5)	Tumor photothermal therapy	[26]
Polymer vesicles	Doxorubicin	At pH 5.3, the DOX release rate of was faster than cross-linked inner hydrophilic PEG layers	Targeted delivery and ultrasensitive MR imaging	[27]
Mesoporous Silica	Melittin	pH-responsive release of melittin from mesoporous silica	Efficient pH sensitive carriers	[28]
Metal-organic frameworks	Doxorubicin	Exhibits pH-triggered controlled drug release properties	Applications in osteosarcoma therapy.	[29]
Metal−organic frameworks	Doxorubicin	At pH 5.0−6.0, it can release during a period of 7−9 days	Multifunctional materials for drug delivery	[30]
Magnetic nanoparticles	Cisplatin	pH-responsive ability	Dual-mode MR imaging and chemotherapy.	[31]
Liposomes	Doxorubicin	At pH 5.0, the shown effective drug release from the liposomes.	Circumvent the multidrug resistance (MDR)	[32]
Microsphere	Irinotecan	At pH 6.6, the was considerably greater release (85%) than at pH 7.4	Reverse the Pgp-mediated MDR	[33]

Biomolecules Based pH-Sensitive Delivering System

Endogenous proteins and DNA can be developed as pH-sensitive carriers. Ferritin, a classic carrier, undergoes a conformational change induced by α-helix under different pH environments. It self-assembles into a hollow cage structure by removing the E-helix, allowing it to encapsulate metal complexes. This "Ferritin" cargo vessel unloads the metal complexes by disassembling in an acidic environment. Leveraging the nature of ferritin, Jung's group has

developed ferritin nanocages that trap Fe (II)-DOX complexes. These nanocages remain stable at pH 6.0 and disassemble at pH 4.0–5.0 (the endosomal pH of tumor cells), enabling the release of cargos under acidic conditions.[35] The pH (low) insertion peptide (pHLIP) can shuttle through the tumor cell membrane when triggered by acidity. When protonated, pHLIP's hydrophobicity increases, and helix structures form spontaneously, facilitating rapid transmembrane shuttling through a non-endocytic pathway. Cheng's group has reported a pHLIP-based platform to carry therapeutic nuclear acid analogs via glutathione (GSH)-responsive disulfide linkages with pHLIP.[36] Upon entering tumor cells, GSH triggers the release of cargos. The efficacy of this pHLIP-carrier has been demonstrated in silencing miR-155 and inhibiting tumor growth in a mouse lymphoma model.[36] The amine group of poly (L-histidine) acts as the trigger of a proton pump in lysosomes after protonation. Jia et al have developed poly(L-histidine)-based pH-sensitive micelles, which release the encapsulated drug into the cytoplasm after proton pump activation and an increase in lysosomal osmotic pressure.[37] Oligodeoxynucleotides (ODNs) can also serve as acidic-stimulating carriers. ODNs tethered to gold nanoparticles (AuNPs) have been reported to co-deliver DOX and antisense ODNs to bcl-2 mRNA.[38] In this system, AuNPs were coated with antisense ODNs and i-motif binding ODNs. A cytosine-rich i-motif sequence acted as the linker for AuNPs assembly. The C-G rich DNA duplexes provided a nest for the cargo DOX. Under acidic conditions (pH 5.0), the partial hybridization of cytosine and protonated cytosine from the i-motif sequence formed a unique tetrameric structure, leading to the disassembly of the gold clusters and subsequent release of DOX and exposure of antisense ODNs. The ODNs-AuNPs have demonstrated 2.5-fold higher tumor-specific accumulation and efficient tumor growth inhibition in A549-bearing nude mice xenografts. The biocompatibility of biomolecules makes them a preferable choice for in vivo drug delivery.

Inorganic Materials-Based pH-Sensitive Delivering System

Several inorganic materials, namely zinc oxide (ZnO), calcium carbonate ($CaCO_3$), and manganese dioxide (MnO_2), have shown considerable sensitivity to acidity.[21–23,39] Zhong's research group has achieved a significant milestone by developing a cutting-edge ZnO-based nanoplatform, boasting tri-modality bioimaging and acid-inducible DOX release capabilities for cancer therapeutics and diagnosis. The ingenious design involves coating lanthanide-doped upconverting NPs (UCNPs) with a mesoporous silica layer, expertly embedding ZnO to facilitate controlled drug release.[40] The ZnO-based acid-inducible nanoplatform has showcased remarkable drug release capabilities at pH 5.0, while its tri-modality imaging system has undergone comprehensive validation both in vitro and in vivo. Also, a study on a novel zinc oxide-functionalized up-conversion nanotherapeutic platform for pH-triggered on-demand drug release for multi-modality bioimaging and therapeutic platforms. Among this platform, zinc oxide effectively blocks the drug in the mesopores of the prepared formulations and promotes the dissolution of the drug in the acidic environment surrounding the tumor, thus enabling a drug-on-demand chemotherapeutic approach.[23] Furthermore, the dual pH-responsive function of MnO_2 nanosheets can be used for MRI and drug-responsive release of cancer. The pH-triggered fracture behavior can further promote the rapid cargo release in the weakly acidic microenvironment and combat the multidrug resistance of cancer cells, which paves the way for biomedical applications of two-dimensional multifunctional pH-responsive nanomaterials.[22] Despite the inherent limitations regarding the scope of applications for acid-sensitive inorganic materials, their solubility variance between neutral and acidic environments firmly establishes these specific inorganic materials as viable alternatives for acid-sensitive diagnosis and therapeutics.

pH-Sensitive Polymers

Poly-L-histidine (polyHis) exhibits a pKa of approximately 7.0 and undergoes reversible transitions between hydrophilic and hydrophobic states. Bae's research group has made significant strides by successfully developing mixed micelles comprising polyHis-b-PEG and poly (L-lactic acid) (PLLA)-b-PEG. These micelles gradually become destabilized under acidic conditions (pH < 7.0) due to the protonation of the polyHis segments within the micelle.[41] In neutral or basic environments, the anticancer drug doxorubicin (DOX) can be encapsulated within the micelle through hydrophobic interactions with the deprotonated polyHis segments. Once these mixed micelles reach the tumor sites, they undergo dissociation, facilitating the release of DOX in the acidic environment. In xenograft models, these pH-sensitive micelles have demonstrated vastly improved antitumor efficacy compared to their pH-insensitive counterparts. Furthermore,

polyHis polymers have found applications in triggering the release of targeting ligands in acidic tumor microenvironments, thereby preventing plasma protein binding at physiological pH. Hyeon's group has pioneered a hybrid system that combines pH-sensitive polyHis polymers with metal oxides.[42] In this system, the PEG-polyHis polymer is functionalized with catechol groups and chlorin e6 (Ce6). The catechol groups effectively anchor the polymers to the iron oxide surface, while Ce6 acts as a fluorescent tracer and photosensitizer for photodynamic therapeutic nanoparticles. Under physiological conditions, the hybrid superstructures remain inert, securely trapping multiple iron oxide nanoparticles and Ce6. However, upon exposure to an acidic environment, the hybrid's charge gradually shifts from negative to positive, resulting in particle swelling, drug release, and cellular internalization. The photodynamic and fluorescence tracking capabilities of Ce6 have been convincingly demonstrated in both colorectal carcinoma xenografts and heterogeneous drug-resistant tumors. Cholesteryl hemisuccinate (CHEMS) possesses a pKa of around 5.8, and its carboxyl group undergoes protonation at acidic pH levels, leading to alterations in the spatial structure of liposomes and promoting drug release. Additionally, poly [2-(diisopropylamino) ethyl methacrylate] (PDPA) and its derivatives have pKa values ranging from 4.0 to 7.4, making them highly sensitive to pH changes in acidic endocytic organelles.[43] Gao's research group has achieved significant advancements in the field of controlled drug delivery by developing star-like nanoparticles (NPs) through the anchoring of PDPA-b-POEGMA on a β-CD core.[24] Under normal physiological conditions (pH 7.4), the PDPA blocks facilitate the copolymers to effectively trap the drug cargo through hydrophobic interactions. However, in an acidic environment (pH<6), the drug release is triggered due to a hydrophobicity-hydrophilicity transition. This innovative approach holds great promise for precise and controlled drug delivery. Furthermore, the research group has successfully modified various PDPA derivatives with linear or cyclic side chains at the tertiary amines to enable the delivery of ovalbumin (OVA) for cancer immunotherapy.[44] This signifies a significant step towards targeted cancer treatment using nanoscale drug carriers. Notably, the PC7A NPs, with a pKa of approximately 7.9, exhibited remarkable OVA-specific splenocyte cytotoxicity and enhanced efficacy, including improved lymph node accumulation and tumor inhibition, in xenograft models of C57BL/6 mice bearing B16F10 melanoma, MC38 colon, and TC-1 cancer cells.[45] These findings highlight the potential of PC7A NPs as a promising platform for cancer immunotherapy. In addition to PDPA-based NPs, sulfonamide-based polymers have been explored as pH-sensitive micelles.[46] The nearly neutral pKa of the secondary amine group in sulfonamide serves as a pH-responsive trigger. In a basic or neutral environment, the polymers aggregate due to electrostatic interactions between the negatively charged sulfonamide and the positively charged polymer. However, as the pH decreases, the cargos are efficiently released or flipped due to the elimination of electrostatic associations. This remarkable feature has been successfully demonstrated in various systems, including pH-sensitive sulfonamide-coated TAT peptide-decorated micelles[25] and zwitterionic gold nanoparticles.[26] By carefully and rationally modifying these easily prepared and multi-loaded polymers with pH-triggering functional groups, they can be further developed as potent carriers for imaging agents and drugs. This promising avenue holds great potential in enhancing diagnostic sensitivity and therapeutic efficacy, thus significantly advancing the field of nanomedicine.

Acid-Labile Chemical Groups

The utilization of pH-sensitive chemical bonds represents a well-established delivery strategy, particularly effective in the acidic tumor environment. In this approach, cargos (drugs or imaging agents) are typically attached to vesicles using various acid-labile moieties, such as hydrazine,[27] acetal,[28] or metal-organic frameworks (MOFs).[47] These linkers can be easily hydrolyzed in acidic environments (pH 4.5–6.5) while remaining relatively stable under physiological conditions. This unique property allows for the specific release of cargos at acidic tumor sites. Numerous reports categorize acid-labile linkers into organic linkers and metal-organic complexes. The organic acid-labile linkers utilized in tumor microenvironment-induced delivery systems are listed in the Table 1. On the other hand, metal-organic complexes consist of organic ligands coordinated with metal ions to form one-, two-, or three-dimensional structures, making them ideal for encapsulating cargos. These complexes are usually stable and demonstrate acceptable biocompatibility in physiological environments. The coordination bonds, at the core of the metal-organic complexes, serve as the trigger for cargo release through acid-mediated bond breakage. For instance, Zhuang's research group successfully encapsulated cargos (eg, fluorescein, camptothecin (CPT), and iron oxide NPs) in acidic-sensitive zeolitic imidazolate framework-8 (ZIF-8) nanospheres. This system demonstrated stability at pH 7.4 and

efficiently released cargos within an acidic buffer (pH 6.0), showcasing the versatility of the ZIF-8 strategy.[47] In a similar study, a pH-responsive Fe_3O_4@ZIF-8 nanocomposite carrier was prepared, which effectively accumulated in mouse tumor tissues to improve the anti-tumor effect.[29] In other studies, researchers assembled DOX-encapsulated MOFs by sequentially coordinating therapeutic molecules with functional carboxyl groups with Zn^{2+} ions for the initial self-assembling, and then introducing another distinct organic linker for coordination complex reassembling.[30] Moreover, Sun's research group developed a yolk-like Fe_3O_4@Gd_2O_3 nanoplatform for acid-inducible T1-T2 dual-mode magnetic resonance imaging (MRI) and cisplatin delivery. By further optimizing the system with PEG and FA to prolong circulation and enhance targeting, both drug release efficacy and T1-T2 dual-mode MRI were significantly improved at pH 4.5.[31]

pH-Responsive Insertion Peptide

A class of peptides, known as pH Low Insertion Peptides (pHLIPs), can serve as a responsive delivery system in acidic tumor microenvironments by integrating into cellular membranes. These pHLIP peptides consist of a transmembrane sequence and two flanking sequences at each terminus. Under neutral or basic conditions, the peptides exist as disordered linear monomers in an aqueous solution. However, in an acidic environment, the transmembrane sequences, containing aspartate (Asp) and glutamate (Glu) residues, facilitate the insertion of the entire peptide into the lipid bilayer or cellular membrane through hydrophobic interactions. Protonation of the carboxyl groups of Asp and Glu residues, as well as the C-terminus, increases the peptide's hydrophobicity. This protonation also promotes the formation of an interfacial helix, which aids the peptide's insertion into the hydrophobic bilayer of the cellular membrane. Studies have demonstrated that the membrane insertion process is thermodynamically favorable, with the peptides exhibiting 30–50 times higher affinity for the bilayer membrane at acidic pH.[48] Furthermore, the insertion process consists of two stages: the formation of the interfacial helix and the movement across the membrane, both of which can be completed within seconds to minutes.[49,50] Therefore, the use of transmembrane peptide sequences as an inducible delivery system in acidic tumor microenvironments is both thermodynamically and kinetically advantageous.[51] The pH-sensitive membrane insertion strategy has been validated by delivering various imaging cargos (eg, near-infrared (NIR) fluorescent dyes, positron emission tomography, and single-photon emission computed tomography) to tumor sites, resulting in significantly high tumor-specific fluorescent signals.[52–54] Additionally, this peptide-induced delivery system has been employed to transport other polar cargos (eg, phalloidin toxin, peptide nucleic acids, and microRNAs) and nanoparticles into the cytosol of cancer cells.[55] Considering the convenience, modifiability, low cost, and high biocompatibility of peptides as pH-responsive delivery agents, the application scope of the system can be further expanded.

Gas Generating Based Systems

Acid-promoted gas generation represents a novel and promising strategy for cargo release in delivery systems.[56] Two extensively studied gas generators are the carbon dioxide gas generator (HCO_3^-) and the nitric oxide (NO)-releasing donor (NONOate). In one study, pH-sensitive liposomes were employed to encapsulate bicarbonate ions and the anticancer drug DOX, enabling the release of DOX from the liposomes upon triggering carbon dioxide generation in an acidic environment.[32] Another study focused on developing injectable PLGA hollow microspheres (HM) armed with a NO-releasing donor (NONOate) and encapsulated with the anticancer agent irinotecan (CPT-11) or Cy5, a fluorescent agent. At pH 6.6, the NO generator released NO bubbles, reversing p-glycoprotein-mediated multidrug resistance (MDR), and disrupting the HM shell, leading to a burst release of the encapsulated CPT-11 or Cy5.[33] The results demonstrated strong fluorescence intensity in MCF-7/ADR tumors and suppressed tumor volume, showcasing the feasibility of acidic tumor microenvironment-initiated release using the NO generator.

Harnessing chemical reactions under certain pH values for precise drug release at the tumor region provides a good paradigm for intelligent drug delivery. However, due to the irregular concentration of reductants such as GSH and reactive oxygen species (ROS) in TME, and redox is the most common reaction in physiological environment. Efficiently releasing drugs over redox-responsive and ROS-responsive nanoplatforms offer additionally smart strategies for precise drug delivery.

Glutathione-Responsive Nanomedicines

GSH is a tripeptide composed of glutamate, cysteine, and glycine, primarily found in the cytoplasm of living cells, where it plays a crucial role in maintaining physiological redox homeostasis. When exposed to oxidizing agents, GSH readily undergoes oxidation, forming oxidized glutathione (GSSG). In normal cells, the concentration of GSH typically ranges from approximately 1–10 mM within the intracellular space, while in the extracellular environment, it remains at only 1–10 μM.[57] However, in cancer cells, the GSH level can increase significantly, reaching levels as high as 4–40 mM, which renders them more reductive compared to the extracellular milieu.[58–60] Perry's group has compiled data on GSH levels in various tumors, proving to be valuable for the development and optimization of GSH-mediated delivery systems.[61] According to their report, colorectal tumors exhibit a GSH level of approximately 90 nmol/mg protein, which is at least four times higher than that observed in ovarian, head and neck, lung, brain, and breast tumors. This high GSH level suggests that GSH-induced delivery systems might be particularly effective for treating colorectal cancer.[61] Several nanocarriers, such as zwitterionic dextran nanoparticles, single-walled carbon nanotubes, chitosan-based nanoparticles, PEGylation micelles, and mesoporous silica nanoparticles, have been utilized in GSH-triggered delivery systems.[62] These carriers have been thoughtfully designed to incorporate GSH-responsive moieties, ensuring stability in the bloodstream and tumor tissue until triggered by GSH. The differences in intracellular and extracellular GSH concentrations can be exploited to fine-tune the stability and targeting efficiency of the delivery system. Moreover, this concentration difference contributes to prolonged circulation time and controlled intracellular molecular release of the GSH-sensitive delivery system. Due to the unique properties of GSH and the diverse reduction-mediated breakage of linkers, GSH has undergone extensive investigation in the development of GSH-responsive carriers.

Based on the functional moieties of GSH-responsive delivery systems, they can be categorized into five main groups: disulfide, diselenide/ditelluride, thioether/selenide/tellurium, metal-thiol-based linkers, and ferrocenium. These moieties, along with their mechanisms and applications, have been summarized in Table 2.[63–75] In this review, we will delve into the specifics of each of these moieties to gain a better understanding of their potential in GSH-responsive delivery systems.

Disulfide

Disulfide bridges provide a highly convenient linkage that can be incorporated into GSH-responsive carriers, such as nanogels, micelles, polymersomes, and mesoporous silica NPs. Disulfide bonds can be easily formed through cost-

Table 2 Summary of GSH Responsive Drug Delivery Systems

Key Moiety	Carriers	Applications	Ref.
Disulfide	Sarcoma-targeting polypeptide-decorated disulfide-crosslinked nanogel (STP-NG)	Inhibition of osteosarcoma and pulmonary metastasis	[76]
	Micelles	decreased tumor growth in A2780CIS tumor-bearing athymic nude mice model	[64]
	Poly (ethylene glycol)-SS-polystyrene (PEG-SS-PS) stomatocyte nanomotor	Application for the delivery of DOX	[65]
	Poly (γ-glutamic acid) (γ-PGA)-coated mesoporous silica nanoparticles (MSNPs)	Promote cellular uptake and intracellular drug release	[66]
	α-PTX- SS-CIT	Slower drug release	[67]
	Nanogel (STP-NG)	Target delivery and against osteosarcoma	[76]
	Silica nanoparticles	Significantly inhibit tumor cell growth	[66]

(Continued)

Table 2 (Continued).

Key Moiety	Carriers	Applications	Ref.
Ditelluride/diselenide bond	Ditelluride-containing poly(ether-urethane) nanoparticles	Release in a controlled manner	[68]
	poly(ether-urethane) nanoparticles	Trigger the drug release and increase the anticancer activity.	[77]
Thioether/selenide/tellurium Thioether-based	Thioether succinimide crosslinked hydrogel	Controlled delivery of drugs	[69]
	Thioether-docetaxol-nano-assemblies	High drug loading efficiency, long circulation	[70]
	PEGylated PTX-S-OA nanoassemblies	Highly efficient anticancer activity	[71]
	PEGylated PTX-S-OA NPs	High efficiency of drug delivery	[71]
Metal-thiol based	Dendrimer-coated gold NPs (DEGNPs)	High drug loading efficiency	[77]
	Fluorescein isothiocyanates-AgNPs	For early diagnosis of cancer, and detect the tumor microenvironment	[73]
	MnO_2 NPs	Photothermal therapy-induced tumor death	[78]
	Iron-copper co-doped polyaniline nanoparticle	Activatable photothermite for tumor-targeted PTT	[79]

effective and robust chemistries, such as L-cystine,[80] di-thiodiglycolic acid anhydride,[81] and pyridyl disulfide chemistry.[82] In many strategies, cargoes are packaged within GSH-responsive carriers using disulfide bridges, which can be readily broken through intracellular thiol-disulfide exchange in GSH-rich environments. For instance, a nanogel (STP-NG) was constructed with sarcoma-targeting polypeptide-modified disulfide linkages, encapsulating the cargo shikonin.[76] The STP-NG system effectively delivered shikonin to osteosarcoma tumors, inhibiting osteosarcoma progression. Within 72 hours, shikonin was released from the nanogel with an efficacy of approximately 98%, thanks to a 10.0 mM GSH-mediated disulfide bond (S-S) breakage. Moreover, the STP-NG selectively aggregated inside the tumor, leading to the inhibition of orthotopic 143B osteosarcoma progression and pulmonary metastasis. Ling's group developed poly (disulfide amide)-based micelles to precisely deliver cisplatin into solid tumors.[64] In this system, the high disulfide density consumed the elevated concentration of cytosolic GSH within tumor cells, facilitating tumor-specific cisplatin release and minimizing off-site toxicity. The poly (disulfide amide)-cisplatin micelles exhibited a significantly higher tumor inhibition rate (83%) compared to control micelles (1.5%) and free cisplatin (1.5%) in the A2780CIS tumor-bearing athymic nude mice model. Optimization of micelle properties, such as particle size, Pt loading capacity, and drug release, can be achieved by incorporating hydrophobic chemical groups, such as aromatic groups or alkyl chain lengths. A stomatocyte nanomotor system of poly (ethylene glycol)-SS-polystyrene (PEG-SS-PS) polymersomes was designed to deliver DOX in response to GSH.[71] Nanomotors are nanoscale devices that convert energy into movement, with specific chemical signaling molecules functioning as energy sources. In the PEG-SS-PS-based stomatocyte nanomotors, Pt NPs catalysts were packaged inside the polymers, and DOX was encapsulated into the lumen of the stomatocytes. The H_2O_2 gradients from the human body drove the nanomotors to disease regions, where concentrated GSH initiated disulfide bond breakage, leading to PEG-shell peeling. Consequently, the nanomotor lost mobility and released the encapsulated drug into the lesions. However, the large size of PEG-SS-PS-based stomatocyte nanomotors (around 350 nm) limits their applications in drug delivery. Du's group designed a GSH-sensitive delivery system based on poly (γ-glutamic acid) (γ-PGA)-coated MSNPs.[66] In this design, the γ-PGA shell was formed via electrostatic interaction with the nontoxic poly(ethylenimine) (PEI), which remained stable at a neutral pH environment. At pH 5.0, the protonated γ-PGA dissociated from the cationic PEI. The cargo DOX was modified with an amino group to conjugate with the nanoparticle via the disulfide bond, which is crucial for GSH-mediated drug release. With the dual

stimulation of pH and GSH, the poly (γ-glutamic acid) (γ-PGA)-coated MSNPs effectively delivered DOX into the cytoplasm. It has been proven that the carbonate linkage of disulfide bonds is more suitable for a quick response to GSH than the carbamate linkage. In conclusion, the convenience of disulfide bond formation has made it the most commonly used moiety for GSH stimulation. However, further modifications and integration with other functional moieties are urgently needed in the development of GSH-sensitive delivery systems.

Ditelluride/Diselenide Bond

Ditelluride and diselenide bonds exhibit greater responsiveness to various redox environments compared to disulfide bonds, with their energy levels following the order of Te-Te (149 kJ/mol) < Se-Se (192 kJ/mol) < S-S (240 kJ/mol). Consequently, ditelluride bonds hold significant potential in the development of redox-stimulated delivery systems, particularly for highly sensitive carriers. Wang's group was at the forefront of reporting ditelluride-containing poly(ether-urethane) nanoparticles as a GSH-mediated drug delivery system.[77] Specifically, ditelluride acted as the trigger for GSH-mediated release, rapidly reducing to tellurol by GSH (10 mM) within 5 minutes. DOX was attached to the NPs through hydrophobic interactions. Upon GSH-mediated reduction, the nanoparticles dissociated, releasing the cargo DOX into the environment. The tumor site accumulation and anti-tumor effects of the ditelluride-containing poly(ether-urethane) nanoparticles were demonstrated in the 4T1 tumor mice model. Diselenide-bond-based delivery systems have also been explored, with some exhibiting a more sensitive response to ROS stimulation. The lower energy of ditelluride and diselenide bonds has provided them with an advantage in GSH-mediated delivery systems. However, further investigations are still required to optimize the structural linkages of ditelluride/diselenide bonds, synthesize ditelluride/diselenide bond-based macromolecules, and explore their applications.

Thioether/Selenide/Tellurium Thioether-Based

Thioether-containing polymers are commonly synthesized through the Michael addition of thiols with maleimide, enabling easy dissociation via the concentrated GSH-mediated retro-Michael reaction and thiol exchange. Additionally, a thioether succinimide crosslinked hydrogel was constructed by integrating maleimide-functionalized liposomes with aryl thiol-functionalized 4-arm PEG polymers. The hydrogel's diverse domains create separate compartments for DOX and cytochrome c (cyto-c). Upon treatment with GSH (10 mM), DOX and cyto-c simultaneously released through different mechanisms. The hybrid systems' structural integrity and functionalities facilitate both the burst release of cargos and controlled sequential targeted delivery. In addition to GSH-stimulated release, thioether/selenide/tellurium-based delivery systems are also sensitive to H_2O_2 stimuli. For example, Luo's group developed a series of redox-responsive materials with diverse linkages, including thioether, dithioether, and ester bonds.[71] Paclitaxel (PTX) was conjugated to oleic acid (OA) with long unsaturated alkyl chains via thioether, dithioether, and ester bond-based linkages. These polymers were then assembled into nanoparticles, which were coated with tocopheryl polyethylene glycol 2000 succinate (TPGS 2k) to extend circulation time. Among these linkages, PTX-S-OA demonstrated the best performance in terms of speed and selectivity in releasing free PTX from the nanoparticles in response to redox stimuli.[71] This suggests that the sulfur atom near the ester bond with the attached drug enhances redox-sensitivity. Furthermore, the PEGylated PTX-S-OA nanoparticles, with a drug loading of approximately 57.4%, effectively inhibited the proliferation of human epidermoid carcinoma xenografts. Overall, these findings underscore the potential of thioether-containing and other redox-responsive delivery systems as promising platforms for targeted drug delivery applications.

GSH Responsive NPs of Metal Ions

Polyvalent metal ions exhibit GSH responsiveness through redox reactions. Common used metal ions include Fe^{3+}/Fe^{2+}, Cu^{2+}/Cu^{+}, and Mn^{4+}/Mn^{2+}. Fe^{3+} is synchronized with GSH redox to form Fe^{2+} ions, which can further undergo a Fenton reaction with endogenous H_2O_2 in tumors to generate hydroxyl radicals ($\cdot$OH), thus inducing iron-mutagenic response-based tumor therapy. At the same time, Fe^{3+} ions act as oxidants to deplete GSH to prevent $^1O_2$ quenching.[83] Other multivalent metal ions containing Cu^{2+}/Cu^{+} and Mn^{4+}/Mn^{2+} also have similar functions to those of iron ions. GSH-responsive composites were synthesized by anchoring negatively charged BSA-modified MnO_2 NPs to the surface of

reduced graphene oxide nanosheets (rGO NSs) modified in polyethyleneimine. The MnO_2 NPs were reduced to Mn^{2+} ions by intracellular GSH, which converted H_2O_2 to $\cdot OH$ through a Fenton-like reaction, and the photo-thermal under irradiation of near-infrared light (808 nm) conversion generates high temperatures that increase the Fenton reaction rate, and rGO NSs further kill tumor cells by photothermal therapy.[78] An iron-copper co-doped PANI nanoparticle (Fe-Cu @PANI) was prepared, in which the Cu(II) in the nanoparticle could undergo a redox reaction with endogenous GSH in tumor tissues leading to the etching of the nanoparticle. With the increase of the concentration of GSH, the size of the nanoparticle gradually decreased, inducing the absorption spectrum of the nanoparticle to red-shift from the visible region to the near-infrared region, and activating the photo-acoustic imaging of the tumors and the photo-thermal therapy (PTT) simultaneously.[79]

Thus, GSH-responsive NPs of metal ions are promising for cancer therapy by taking advantage of the synergistic effect of PTT and the photothermal/delivery effect. Metal-organic frameworks (MOFs) have emerged as a novel therapy for the treatment of malignant tumors. Thus, another study developed a GSH-sensitive MO material to encapsulate an inhibitor of the immunosuppressive enzyme indoleamine 2,3-dioxygenase (IDO), and s-nitrosothiol groups (SNAP), a nitric oxide (NO) donor, to obtain the nanomedicine BMS-SNAP-MOF. In the presence of high concentrations of GSH, this MOF was effective in producing NO. IDO inhibitors and NO can synergistically modulate the immunosuppressive tumor microenvironment by increasing $CD8^+$ T cells and decreasing Treg cells, resulting in an efficient immunotherapeutic effect.[84] These moieties, along with their mechanisms and applications, have been summarized in Table 2.

ROS Stimulated Delivery Systems

ROS, such as H_2O_2, $O^{2\bullet}$, $\bullet OH$, $ONOO^-$, and OCl^-, play a crucial role in cellular metabolic pathways. Various pathological conditions, including cancers, inflammations, diabetes, and neurodegenerative diseases, have been linked to oxidative stress and inflammatory events resulting from an imbalance in ROS levels. Among these ROS, H_2O_2 stands out as one of the most prevalent. It is present in significant concentrations in both cancer tissues (50–100 μM) and normal tissues (20 nM). However, the physiological concentration of H_2O_2 in cancer tissues is not sufficient to trigger drug release. Consequently, exogenously generated ROS can be employed to enable H_2O_2-mediated delivery systems. Two primary types of exogenous and biocompatible ROS generators are commonly used: photodynamic therapy (PDT) and ROS-producing agent treatments (Figure 4).[85] Through the amplification of ROS concentration, drug release can be facilitated via amphiphilicity transition and bond cleavage mechanisms, which will be discussed in detail below.
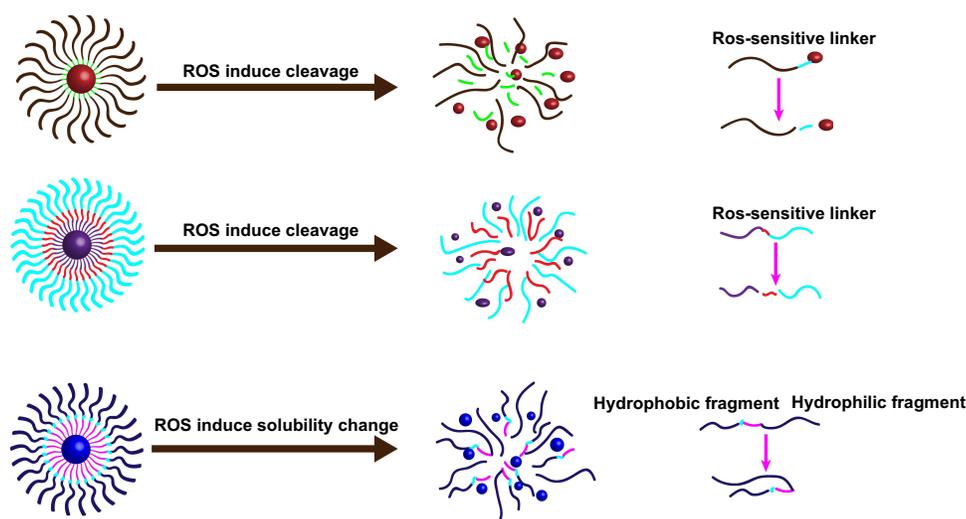
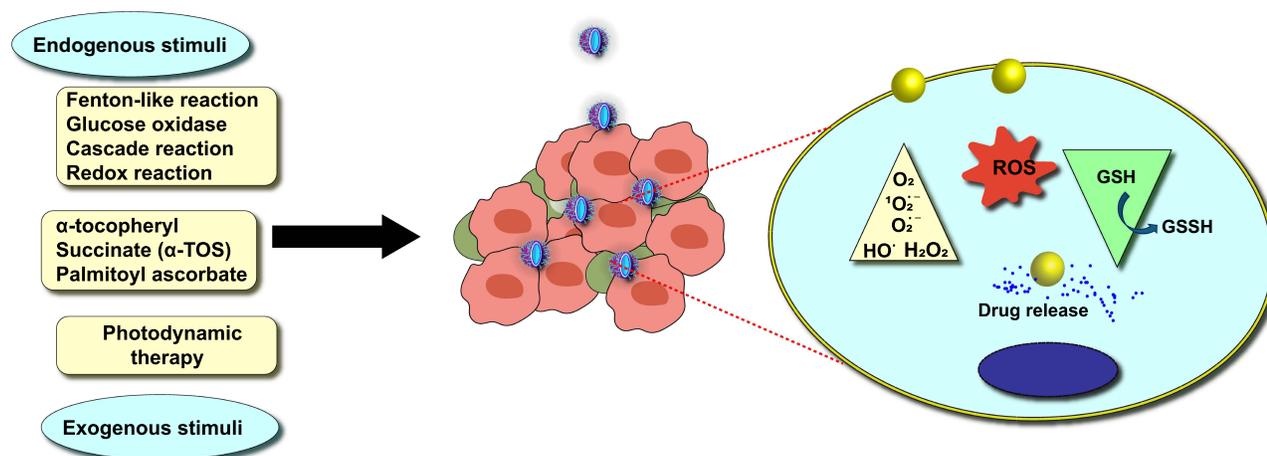**Figure 4** Illustration of ROS-sensitive drug delivery systems.

Figure 5 ROS-responsive nano-drug delivery system.

Amphiphilicity Transition Models

Polymers containing hydrophobic mono-sulfide, mono-selenium, or mono-tellurium groups can undergo easy conversion into hydrophilic oxidative products using H_2O_2 (Figure 5).[86,87] This process disrupts the amphiphilicity of the NPs, leading to the dissociation of the NPs and subsequent release of their cargo. Yang's group has developed a ROS-responsive delivery system that integrates 6-maleimidocaproic acid (MAL) with PTX through a mono-sulfide linkage. The resulting PTX-S-MAL NPs self-assemble into uniform-sized nanoparticles, releasing their cargo in response to H_2O_2 concentrations exceeding 1 mM.[86] Duvall's group reported a curcumin delivery system based on sulfide-containing poly (propylene sulfide) (PPS) NPs.[71] In this case, the hydrophobic PPS-based NPs were converted to hydrophilic poly (propylene sulfoxide) and poly (propylene sulfone) with H_2O_2 treatment at concentrations ranging from 0.5 to 500 mM. Although the systems discussed above displayed a good morphological hydrophobic-to-hydrophilic transition at high concentrations of H_2O_2, their application in controlled release at tumor sites has been limited due to the physiological concentrations of ROS (50–100 μM). Therefore, it is necessary to explore more sensitive moieties to ROS at endogenous concentrations or simultaneous ROS accumulation. Wang's group constructed an ultra-sensitive ROS-responsive system that functions at a concentration of 100 μM. The H_2O_2-mediated hydrophobic-to-hydrophilic transition induces cargo release, and this process can be reversed using mild reductants, such as vitamin C.[88] Another group also reported ultra-sensitive polymeric micelles with diselenide linkages, which exhibited a response to H_2O_2 at 100 μM. The delivery efficacy of these micelles was demonstrated to be 3.73-fold and 1.69-fold higher in terms of drug amount when compared with free drugs and their non-crosslinked counterparts in PC3 tumor-bearing mice, resulting in an efficient inhibition of tumor size.[89] However, the diselenide-bond-based mesoporous silica nanoparticles (MSNPs) did not exhibit a preference in releasing efficacy upon GSH treatment (5 mM). Considering the different responses of diselenide-bond-based MSNPs to H_2O_2 and GSH, exploring this aspect might offer a new option to overcome tumor redox heterogeneity. Additionally, the effects of thioether-/selenoether-based delivery systems have been demonstrated in 4T1 murine breast subcutaneous tumor models. The anti-tumor effect, circulation time, and tumor distribution of both CTX and pyropheophorbide have been prolonged, indicating the synergistic potency of the dual-functional delivery system.

Bond Cleavage

Linkage bond cleavage can also be utilized for the dissociation of NPs through H_2O_2-mediated bond cleavage. Once the linkers are broken, the structure of the NPs is disrupted, leading to the release of the cargo. Commonly, boronic acid and poly(thioketal) are designed as bond cleavage moieties, which can be cleaved by H_2O_2-mediated oxidation. Wang's group incorporated aryl boronic acid into a system for reversible anticancer protein restoration.[90] Specifically, they used RNase A as the model protein, where lysine residues are crucial for its activity. The lysine residues were capped with aryl boronic esters (NBC) via a carbamate ester linker, rendering RNase A inactive. Additionally, the NBC-capped lysine

residues facilitated the surface charge transition of RNase A from positive to negative, promoting co-assembly with cationic lipid NPs through electrostatic binding. Cationic lipids protected the NBC from degradation during circulation and facilitated internalization into cell membranes through electrostatic interactions. However, NPs with a positively charged surface still face the risk of elimination by the RES systems. The NBC-based delivery system requires further optimization to maintain the advantages while improving the drawbacks. Another H_2O_2-cleavable linkage is the thioketal bond. Farokhzad's group developed a novel ROS-triggered mitoxantrone (MTO) delivery system containing a poly-(thioketal)-based poly-prodrug.[91] This delivery system consists of three key modules: a PEG outer shell to prolong circulation time, surface-attached internalizing RGD (iRGD) for tumor targeting and internalization, and a polyprodrug inner core modified with thioketal groups responsible for drug release upon ROS stimulation. The thioketal linkage can be cleaved in response to H_2O_2, resulting in cargo release and cancer cell inhibition. Well-known ROS-producing agents, such as copper ions,[92] α-tocopheryl succinate (α-TOS),[93] and palmitoyl ascorbate,[94] have been integrated with therapeutic anticancer drugs within nanostructures. The ROS-producing mechanisms are discussed below. Copper ions can generate H_2O_2 through a Fenton-like reaction. α-TOS, a vitamin E analogue, can rapidly produce ROS intracellularly by interacting with mitochondrial respiratory complex II and interfering with the electron transport chain. The ascorbate group of palmitoyl ascorbate can be oxidized to ascorbate radicals, which form superoxide radicals through electron transfer. These superoxide radicals contribute to the production of tumoricidal H_2O_2. Zhang's group reported a ROS-sensitive delivery system using positive feedback MSNPs loaded with α-TOS and DOX.[95] In this case, β-cyclodextrin crystalline (β-CD) was conjugated on the surface of MSNPs via the thioketal linker. The MSNPs were also coated with adamantane-conjugated PEG (AD-PEG) to prolong circulation time. Upon internalization into cell membranes, endogenous ROS induced the opening of limited pores on the MSNPs, leading to the simultaneous release of α-TOS. The generated α-TOS-induced ROS further mediated the breakage of the thioketal linkers, resulting in an explosive release of DOX. Moreover, the newly generated ROS facilitated the production of more α-TOS, reinforcing the ROS-mediated thioketal linker cleavage. The delivery system efficiently released DOX at 100 μM H_2O_2 in vitro and exhibited remarkable antitumor effects in human breast cancer mouse models. The integration of nanostructures and ROS-generating moieties has significantly improved the properties of ROS-responsive delivery systems. The application of ROS-mediated delivery systems can be further expanded by exploring more suitable ROS-sensitive moieties, discovering novel cargos, and rationally substituting functional modules.

Enzymatic Activation

The tumor microenvironment exhibits elevated secretion of various enzymes, including proteases, peptidases, and lipases, each with specific chemical properties. Produced by tumor cells and stromal cells, these enzymes not only promote tumor growth, angiogenesis, invasion, and metastasis but also offer potential for controlled delivery of therapeutics or diagnostic agents. Leveraging the unique enzymatic environment within tumors, the enzyme-stimulated delivery system allows for the precise release of drugs or imaging agents in response to the tumor microenvironment. Notably, solid tumors overexpress enzymes such as proteases (eg, matrix metalloproteinase and cathepsin B),[96,97] peptidases (eg, aminopeptidase),[98,99] and lipases (eg, phospholipase A2),[100] with their respective cleavage sites listed in Table 3.[101–105]

Cathepsin B, a tumor-specific protease, has long been recognized as a key regulator of the tumor microenvironment and has been utilized as a trigger for various delivery systems. For example, when loaded the cathepsin B-sensitive moiety (GFLGK) onto the branches of polyHPMA copolymers. This dual functional delivery system involved covalent conjugation of the drug (DOX) to the copolymer via a pH-sensitive hydrazine bond.[95] Upon reaching the tumor site, cathepsin B cleaved the GFLGK moiety, leading to the release of the DOX-hydrazine-HPMA polymer into the tumor microenvironment. Subsequently, the acidic pH of the tumor microenvironment triggered the breakage of the hydrazine bond, inducing conformational changes in HPMA and causing the release of DOX. This HPMA-based dual functional (enzyme- and pH-sensitive) delivery platform was successfully applied in 4T1 tumor models, demonstrating highly effective tumor targeting and suppression efficacy. Matrix metalloproteinase-2 enzymes, another tumor-specific protease family, show promise as initiators of tumor-targeting delivery systems. Fan's group developed a gelatin nanoparticle armed with polyamidoamine (PAMAM) dendrimer-loaded methotrexate (MTX) to enhance tumor targeting and anti-tumor effects.[108] The gelatin nanoparticles were designed to be susceptible to the concentrated matrix metalloproteinase-

Table 3 Enzymatic Activation for Tumor Microenvironment Drug Delivery

Enzyme Types	Types	cleavable Peptide	Position	Function
Metalloproteinases	MMP-2/9	GPLGVRGK, PLGLAG	Extracellular matrix	[96,97]
Metalloproteinases	MMP7	VPLSLYSGCG	Extracellular matrix	[101]
Metalloproteinases	MMP-I	GPQGIWGQ	Extracellular matrix	[102]
Cysteine protease	Cathepsin B (CatB)	DRGETGPAC, AVPIAQFRRG	Intracellular(lysosome)	[103]
Cysteine protease	Cathepsin-K	GGGMGPSGPWGGK	Intracellular	[104]
Peptidase	Aminopeptidase	Unacylate amino acide	Extracellular matrix	[98]
Peptidase	peptidase D (PEPD)	Xaa-pro dipeptides	Extracellular matrix	[99]
Lipase	Cytosolic phospholipaseA2 (cPLA2)	Acyl ester bond of membrane phospholipids at the sn-2 position	Extracellular matrix	[100]
Membrane protease	Fibroblast activation protein (FAP)	DRGETGPAC	Extracellular matrix (cancer-associated fibroblasts, CAFs)	[105]
Hydrolytic enzymes	N-acetyl-beta-D-hexosaminidase, lysozyme/N-acetyl-β-D-glucosaminidase, lysosomal α-glucosidase	N/A	Cell cytoplasm	[106,107]

2 enzymes in the tumor microenvironment, leading to their breakdown and subsequent release of PAMAM dendrimers into the tumor. This sequential drug release to the tumor site improved the antitumor effect while minimizing cytotoxicity to normal tissues. The smart nanoscale drug delivery and imaging platform (NDDIP) delivery system has been successfully applied by Chau and Rastegari's group and Zhong's group in tumor-specific release during cancer therapies.[106,107] Enzyme-triggered nanocarriers not only facilitate drug delivery but also offer the potential for delivering imaging agents for fluorescence or radiography with high spatial resolution. Tumor-specific enzymes, as ignition triggers of the delivery system, have significant potential for broad development as completely biocompatible agents with minimal toxicity to normal tissues. When integrated with other tumor environment-specific strategies, tumor-specific enzymes become crucial in the fields of anticancer therapies and imaging.

Hypoxic Activation

The entire tumor tissue is often in a hypoxic state due to the abnormal vascular network inside solid tumors and the high oxygen consumption of malignant proliferating tumor cells. Tumor cells in the hypoxic region tend to proliferate slowly compared to their well-oxygenated counterparts, making them relatively resistant to traditional anti-cancer drugs. Additionally, hypoxia can promote the emergence of cell variants with lethal mutations or acquired resistance to traditional therapies.[109] Therefore, there is an urgent need to develop more efficient delivery systems or drugs that can target hypoxic solid tumors. The hypoxic property of solid tumors holds the potential for a tumor-specific trigger. Hypoxia-activated delivery systems targeting solid tumors have attracted interest from both the industry and academic scientists. Lin et al constructed a selective photorelease system using chitosan nanoparticles, in which the coumarin phototrigger incorporated nitroimidazole as an electron acceptor. Only under unique tumor-hypoxic physiological conditions, the phototrigger can be unlocked by bioreduction, thereby releasing the drug load under excitation by either single-photon visible light or two-photon near-infrared light. This approach distinguishes highly anticancer effects on hypoxic tumor cells rather than healthy normal cells (Figure 6).[110] Hypoxia-activated prodrugs (HAP) have been extensively studied in the field of hypoxia-targeted cancer therapy, with several HAP candidates now in clinical trials. One notable example is TH-302, which is in Phase 3 clinical trials under a Special Protocol Assessment with the United States Food and Drug Administration, developed by Threshold Pharmaceuticals.[111] In this system, nitroimidazole serves as the hypoxia-responsive electron acceptor, leading to nanoparticle disassembling via a hydrophobic to hydrophilic transition. The second functional moiety is the coumarin-cage, which is conjugated with drugs in glycol-chitosan nanoparticles. Coumarin dyes are usually quenched via photoinduced electron transfer (PET) to the nitroimidazole
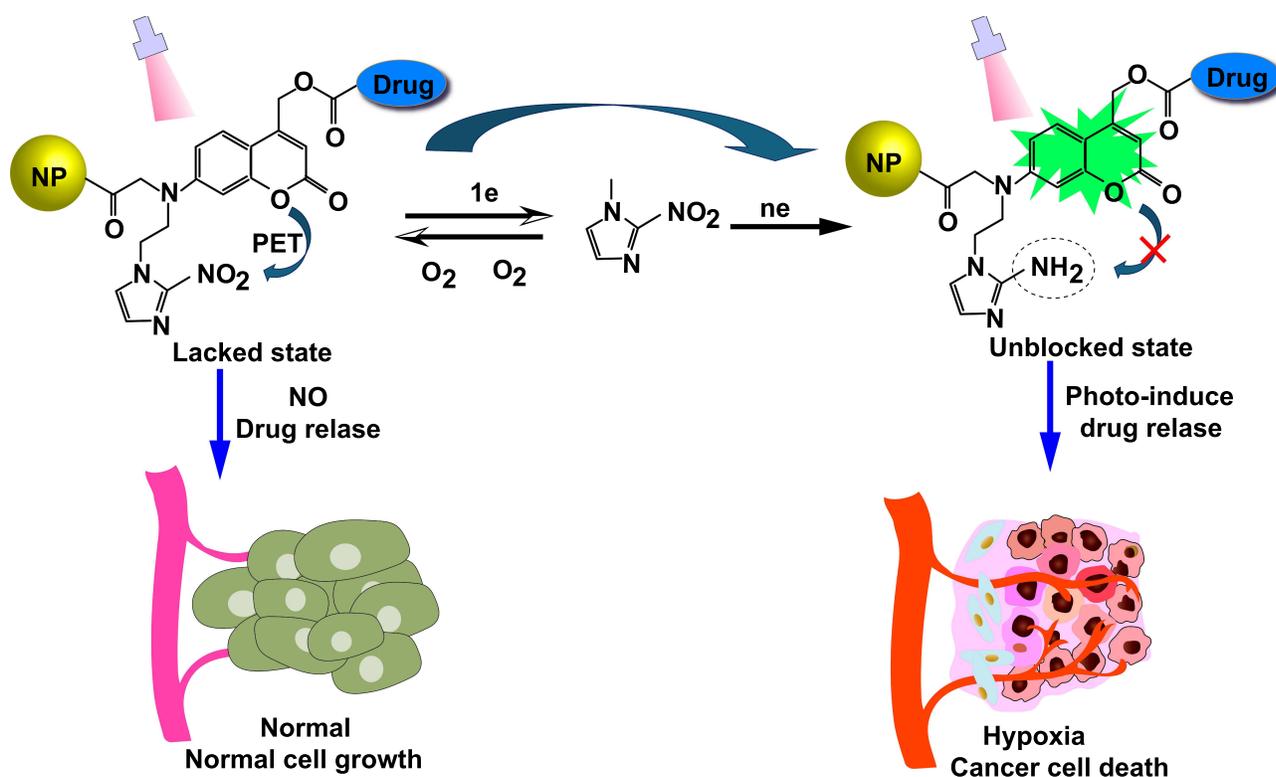
Figure 6 Schematic illustration of a phototrigger that specifically releases drugs under tumor-hypoxic physiological conditions.

electron acceptor in normal tissues. However, the reduction of the nitroimidazole to an amine eliminates the PET quenching and initiates the cleavage of the drug-coumarin linkage under hypoxic environments. In addition to excitation with short-wavelength lights (UV to blue excitation light sources), two-photon excitation at 800 nm has been shown to effectively break the drug-coumarin linker. Although excitation efficacy is sacrificed, penetration depth within tissues is greatly improved by excitation at 800 nm. Considering that hypoxia is usually deeper inside solid tumors, long-wavelength excitation could ensure tissue penetration and the efficacy of drug release within the tumor. The second well-studied strategy for hypoxia-mediated delivery systems is based on the azobenzene group, which is fragile under hypoxic conditions and becomes positively charged. Torchilin's group has utilized the azobenzene group to construct hypoxia-sensitive siRNA nanoparticles. In this system, the azobenzene group serves as the linker between PEG and polyethy-leneimine (PEI) polymer segments.[112] When the nanocarriers enter the oxygen-deprived environment inside the solid tumor, the azobenzene bond is cleaved, and the PEG surface is removed. After hypoxia-mediated azobenzene cleavage, the remaining PEI/siRNA complex becomes positively charged, facilitating easy intracellular uptake. The efficacy of tumor targeting and release of PEI/siRNA nanocarriers has been demonstrated both in vitro and in vivo. The hetero-geneity and complexity of solid tumors have made it challenging to deliver anticancer drugs or imaging agents into hypoxic regions. Nanoparticle systems have been considered powerful tools for the delivery of both small molecules and biomacromolecules. However, the insufficient diffusion inside solid tumors has limited their applications in cancer therapy and diagnosis. Therefore, hypoxia-responsive nanocarriers hold the potential to deliver anticancer drugs or imaging agents with high diffusion rates and tumor targeting efficacy.

ATP- Responsive Drug Delivery Systems

As mentioned above, pH and redox species are utilized for stimulating drug release based on chemical reactions breaking the bonding linkage between the carrier and drug. In addition to these chemistry-related process, energy-related process might also be made the best of due to the drastic differences of ATP concentrations between TME and the microenvir-onment in normal tissues.

ATP plays a pivotal role in cellular signaling and metabolism. Intracellularly, ATP concentrations vary significantly, ranging from 1 to 10 mM, while extracellularly, they remain below 0.4 mM. Interestingly, in some tumor tissues, the ATP concentration is substantially higher compared to normal tissues, displaying a 1.2-fold increase in cancer cells.[113] Recent reports have illuminated four commonly used delivery systems that rely on ATP-sensitive moieties: Zinc-dipicolylamine (TDPA-Zn^{2+}),[114] phenylboronic acid-sugar-functional polymers,[115] ATP-consuming enzymes,[116] and ATP aptamers.[117] In the following sections, we will explore the application of these modules in ATP-sensitive delivery systems.

Zinc-Dipicolylamine (TDPA-Zn^{2+}) Based

Zinc-dipicolylamine (TDPA-Zn^{2+}) possesses a unique ability to coordinate with oligo-aspartate containing polypeptides, however, this coordination can be disrupted by intracellular ATP. TDPA-Zn^{2+} exhibits a higher binding affinity for ATP compared to the oligo-aspartate containing polypeptides. Taking advantage of this property, TDPA-Zn^{2+} was employed to coordinate peptides into upconversion nanoparticles with a mesoporous-silica shell (UCNP@MSN), and these functional nanoparticles were utilized for ATP-stimulated drug delivery.[114] In this case, the UCNP@MSNs could be excited at 980 nm, resulting in a distinct emission in the UV-NIR region. The emission of UCNPs in the UV-visible region was quenched due to the multivalent coordination of the UCNP shell, peptide, and TDPA-Zn^{2+}, but exhibited strong NIR emission. DOX served as both the encapsulated cargo and the acceptor for luminescence resonance energy transfer (LRET) from the UCNPs (donor) in the UV-visible range. The TDPA-Zn^{2+}-peptide-UCNP complex with DOX trapped inside was applied in tumor models, demonstrating efficient drug release and a difference in luminescence and UV-Vis emission. Besides the therapeutic effect of the released DOX, the changes in LRET and UV-Vis emission could also be utilized to dynamically monitor drug release.

Phenylboronic Acid-Sugar-Functional Polymers

The unique chemical properties of phenylboronic acid (PBA) make it an exceptionally attractive moiety for on-demand (pH or/and ATP-sensitive) delivery systems. Its ability to undergo reversible ester formation with diols provides excellent circulation stability and controlled release characteristics. Moreover, PBA-ATP conjugation demonstrates favorable thermodynamic stability, readily forming a bond with ATP modified with a cis-diol moiety in its ribose ring and PBA with diols. Additionally, PBA acts as a potential ligand for sialyl epitopes overexpressed on the surface of cancer cells. Furthermore, PBA exhibits sensitivity to pH below its pKa, enabling a seamless transition to a hydrophilic state. Naito's group has published a study on a PBA-functionalized polyion complex micelle that effectively encapsulates the therapeutic agent "siRNA" as cargo.[115] In this system, the micelle scaffold was constructed using cationic poly (ethylene glycol)-block-poly(L-lysine) (PEG-b-pLys) with terminal lysine residues, to which 3-fluoro-4-carboxyphenyl boronic acid (FPBA) was conjugated via carbodiimide chemistry. The functionalized cationic polymers were then packaged with siRNA and assembled into micelles. These siRNA-encapsulated micelles remained stable at extracellular ATP levels but disassembled at the intracellular concentration of ATP, facilitating the release of siRNA into the cytosol. Similarly, a comparable strategy was employed to successfully deliver an anti-angiogenic gene (pDNA) into MCF-7-xenografted mice using PBA-galactose grafted poly(ethylenimine) (PEI) copolymers.[118] Furthermore, a cationic PEI-PBA-alginate structure (CrossPPA)/siRNA NPs strategy proved effective in delivering and releasing siRNA into 4T1 tumor-bearing mice.[119] The feasibility and efficacy of PBA-based delivery and release have been demonstrated in multiple delivery systems and cargos.

ATP Consuming Enzymes Based

ATP-consuming enzymes can also serve as triggers for ATP-sensitive delivery systems, based on the binding or hydrolysis of ATP to responsive proteins. One such enzyme is the chaperone GroEL, which can capture denatured proteins and hydrolyze ATP to ADP. Aida's group utilized GroEL to construct an ATP-responsive delivery system. In this system, GroEL contains cysteine residues that coordinate with merocyanine (MC)-Mg^{2+}-MC, resulting in the formation of nanotubes (NB).[116] Cargos were then encapsulated within the NBs. The conformation of ATP-bound GroEL differed from apo-GroEL, leading to the disruption of MC-Mg^{2+}-MC interaction. Consequently, the NBs would dissociate, releasing the cargos. Furthermore, this system could be further modified with boronic acid to improve cell membrane

permeability. The delivery study of the system in the HeLa xenograft model indicated that the GroEL-based delivery system exhibited preferential accumulation at the tumor site and intracellular ATP-induced cargo release. In addition to utilizing natural ATP protein carriers, another approach involves a polymer that responds to ATP, composed of poly (ethylene oxide)-b-polymethacrylate (PEO45-b-PHM126) and β-CD, serving as the backbone and macrocyclic pendant, respectively.[120] Short bi-guanidine spacers crosslinked the copolymer to form a pocket-like polymer receptor, acting as the ATP habitat. The ATP/polymer complexes formed, resulting in a decrease in ATP in the hydrophilic site. Additionally, the ATP/polymer hybrid transitions between an aggregate and disassembled state in response to phosphatase. The integration of the ATP-binding polymer and phosphatase into the multifunctional polymer offers novel options for ATP-sensitive delivery systems.

ATP Aptamers-Based

ATP aptamers are single-stranded DNA (ssDNA) molecules with a high affinity for ATP, typically identified through in vitro screening from a large pool of random ssDNA sequences. These aptamers are characterized by rich "GC" pairs and negatively charged surfaces, enabling the encapsulation of multiple anticancer agents and cationic polymers. Due to their short sequences (around 30 bases), they can be easily modified to specifically respond to ATP, making ATP aptamers the most popular module for ATP-sensitive delivery systems. Moreover, ATP aptamers have the ability to form DNA duplexes through complementary base pairing, offering potential as habitat nanocarriers. These unique physical and chemical features have established ATP aptamers as popular modules for ATP-sensitive delivery systems for a considerable time.[117] An ATP aptamer-based dual delivery system was developed to simultaneously deliver DOX and siRNA. In this system, GC-rich DNA duplexes provided a cavity for DOX, while cationic PEI condensed the negatively charged DOX duplexes and miRNA. Ultimately, the ternary nanocomplex of PEI/DOX-Duplex/siRNA formed, displaying synergistic effects in cancer treatment.[121] Additionally, ATP aptamers serve as ATP-sensitive gate-keepers for drug release in porous materials.[122] For example, Chen's group constructed a MOF nanoparticle with Zr^{4+} and triphenyl dicarboxylic acid (TPDC) terminated with an amino group. ATP aptamers were conjugated to the MOF nanoparticle through DBCO modification and the azide group from the terminal amino group.[123] Another ingenious design by Gu et al involved a nanogel with a DNA duplex core coated with HA, responding to ATP stimuli. The DNA duplex, rich in "GC" pairs and negatively charged, formed a cationic core complex with the positively charged protamine (a cell-penetrating peptide) via electrostatic interaction.[124] The core complex acted as the cavity for DOX and mediated DOX release in response to the formation of aptamer/ATP complexes. Anionic HA formed the outer shell and facilitated complex intracellular delivery. The binding of HA to tumor-specific overexpressed receptors (eg, CD44 and RHAMM) enhanced tumor targeting. The system's high selectivity for intra- and extracellular environments resulted in enhanced anti-tumor effects, demonstrated in both in vitro and in vivo experiments. The same group also developed an advanced co-delivery system by introducing exogenous ATP to accelerate drug release. Similar to the previous design, the system consisted of a negatively charged duplex loaded with DOX and coated with the positively charged protamine peptide. A second liposome, featuring fusogenic dioleoyl phosphatidylethanolamine (DOPE), was integrated into the delivery system, acting as the releasing accelerator. Once the dual-liposome system was recognized by tumor cell membrane receptors and internalized, the acidity of endocytic vesicles triggered a releasing cascade, accelerating DOX release in the cytosol. This dual-functional system combined targeting, ATP responsivity, therapeutic agents, and exogenous ATP generation.[125] Its dual functionality and excellent anti-cancer efficacy were demonstrated in cancer xenograft nude mice, outperforming the control and the original design. Another ATP-sensitive delivery system was composed of a $CaCO_3$ or SiO_2-based core and an aptamer-modified polymer shell.[126] The $CaCO_3$ or SiO_2-based core could form microcapsules after dissolving with EDTA. Meanwhile, aptamer-modified polymers crosslinked different polymer layers to the shell, releasing the drug upon ATP stimulation. Considering the diversity of sequence-specific carriers, ease of modification, and the urgent need for selectively delivered payloads, further investigation of more ATP aptamer-based delivery systems and the expansion of their application fields are crucial.

Conclusion and Perspectives

Nanocarriers within a specific size range of 20 to 200 nm demonstrate active transcytosis or passive targeting to tumor sites through the enhanced permeability and retention effect (EPR).[127] This characteristic leads to improved therapeutic efficacy and reduced toxic side effects. Tumors possess distinct microenvironmental characteristics, including high levels of L-Glutathione (GSH), low pH values, and hypoxia. Stimulus-responsive nano-drug delivery systems, which are specifically engineered to respond to the TME, exhibit enhanced accumulation at the tumor site via the EPR effect. As a result, the drugs exhibit selective release in response to the tumor microenvironment, leading to enhanced utilization of chemotherapeutic agents by tumor cells. This mechanism ultimately improves the effectiveness of therapy while simultaneously reducing the occurrence of adverse effects. This comprehensive review provides an overview of nanocarriers developed for TME responses, specifically acidity and hypoxia, and highlights their biomedical applications. Despite the promising potential of TME-responsive nanoplatforms, their practical application still faces challenges, particularly concerning the safety of nanomaterials, which limits their clinical use. To address these concerns, advanced strategies involving biomimetic nanoparticles, such as exosomes, cell membrane-encapsulated nanoparticles (CNPs), and virus-like particles (VLPs), have emerged, showing promise in enhancing the safety of carriers. Notably, exosomes play a pivotal role as signaling mediators in regulating the TME, and several studies have explored their engineering for targeted drug delivery in cancer therapeutics.[128–131] Most of the current TME-responsive nanocarriers only target individual elements of the tumor microenvironment and lack the ability to target the entire tumor microenvironment at the same time, thus there is a need to develop multilevel responsive nanodelivery systems in the future. With the deeper understanding of TME, synergistic multifunctional tumor stimulation-responsive drug delivery systems targeting the microenvironmental response in effective combination with other therapeutic modalities, such as chemotherapy, photo-thermal therapy, and immunotherapy, have also attracted much attention. These innovative multimodal combination therapy nanoplatforms can effectively realize targeted drug delivery and smart release function, which is an important direction for the development of responsive nanodrug delivery systems in the future.

Despite the significant progress in stimuli-responsive nano drug delivery system particles for tumor therapy, serious challenges still exist. From animal experiments to clinical applications, a series of problems still need to be solved, especially the animal model does not simulate human characteristics, but of course we can use tumor-like organ models to make up for the shortcomings of the traditional tumor models, which can better reproduce the in vivo characteristics of primary tumors and become a reliable model for simulating human tumors. Secondly, individual differences of patients, different stages of disease development and heterogeneity of tumor cells may produce different drug delivery efficiencies. Since the expression and distribution of specific stimulus sources in TME are highly heterogeneous and dynamically variable, which may lead to the occurrence of unexpected stimulus response processes. In addition, the biosafety of nanodelivery systems greatly affects their clinical translation. When designing TME-responsive nano-delivery systems, biocompatibility, scaled-up production during clinical translation, quality controllability, and production cost should be prioritized. The activation of anti-tumor immune response of the body is systemic, and when multiple combined delivery is performed, not only the generation of therapeutic efficacy should be focused on, but also the possible toxic side effects, such as cytokine storm, should also be considered. In conclusion, although facing the above problems, it is believed that with the development of tumor immunology, pathophysiology, materials science and other interdisciplinary disciplines, the combination of TME-responsive nano-delivery systems will bring a major breakthrough in the clinical treatment of tumors in the near future.

Abbreviations

TME, the tumor microenvironment; DOX, doxorubicin; EPR, enhanced permeability and retention effect; ODNs, oligodeoxynucleotides; ZnO, zinc oxide; $CaCO_3$, calcium carbonate; Ce6, chlorin e6; CHEMS, cholesteryl hemisuccinate; NPs, nanoparticles; OVA, ovalbumin; MOFs, metal-organic frameworks; CPT, camptothecin; OA, oleic acid; MTO, mitoxantrone; HAP, Hypoxia-activated prodrugs; LRET, luminescence resonance energy transfer; PBA, phenylboronic acid.

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