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EDITORIAL

Tumor microenvironment-responsive polymeric nanoparticles for enhanced immunotherapy

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Cancer remains a major global health threat with the World Health Organization reporting 20 million new cases and 9.7 million deaths worldwide in 2022 that is projected to surge by 77% to 35% million annual cases by 2050[1]. In recent years immunotherapy has rapidly advanced, offering new hope against cancer by harnessing the immune system to target and eliminate tumor cells with greater specificity and lower toxicity than traditional treatments[2,3]. Although cancer immunotherapy has shown promising results in early clinical studies, only a small subset of patients exhibit a response. This finding is primarily due to the presence of "cold" tumors, which are characterized by a lack of immune cell infiltration and show limited responsiveness to immune checkpoint blockade [ICB] (**Figure 1A**)[4]. In addition, some patients may have severe immune-related adverse events caused by the off-target toxicity of immunotherapeutic agents[4]. For example, traditional cancer immunotherapies, such as cytokines and checkpoint inhibitors, frequently encounter challenges, including significant systemic toxicity, poor tumor targeting, and immunosuppressive microenvironments, resulting in limited efficacy and pronounced side effects. Therefore, new strategies are needed to enhance antitumor immune responses and minimize off-target toxicity. With advances in nanotechnology, nanodrug delivery systems may help overcome the limitations associated with "cold" tumor therapy. Nanodrug delivery systems can enhance drug pharmacokinetics by optimizing key parameters, such as size, morphology, and surface characteristics, while ligand modifications enable targeted delivery to cancer/immune cells and improve intracellular drug transport (**Figure 1B, C**)[5]. In addition, nanodrug delivery systems can accumulate at tumors *via* the enhanced permeation and retention (EPR) effect, work with multiple drugs, or respond to external stimuli to enhance tumor immunogenicity (**Figure 1D**)[5]. Nanotechnology-enabled strategies can significantly enhance therapeutic efficacy and reduce systemic toxic side effects by precisely delivering immunotherapeutic agents to target sites and synergistically modulating the immune microenvironment. However, conventional nanodrug delivery systems often fall short due to multiple *in vivo* barriers, such as immune clearance, drug leakage, a complex tumor microenvironment (TME), and cellular or lysosomal obstacles, all of which significantly limit delivery efficiency at tumor sites.

The TME: barrier and opportunity for targeted drug delivery

The TME is regarded as a critical obstacle in antitumor drug delivery (**Figure 2A**)[6]. The TME constitutes a complex ecosystem surrounding tumor cells that is comprised of diverse cell types (immune cells, fibroblasts, endothelial cells, vascular smooth muscle cells, and stromal cells), an extracellular matrix (ECM), and various molecular components. Tumor cells secrete cytokines and growth factors (such as transforming growth factor-β (TGF-β), interleukin-6 (IL-6) and vascular endothelial growth factor (VEGF)) in the TME to communicate with surrounding cells, which fosters tumor progression and metastasis. Immune cells, such as T cells, B cells, natural killer (NK) cells, and dendritic cells (DCs), have important roles in the TME but are often unable to effectively exert antitumor effects due to the immunosuppressive conditions within the TME[6]. The TME contains immunosuppressive cells, such as tumor-associated macrophages (TAMs), regulatory T cells (Tregs), and myeloid-derived suppressor cells (MDSCs), all of which contribute to the formation of an immunosuppressive microenvironment and the immune escape of tumors[7]. Fibroblasts and cancer-associated fibroblasts (CAFs) promote tumor invasion and metastasis by secreting ECM components (such as collagen and glycoproteins)[7]. In addition, due to the rapid growth of tumors compared to normal tissues, the TME exhibits abnormal physiologic features, including acidity (pH = 6.5), overexpression of specific enzymes, elevated levels of reactive oxygen species (ROS) and glutathione (GSH), hypoxia, and increased concentrations of adenosine

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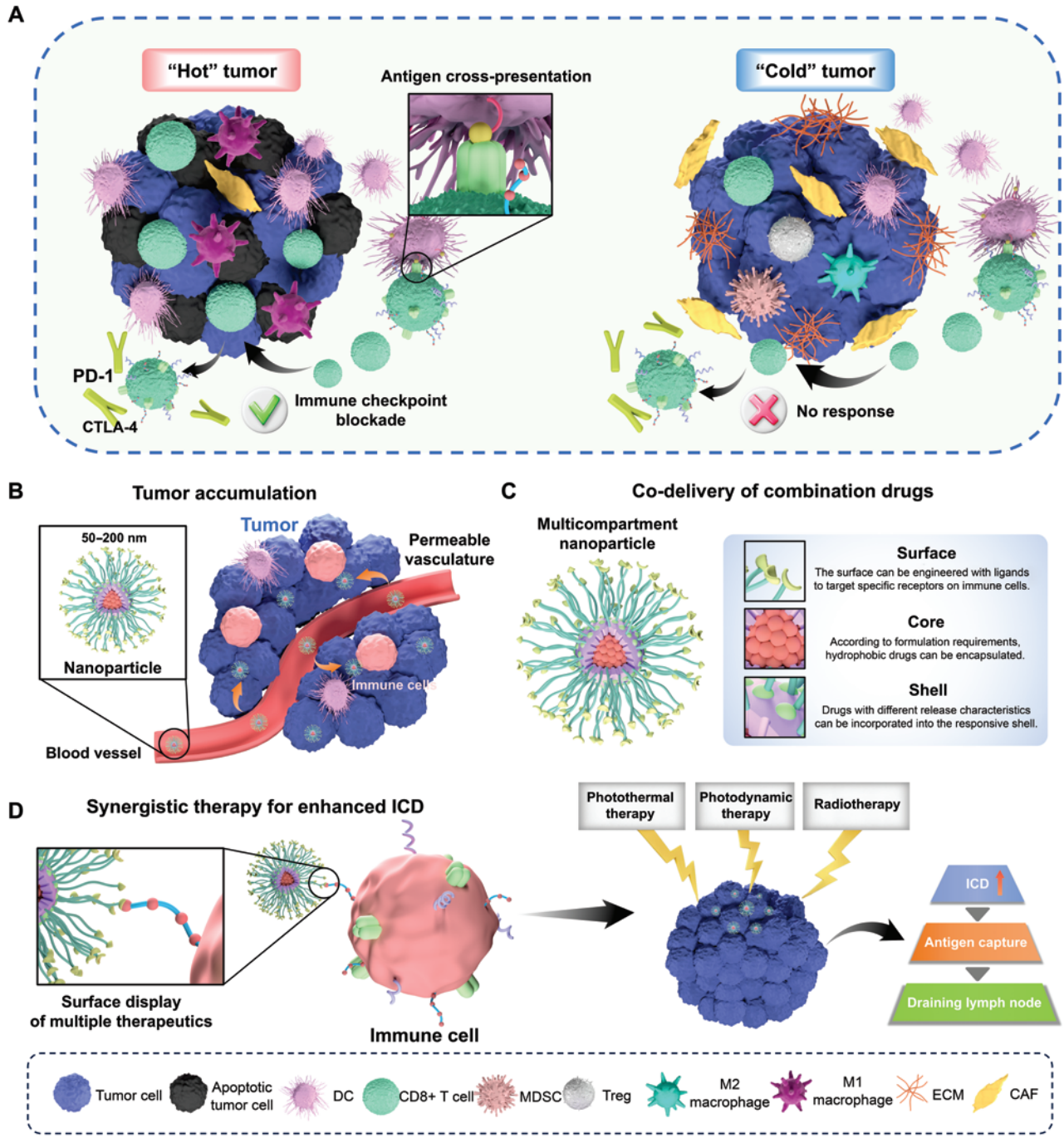


Figure 1 (A) Schematic diagram of the characteristics of "hot" tumors and "cold" tumors. (B) Size-optimized nanoparticles accumulate within tumors *via* the EPR effect. (C) Nanoparticles can combine multiple therapeutic drugs with distinctly different properties for co-delivery to tumor sites. (D) Nanoparticles may be engineered to interact synergistically with multiple drugs and external energy sources, thereby enhancing immunogenic cell death (ICD).

triphosphate (ATP)[8]. These features can serve as endogenous stimuli to activate smart responsive drug delivery systems, triggering targeting molecule activation, inducing shape and size changes in nanocarriers, and enabling controlled drug release, thus enhancing tumor-targeted delivery. Therefore, although the TME promotes tumor cell proliferation, invasive metastasis, and efficient drug resistance, the TME also provides new strategies for the precision treatment of malignant tumors.

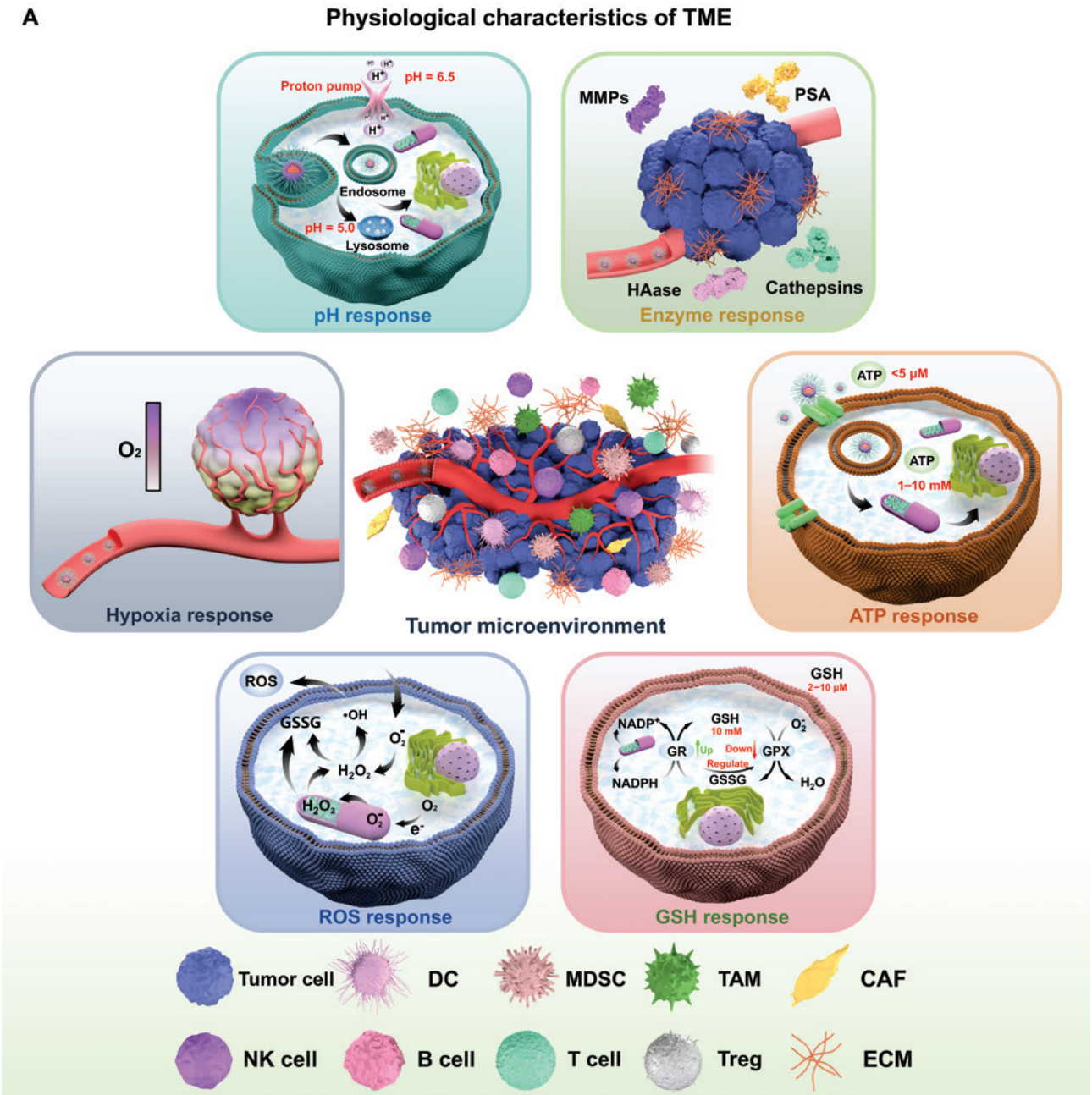


Figure 2 Continued

Stimuli-responsive polymeric nanoparticles

Stimuli-responsive nanodrug delivery systems can be designed based on pathophysiologic signals in the TME to enhance the spatial precision of drug delivery[8,9]. Specifically, functional polymer-based delivery systems hold great promise in addressing key issues in cancer immunotherapy due to excellent biocompatibility, stable physicochemical properties, and flexibility modifiability in structure and morphology. Functionalized polymers can respond to biological stimuli, such as variations in pH, enzymes, ROS, GSH, hypoxia, and ATP, by changing the hydrophobicity/hydrophilicity, degradability, and ionization. Stimuli-responsive polymer nanoparticles that specifically modulate the TME have been extensively used to develop smart nanocarriers for the targeted delivery of therapeutic and diagnostic agents, thereby enhancing the

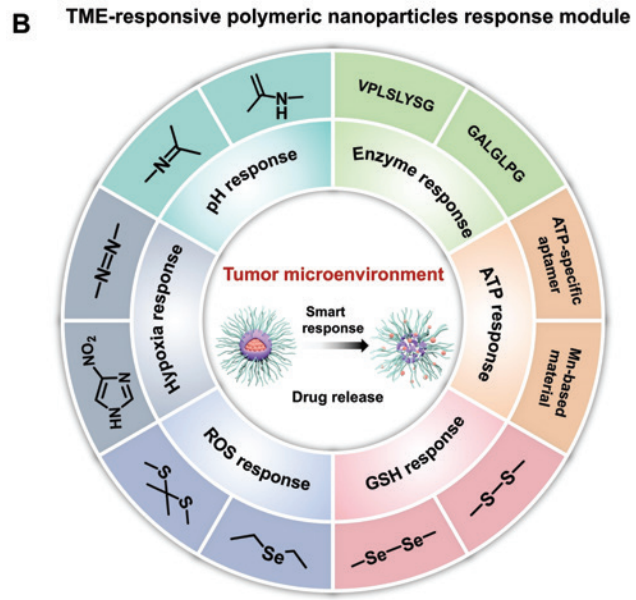


Figure 2 (A) Schematic diagram of TME characteristics, including low pH, enzyme overexpression, redox imbalance, ATP overexpression, hypoxia, and immunosuppressive microenvironment. (B) Schematic diagram of the TME-responsive polymeric nanoparticles response module.

efficacy of immunotherapy[9]. In view of traditional drug shortcomings, including poor water solubility, high toxicity and side effects, short half-life, and low absorption rates, stimuli-responsive polymer nanoparticles can effectively load hydrophobic drugs into polymer networks during the self-assembly process through physical encapsulation, chemical bonding, or poly-ionic compounding, thus achieving stable drug encapsulation, controllable release, enhanced therapeutic efficacy, and targeting performance. In addition, more precise targeted and controlled drug release can be achieved by modifying the nanoparticles through attachment of functional groups or ligands with biological recognition capabilities[8]. In recent years, the use of TME-responsive polymeric nanoparticles as controlled drug release systems have become an important research direction to break the bottleneck of cancer immunotherapy. Examples of polymeric nanoparticles responsive to different types of TME have been summarised in **Table 1**.

Different types of TME-responsive polymeric nanoparticles

Tumor cells undergo aerobic glycolysis (the Warburg effect), converting glucose to lactate and resulting in extracellular lactate accumulation and acidification of the TME. Consequently, the TME is mildly acidic pH (~6.5) in contrast to the neutral pH (~7.4) of normal tissues[6]. The mild acidity of the TME is often exploited in the design of acid-responsive drug delivery systems, typically incorporating acid-labile linkages, such as hydrazone, imine, acetal/ketal, amide, and ester bonds, as shown in **Figure 2B**. Some groups can be deprotonated at physiologic pH but protonated in an acidic TME. Polymeric nanodelivery systems based on this mechanism enable nanoparticle disassembly, controlled drug release, enhanced cellular uptake, and improved tumor penetration. pH-sensitive carriers can also be designed to rapidly degrade and release the carried antigens under the acidic conditions of the TME or DC endosomes/lysosomes, thereby greatly improving the efficiency of antigen cross-presentation by DCs to T cells and ultimately activating a strong T cell immune response. For example, nanochaperones based on mixed-shell polymer micelles can load protein drugs (antigens, antibodies, cytokines, and chemokines) using hydrophobic microdomains consisting of a poly(β-ammonia) ester, which can enhance cancer immunotherapy by prolonging the circulation time of the drugs and responsively releasing the drugs after protonation at tumor sites[10,11]. The TME exhibits excessive secretion of enzymes, including proteases [e.g., matrix metalloproteinases (MMPs) and histone C], peptidases (e.g., aminopeptidases), lipases (e.g., phospholipases), and esterases, compared to normal tissues[6]. Aberrant enzyme expression in the TME can trigger enzyme-responsive polymeric nanoparticles to undergo disintegration, size, or shape transformation and charge reversal, enabling targeted drug release and promoting deep tumor penetration and uniform distribution. MMP-responsive linkers are typically composed of peptide sequences that are cleaved by the enzyme at specific recognition sites, enabling targeted drug release (**Figure 2B**). MMP-cleavable peptides (VPLSLYSG-modified dendrimer polymeric nanoparticles) have been

Table 1 Summary of TME-responsive polymeric nanoparticles enhancing cancer immunotherapy

Response type	Polymer formulation	Loaded medication	Therapeutic model	Therapeutic outcomes	Ref.
pH response	PBA modified poly(ethylene glycol)-*b*-poly(ε-caprolactone) (PBA-PEG-*b*-PCL); poly(ε-caprolactone)-*b*-poly(β-amino ester) (PCL-*b*-P(D)AE)	Interleukin (IL)-12	Mouse melanoma: large advanced tumors, primary and distant model, lung metastasis model	This system demonstrated significant inhibitory effects on melanoma, produced a distant effect, and suppressed postoperative tumor recurrence and metastasis.	[10]
	COOH-PEG-*b*-PCL; PCL-*b*-PAE	Chemokine (CXCL)-9; BRD4-PROTAC (dBET6)	Mouse breast cancer model	CXCL9 and dBET6 synergistically enhanced T-cell-dependent antitumor immunity by promoting CD8+ T-cell infiltration and inducing programmed cell death.	[11]
Enzyme response	Dual-sensitive nanoparticle (Dual-NP) system composed of VPLSLYSG-modified dendrimer and dextran nanoparticles	DOX	Mouse glioblastoma model	Within the glioblastoma model, the dual-NPs exhibited exceptional deep tumor penetration and a retention period extending to 6 days.	[12]
	Photosensitizer was conjugated with methoxy poly(ethylene glycol) *via* GALGLPG (mPEG-GALGLPG-PPa)	Indoleamine 2,3-dioxygenase 1 (IDO-1) inhibitor	CT26 colorectal and 4T1 breast mouse models	Compared with photodynamic therapy alone, this combined immunotherapy regimen demonstrated significantly enhanced antitumor efficacy.	[13]
ROS response	PPCD, CpG/PAMAM-TK-Ad, mPEG-TK-Ad	Pt (IV), CpG	Mouse colorectal model	This system promoted antigen-presenting cell activation, antigen presentation, and robust antitumor immune responses.	[14]
GSH response	Phosphorus dendrimer-copper(II) complexes ($1G_3$-Cu), PCL-SS-PEG	Toyocamycin (Toy)	Mouse melanoma model	This nanoparticle eradicated tumors and suppressed recurrence and metastasis by synergistically inducing ICD through dual mitochondrial/endoplasmic reticulum pathway.	[15]
Hypoxia response	PNBJQ	Immunomodulating agent JQ1	Mouse colorectal model	PNBJQ responded to tumor hypoxia to overcome innate and adaptive immune resistance by triggering ICD and downregulating PD-L1 under near-infrared light irradiation.	[16]
ATP response	ALG-Aapt/CpG	Oxaliplatin, CpG	CT26 colorectal model	Smart hydrogels released immune adjuvants concurrently with low-dose repeated chemo/radiotherapies to enhance antitumor immune responses.	[17]
	E. coli@PDMC-PEG	Mn^{2+}	Mouse subcutaneous melanoma, rabbit *in situ* liver cancer	This system was degraded in an ATP-excessive TME, synergistically activating the cGAS-STING pathway by releasing Mn^{2+} and exposing bacteria, thereby effectively inhibiting tumor growth.	[18]

Table 1 Continued

Response type	Polymer formulation	Loaded medication	Therapeutic model	Therapeutic outcomes	Ref.
Multiple responses	mPEG-*b*-P(MTE-*co*-PDA)	Niclosamide	Murine triple-negative breast cancer and syngeneic oral cancer models	ROS/pH dual-responsive MPNPs combined with oncolytic viruses enhanced tumor penetration, induced pyroptosis, and stimulated antitumor immunity.	19
	COOH-PEG-PAEMA	Fe_2O_3, DOX	4T1 breast mouse model	This triple-responsive nanoplatform accumulated in tumor tissue, enhanced ICD, and promoted T-cell proliferation.	20

designed to enhance drug penetration in tumors[12]. In addition, prodrug vesicles obtained by coupling photosensitizers with methoxy polyethylene glycol (PEG) *via* the MMP-2-cleavable peptide, GALGLPG, can mediate photodynamic immunotherapy and enhance T-cell infiltration within tumors[13].

The abnormal metabolic behavior of tumor cells results in a redox microenvironment that differs from normal cells, which is mainly characterized by elevated levels of ROS and GSH. ROS are important substances affecting tumorigenesis and progression, such as hydrogen peroxide (H_2O_2), monoclinic oxygen ($^1O_2$), hydroxyl radicals (OH), and superoxide (O^{2-}), which are found in much higher concentrations in the TME than in normal tissues[8]. For example, while H_2O_2 levels remain at approximately 20 nM in normal tissues, the elevated metabolic activity in tumors causes H_2O_2 accumulation to 50–100 nM[9]. ROS-responsive polymeric nanoparticles can achieve tumor site-specific drug release by introducing ROS-sensitive chemical bonds, such as thiols, thioethers (R-S-R), selenium (Se), tellurium (Te), amino acrylates, and boronic esters, while also utilizing the antioxidant function of the carrier material to regulate TME to enhance the therapeutic effects (**Figure 2B**)[9]. The polymeric nanoparticle constructed through host-guest interactions between poly-[(N-2-hydroxyethyl)-asparagine]-Pt(IV)/β-cyclodextrin (PPCD), an immunoadjuvant [CpG/polyamidoamine-thioketal-adamantane (CpG/PAMAM-TK-Ad)], and methoxy poly(ethylene glycol)-thioketal-adamantane (mPEG-TK-Ad) have shown tumor accumulation post-intravenous injection and ROS-triggered release of antigens and CpG, eliciting a potent antitumor immune response[14]. GSH is one of the most important reductants in tumor cells, can scavenge excess ROS, and has an important role in maintaining the balance of intracellular redox state[9]. However, excess GSH in the vicinity of tumor cells disrupts the redox balance. The GSH concentration in tumor cells can be as high as 2–10 mM, which is 7–10 times higher than normal tissues. Common functional chemical bonds in GSH-responsive polymeric nanocarriers include disulfide bonds, diselenide bonds, ditelluride bonds, and thioether bonds (**Figure 2B**). The GSH-responsive platform can eliminate excess GSH in the TME, reversing immunosuppression, reducing T-cell exhaustion, and promoting cytokine release, which significantly enhances T-cell infiltration and cytotoxic activity. Disulfide containing amphiphilic block copolymer poly(ε-caprolactone)-SS-polyethylene glycol (PCL-SS-PEG) has been shown to enable GSH-responsive drug release at tumor sites, promote DC maturation, and increase tumor-infiltrating cytotoxic T lymphocytes[15].

The rapid growth of tumor cells, highly expanded tumor volume, and defective vascular systems in solid tumors lead to widespread hypoxia in the TME, thereby promoting drug resistance and tumor metastasis[6,7]. Therefore, modulating the hypoxic environment at the tumor site is an important aspect of tumor treatment. Notably, nitroimidazoles, azo derivatives, and nitrobenzyl alcohol derivatives have been used as hypoxia-sensitive linkers to prepare responsive polymers and construct nanodrug delivery systems to improve the efficiency of cancer immunotherapy (**Figure 2B**). For example, self-assembled drug delivery systems linking type I photosensitizers to PEG *via* azo bonds (PNBJQ) can co-deliver immunomodulators that induce immunogenic cell death (ICD) and overcome immune resistance to activate antitumor immunity[16]. ATP, as a key metabolite, has a crucial role in various physiologic and pathologic processes within the body. Hypoxia, acidosis, and metabolic reprogramming can trigger massive ATP release from tumor cells[8]. The differences in ATP concentrations between normal and tumor cells, as well as between extracellular and intracellular environments (1–10 mM intracellularly; 0.4 mM extracellularly), and among different organelles have prompted the development of ATP-triggered polymeric nanoparticles. A smart hydrogel combining sodium alginate (ALG), ATP-specific aptamer (Aapt), and CpG oligonucleotides (ODNs) enables the controlled release of CpG ODNs during chemotherapy or radiotherapy, thereby enhancing anti-tumor immune responses[17]. Furthermore, an ATP-responsive Mn-based bacterial material (*E. coli*@PDMC-PEG) was shown to synergistically activate the cGAS-STING pathway, effectively suppressing melanoma and hepatocellular carcinoma in animal models[18].

Due to the complexity of TME, polymeric nanodelivery systems based on a single stimulus may face challenges, such as insufficient responsiveness or off-targeting of drugs. For example, the levels of different enzyme expression are limited by tumor heterogeneity and the concentrations of ROS and GSH vary across different tumor models. Thus, designing multi-stimuli-responsive polymeric nanoparticles that synergistically exploit the characteristics of the TME can enable precise tumor-targeted drug delivery with enhanced selectivity, controlled release kinetics, and reduced systemic toxicity, ultimately improving the outcomes of cancer immunotherapy. An ROS/pH dual-responsive nanocarrier (MPNPs), polyethylene glycol-*b*-poly(2-(methylthio)ethyl methacrylate-*co*-2-(diisopropylamino) ethyl methacrylate) (mPEG-*b*-P(MTE-*co*-PDA)), was designed to deliver the transcription 3 inhibitor, niclosamide, and synergized with oncolytic viruses (OVs), enhancing tumor penetration and inducing gasdermin E-mediated pyroptosis, thereby remodeling the TME and converting immunologically "cold" tumors into "hot" tumors[19]. Furthermore, a ROS/GSH/pH triple-responsive prodrug nanoplatform was shown to enable multimodal cancer therapy. The prodrugs, formed by conjugating diselenide to carboxypoly(ethylene glycol)-2-((tert-butoxycarbonyl) amino) ethyl methacrylate (COOH-PEG-PAEMA) and attaching adriamycin (DOX) *via* disulfide bonds, were effectively adsorbed on Fe_2O_3 nanoparticles. Upon intravenous injection, the nanoplatform accumulated in tumor tissue, enhanced ICD, promoted T-cell proliferation, and inhibited breast tumor growth[20].

Conclusions and future perspectives

Advances in nanotechnology and stimuli-responsive polymers have opened new avenues for TME-responsive drug delivery in cancer immunotherapy. By constructing responsive polymeric nanodelivery systems that normalize TME pH, alleviate hypoxia, regulate ROS/GSH concentrations, and deplete ATP, it is possible to achieve size and morphologic transformations, charge reversal, PEG detachment, ligand-targeted activation, and controlled drug release, thereby maximizing the efficacy of immunotherapy. Through an in-depth review of existing content and therapeutic evidence, we recognize that although TME-responsive polymeric nanoparticles have shown great potential in preclinical studies, many challenges still exist from experimental-to-clinical application:

(1) Biosafety, quality control, and simplicity

Designing TME-responsive polymeric nanoparticles should prioritize biocompatibility, scalability, reproducible quality control, and cost-effectiveness. The core challenge in scaling up functional polymeric nanoparticles is translating the complex lab-grade characteristics into consistent, stable, and cost-effective mass production. Therefore, the preparation process should be simplified and optimized as much as possible to improve process stability and manufacturing efficiency. At the same time, a reasonable balance should be achieved between maximizing therapeutic efficacy and minimizing toxicity to ensure both safety and effectiveness of the clinical application. Given the systemic nature of antitumor immunity, combination immunotherapies must balance therapeutic efficacy with potential long-term toxicities or immunogenicity, such as cytokine release syndrome and tissue damage. Thus, combining responsive polymeric nanoparticles with strategies to mitigate the toxic side effects of existing immunotherapies may address current clinical challenges.

(2) Stability and targeting efficiency of nanoparticles

TME-responsive nanodelivery systems are easily cleared from the bloodstream. The tumor targeting efficiency is often limited by individual differences in the EPR effect, resulting in inadequate drug delivery. Consequently, the stability and targeting efficiency of polymeric nanoparticles can be improved by optimizing surface modification, such as employing a dynamic PEGylation strategy that enables the nanoparticles to remain invisible in the bloodstream, then shed PEG in response to pH or enzyme upon reaching the TME to expose the targeting ligand (e.g., RGD peptide). In addition, biomimetic nanocarriers can be fabricated by encapsulating nanoparticles with cell membranes (e.g., red blood cell membranes and macrophage membranes), thereby prolonging circulation time and enhancing tumor chemotaxis. In the future, it is necessary to optimize material design through multidisciplinary approaches that combine computational simulation with high-throughput screening. Computational simulation can narrow the screening scope by predicting molecular interactions and high-throughput screening can enable rapid experimental validation, synergistically accelerating the discovery of optimal polymer materials.

(3) Heterogeneity affects response efficiency

Individual patient differences, disease progression stages, and tumor cell heterogeneity can lead to varying drug delivery efficiencies. The expression and distribution of specific stimuli in the TME are highly heterogeneous and dynamic, resulting in uncontrollable nanoparticle responsiveness and insufficient drug concentrations in some regions. As mentioned above, several multi-responsive polymers have been developed to adapt to different TME conditions, such as polymers co-modified with thioether bonds (ROS-sensitive) and hydrazone bonds (pH-sensitive). Furthermore, intelligent feedback-controlled systems can be designed to incorporate real-time biosensing of the TME to dynamically modulate drug release kinetics. Alternatively, exogenous stimuli, such as photo-irradiation and ultrasound, can be used for local combination therapy to enhance the uniformity of TME regulation.

(4) Preclinical models differ significantly from humans

Animal tumor models cannot fully simulate the complex immunosuppressive environment of the human TME, resulting in discrepancies between experimental results and clinical efficacy. Polymeric nanoparticles must be designed to act in synergy with clinical immunotherapies, such as checkpoint

inhibitors and CAR-T therapies, within the specific immune context and without causing additive toxicity or interference. Regulatory authorities have not clarified the approval standards for new nanomedicines and safety evaluations, such as immunogenicity and organ accumulation toxicity, require more comprehensive and rigorous data. Moreover, the core regulatory hurdle for combined nanomedicine and immunotherapy treatments lies in the absence of assessment criteria for composite products, making it challenging to accurately evaluate the unique *in vivo* behavior, synergistic mechanisms of action, and cumulative toxicity risks. Patient-derived xenografts (PDX) or 3D tumor organoids can be used in preclinical studies to more accurately assess the permeability and immunomodulatory effects of polymeric nanoparticles. Alternatively, humanized mouse models with reconstituted immune systems can be constructed to better simulate human immune responses.

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Conflict of interest statement

No potential conflicts of interest are disclosed.

Author contributions

Conceived and designed the analysis: Shaobing Zhou, Jingya Zhao.
Wrote the paper: Yongxin Zhang.

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