Review

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Development of stimuli responsive polymeric nanomedicines modulating tumor microenvironment for improved cancer therapy

Abstract: The complexity of the tumor microenvironment (TME) severely hinders the therapeutic effects of various cancer treatment modalities. The TME differs from normal tissues owing to the presence of hypoxia, low pH, and immune-suppressive characteristics. Modulation of the TME to reverse tumor growth equilibrium is considered an effective way to treat tumors. Recently, polymeric nanomedicines have been widely used in cancer therapy, because their synthesis can be controlled and they are highly modifiable, and have demonstrated great potential to remodel the TME. In this review, we outline the application of various stimuli responsive polymeric nanomedicines to modulate the TME, aiming to provide insights for the design of the next generation of polymeric nanomedicines and promote the development of polymeric nanomedicines for cancer therapy.

Introduction

Cancer is among the leading cause of death worldwide [1]. A major obstacle to effective cancer treatment is the extreme complicated tumor microenvironment (TME), which greatly contributes to the growth, progression, and invasion of solid tumors [2]. The TME is unique and complex, containing proliferating tumor cells, endothelial cells, vasculature, extracellular matrix (ECM), tumor-associated fibroblasts (TAFs), lymphocytes, bone marrow-derived inflammatory cells, and signaling molecules [3]. The rapid proliferation of tumor cells and dysfunctional vascular growth lead to tumor hypoxia and acidosis and decrease the efficacy of various anti-tumor therapies, including chemotherapy and radiotherapy [4]. In addition, the tumor ECM consists of a network of macromolecules, including glycoproteins and fibrous proteins [5]. The physical properties, composition, and morphology of the ECM affect the migration and invasion of tumor cells [6]. Moreover, the TME is immune suppressive, containing very high levels of suppressive immune cells. For example, tumor-associated macrophages (TAMs) support cell invasion and expansion by producing various molecules that promote tissue remodeling (e.g., matrix metalloproteinases [MMPs]) and pro-inflammatory molecules (e.g., tumor necrosis factor alpha [TNF-α]) [7]. Regulatory T cells (Tregs) suppress the anti-tumor immune responses of effector T cells by activating transforming growth factor-β (TGF-β) produced by cancer cells, thereby promoting cancer immune escape [8]. Numerous studies have shown that modulation of the TME is crucial for effective cancer treatment [9].

An increasing number of approaches have been developed to modulate the TME [10–13]. For example, tumor hypoxia can be alleviated by improving tumor blood flow [14], delivering oxygen to the tumor site [15], generating

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oxygen *in situ* [16], or reducing oxygen consumption [17]. Many research groups have explored pH interference therapies that target pH-regulated membrane transport proteins or vacuolar-type H^+-ATPase (V-ATPase), using proton pump inhibitors such as V-ATPase inhibitors to reverse the development of the acidic TME [18, 19]. In addition, the TME can be modulated by disrupting the tumor ECM. By decreasing the number of TAFs or the intratumoral collagen content, the interstitial flow pressure within the tumor can be decreased and blood perfusion inside the tumor can be increased, thereby improving drug accumulation and penetration [20]. Furthermore, the development of immunotherapy has enabled the modulation of the immune-suppressive microenvironment [21]. For instance, effective strategies have been developed to polarize TAMs from M2-like macrophages to M1-like macrophages to enhance anti-tumor immune responses [22]. Other approaches including delivering immunomodulators, promoting dendritic cell (DC) activation and antigen cross-presentation, enhancing the effector function of T cells, and attenuating immunosuppressive activities such as those of Tregs and myeloid-derived suppressor cells (MDSCs) have also been used to remodel the tumor immune-suppressive microenvironment [23, 24].

Nanomedicines are widely used in cancer therapy because their prolonged blood circulation time and enriched tumor accumulation through the enhanced permeability and retention (EPR) effect [25, 26]. In particular, advances in polymer chemistry have made it possible to synthesize a variety of smart polymeric nanocarriers with versatile functionalities [27]. Polymeric nanomedicines could be prepared from natural or synthetic polymers with precise control of their structure and properties, including size, charge, and morphology [28]. Therapeutic agents are encapsulated within the nanoparticle core, or chemically coupled to the polymer backbone or the nanoparticle surface. This allows polymeric nanomedicines to deliver a variety of payloads, including hydrophobic and hydrophilic small-molecule drugs and biomacromolecules (proteins or genes) [25].

Here, we summarize the recent progress in the development of stimuli responsive polymeric nanomedicines (including those responding to endogenous stimuli such as pH, enzymes, hypoxia, redox, and ATP, as well as exogenous stimuli such as photo, thermal, and ultrasound) to modulate the TME (Figure 1). These nanomedicines typically contain responsive chemical groups/bonds that are summarized and can achieve stimuli-triggered responses to achieve the desired properties (Table 1). Such stimuli responsive polymeric nanomedicines modulate the TME by disrupting and interfering with the tumor ECM, disrupting TAFs, causing tumor vascular rupture or normalization, modulating tumor hypoxia, or changing the suppressive immune microenvironment. The aim of this review is to provide insight into the next generation of polymeric nanomedicines that may help to improve cancer therapy in the future.

Characteristics of the tumor microenvironment

The physical heterogeneity of a solid tumor leads to a complex system inside the tumor, including not only tumor cells but also vasculature, ECM, infiltrating immune cells, TAFs, multiple signaling molecules, and an abnormal metabolic environment [78]. A major feature of the TME is the inhibition of tumor suppressor genes and the activation of pro-oncogenes, resulting in the proliferation and invasion of tumor cells. Compared with normal tissues, the TME usually exhibits an acidic, hypoxic, redox environment with high levels of reactive oxygen species (ROS), glutathione (GSH), enzymes, and ATP (Figure 2) [79].

The proliferation of tumor cells requires more oxygen than that of normal cells and produces large amounts of lactic acid, resulting in an imbalance in oxygen supply and causing a low pH and hypoxic microenvironment [80]. Furthermore, the production and regulation of ROS in cancer plays an important part in determining the progression of cancer [81]. Tumor cells promote their own proliferation, metastasis, and epithelial–mesenchymal transition by ROS production in the TME. Moreover, elevated ROS leads to the adaptive development of an enhanced antioxidant defense system in tumor cells that scavenges ROS by elevating the concentration of GSH [82]. GSH is the primary ROS quencher and is considered to be another key regulator of tumor initiation, progression, and metastasis. High GSH concentration in tumors has been associated with resistance to chemotherapy and radiotherapy. Therefore, eliminating intracellular GSH to enhance cancer therapy is considered an attractive approach [83].

An increase in extracellular ATP is a hallmark of the TME [84]. Elevated extracellular ATP is mainly from intratumoral cells, including stromal and parenchymal cells. Tumor tissue is relatively hypoxic owing to its excessive growth rate. In addition, there is an immune response in the TME with infiltration of interstitial inflammatory cells leading to massive tumor and stromal cells necrosis. Release of intracellular ATP results in ATP enrichment within the TME, which in turn promotes cancer cell growth by activating purinergic receptors (e.g., P2X7) [85].

Enzyme expression and secretion in the TME is also different from that in normal tissues [86]. In particular, the TME overexpresses multiple enzymes, including MMP,
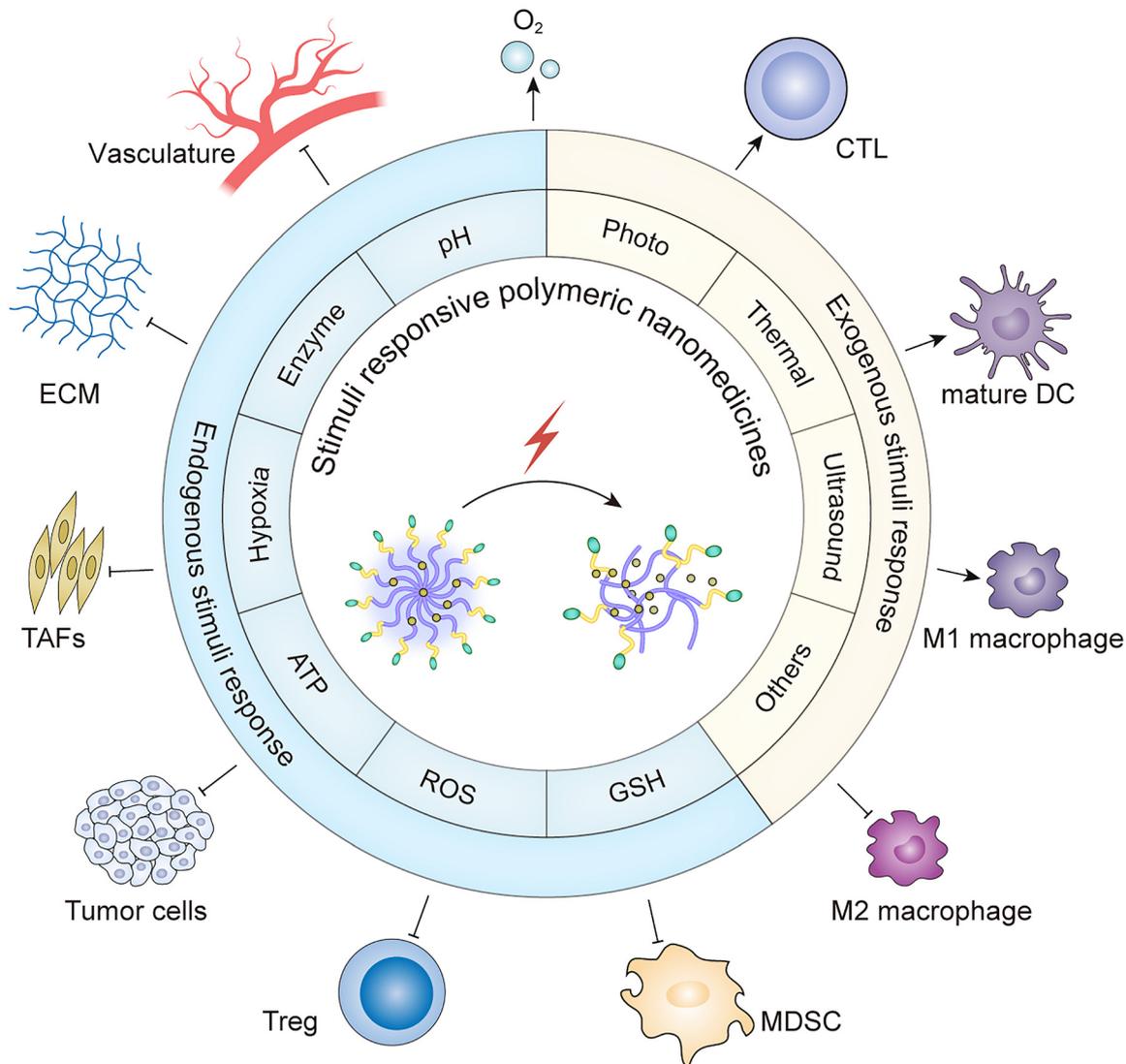
Figure 1: Schematic diagram of stimuli responsive polymeric nanomedicines modulating the tumor microenvironment to improve cancer therapy. Reactive oxygen species (ROS); Glutathione (GSH); Extracellular matrix (ECM); Tumor-associated fibroblasts (TAFs); Regulatory T cell (Treg); Dendritic cell (DC); Myeloid-derived suppressor cell (MDSC); Cytotoxic T lymphocyte (CTL).

hyaluronidase, and esterase [87]. For example, MMPs are hydrolytic enzymes that are highly expressed in the ECM of tumors and are closely related to the development and metastasis of tumors. Therefore, these enzymes are attractive therapeutic targets for cancer treatment strategies [88].

Solid tumors use negative regulatory mechanisms to suppress the anti-tumor activity of the immune system. The TME contains many immunosuppressive cells and cytokines [89]. MDSCs, Tregs, and M2-like macrophages are three major immunosuppressive cell types that exert their suppressive function by secreting negative immunoregulatory cytokines such as interleukin-10 and TGF-β [90, 91]. This immunosuppressive environment not only promotes tumor

cell growth and metastasis but also impedes DC maturation and antigen presentation, further reducing the immune efficacy of T cells and exacerbating immunosuppression. In addition, tumor cells express immune checkpoint proteins such as programmed death ligand 1 and the "don't eat me" signal CD47, which inhibit the attack of effector T cells and phagocytes for immune escape [92, 93].

Nanomedicine systems are currently used to deliver anti-tumor drugs to tumor sites by active or passive targeting; this approach is more effective and safer than traditional treatment methods [94]. To achieve better antitumor efficacy, responsive nanomedicines have been widely designed. According to their type of responsiveness,

Table 1: Summary of stimuli responsive groups/bonds.

Type of responsive	Responsive group/bond	Chemical structure	Ref.
pH	Imidazole		[12]
pH	Carboxylic acid		[29]
pH	Sulphonamide		[30]
pH	Amine		[31, 32]
pH	Imine		[33]
pH	Acetal/ketal		[34]
pH	Boronate ester		[35, 36]
pH	Hydrazone		[37]
pH	Enamine		[38]
pH	Oxime		[39]
pH	Amide		[40]
pH	Orthoester		[41]
Enzyme (γ-glutamyl transpeptidase)	γ-glutamylamide		[42]
Enzyme (esterase)	Ester		[43]
Enzyme (cathepsin B)	Peptide	LL/RR/AL/FR/FK/GFLG/ALAL	[44]
Enzyme (MMP)	Peptide	GPLGV/PVGLIG	[45]
Enzyme (Caspase-3)	Peptide	DEVD	[46]
Enzyme (legumain)	Peptide	AADL	[47]
Hypoxia	Azobenzene		[48]
Hypoxia	2-Nitroimidazole		[49]
ROS	Thioketal		[50, 51]
ROS	Phenylborate ester		[52]
ROS	Thioether		[53]
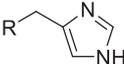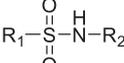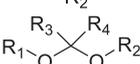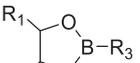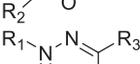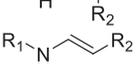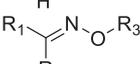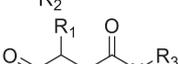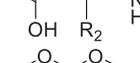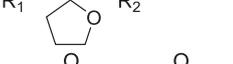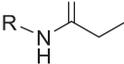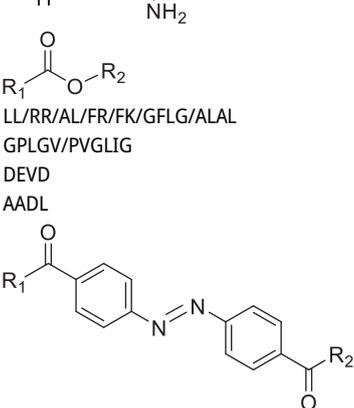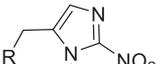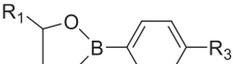
Table 1: (continued)

Type of responsive	Responsive group/bond	Chemical structure	Ref.
ROS	Selenoether	R_1–Se–R_2	[54]
ROS	Aminoacrylate		[55]
ROS	Peroxalate ester		[56]
GSH	Disulfide	R_1–S–S–R_2	[57]
GSH	Thiol-pyridazinedione		[58]
GSH	2,4-Dinitrobenzenesulfonyl		[59]
GSH	Trisulfide	R_1–S–S–S–R_2	[60]
GSH	Platinum (IV)		[61]
ROS/GSH	Diselenide	R_1–Se–Se–R_2	[62]
ATP	Host-guest interaction		[63]
ATP	DNA/RNA (hydrogen bond)	ACCTGGGGGAGTATTGCGGAGGAAGGT	[64]
ATP	Metal coordination (coordination competition)	Zn^{2+}	[65]
ATP	Phenylborate ester (ester exchange reaction)		[66]
Photo	*o*-nitrobenzyl		[67]
Photo	Coumarin		[68]
Photo	Boron-dipyrromethene		[69]
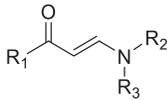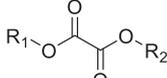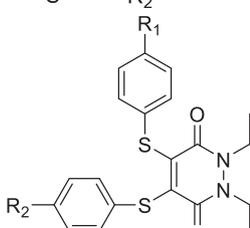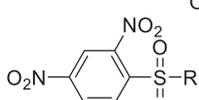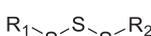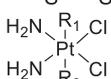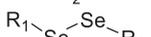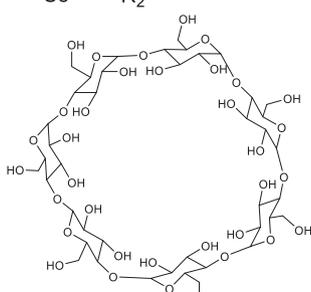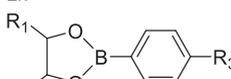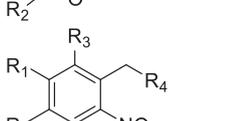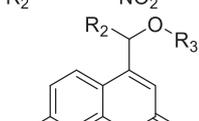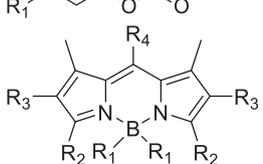
Table 1: (continued)

Type of responsive	Responsive group/bond	Chemical structure	Ref.
Thermal	Azo	$R_1{-}N{=}N{-}R_2$	[70]
Thermal	Poly(N-isopropylacrylamide)		[71]
Thermal	Elastin-like polypeptide	VPGXG (X is any amino acid other than proline)	[72]
Ultrasound	Disulfide	$R_1{-}S{-}S{-}R_2$	[73, 74]
Ultrasound	Poly(methoxyethyl methacrylate)		[75]
Magnetic	Superparamagnetic iron oxide	Fe_3O_4	[76]
X-ray	Diselenide	$R_1{-}Se{-}Se{-}R_2$	[77]
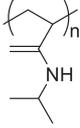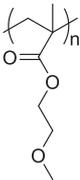
polymeric nanomedicines can be classified into two types: endogenous stimuli responsive and exogenous stimuli responsive nanomedicines, and we summarize these polymeric nanomedicines separately according to different types of responsiveness in this review.

Endogenous stimuli responsive polymeric nanomedicines

pH responsive polymeric nanomedicines

Since the concept of pH-sensitive linkage release of drugs was first proposed in 1981 [95], large numbers of acidity-triggered polymeric nanomedicines have been developed for cancer treatment [96–100]. The TME (pH 6.5–7.2) and the endosome/lysosomal envelope (pH 4.5–6.5) are weakly acidic, in contrast to the neutral pH level of normal tissue (pH 7.4) [101]. pH responsive linkers including hydrazone bonds, acetal bonds, *cis*-aconityl groups, Schiff bases, and β-thiopropionate linkages have been used in the design of polymeric nanomedicines [102]. The incorporation of pH responsive linkers between polymers and drugs enables acidity-triggered release of therapeutic agents in the ECM or after intracellularization in endosomes/lysosomes in tumor tissues. Numerous studies have shown that such pH responsive nanomedicines can effectively modulate the TME to treat refractory cancer [75, 103–107].

For instance, Chen and Ding group designed a pH responsive nanomedicine for the biomineralization therapy of osteosarcoma [12]. They synthesized novel biomineralization-inducing nanoparticles (BINP) composed of dodecylaminepoly([γ-dodecyl-L-glutamate]-*co*-L-histidine)-*block*-poly(L-glutamate-*graft*-alendronate) (DDA-P[DLG-*co*-LH]-*b*-P[LG-*g*-ALN]). BINP assembled into nanoparticles under normal physiological conditions, but the self-assembly process was disturbed and the internal aliphatic chains were exposed under weakly acidic conditions. After injection of the nanoparticles into osteosarcoma tumor-bearing mice, BINP was cleaved in the weakly acidic TME, exposing the dodecyl groups on the surface of the nanoparticles, which promoted insertion of the nanoparticles into the cell membrane. Owing to the subsequent continuing ion deposition triggered by the protruding bisphosphonic acid group, a mineralized barrier that could block substance exchange between the tumor and surrounding normal tissues was constructed. The progression of osteosarcoma was suppressed with minimal side effects (Figure 3).

Yu group engineered intracellular pH responsive nanomedicines which could promote ferroptosis of tumor cells and generate an anti-tumor immune response [108]. At neutral pH (pH 7.4), the nanoparticles could stably encapsulate pyropheophorbide-a (PPa) to mediate photodynamic therapy (PDT), as well as ferroptosis inducer RSL-3. However, in an endocytic vesicle (pH 5.8–6.2), the payload was released *via* acid-triggered cleavage of the dynamic covalent bond of the phenylboronate ester (Figure 4). PDT treatment resulted in infiltration of IFN-γ-positive T cells,
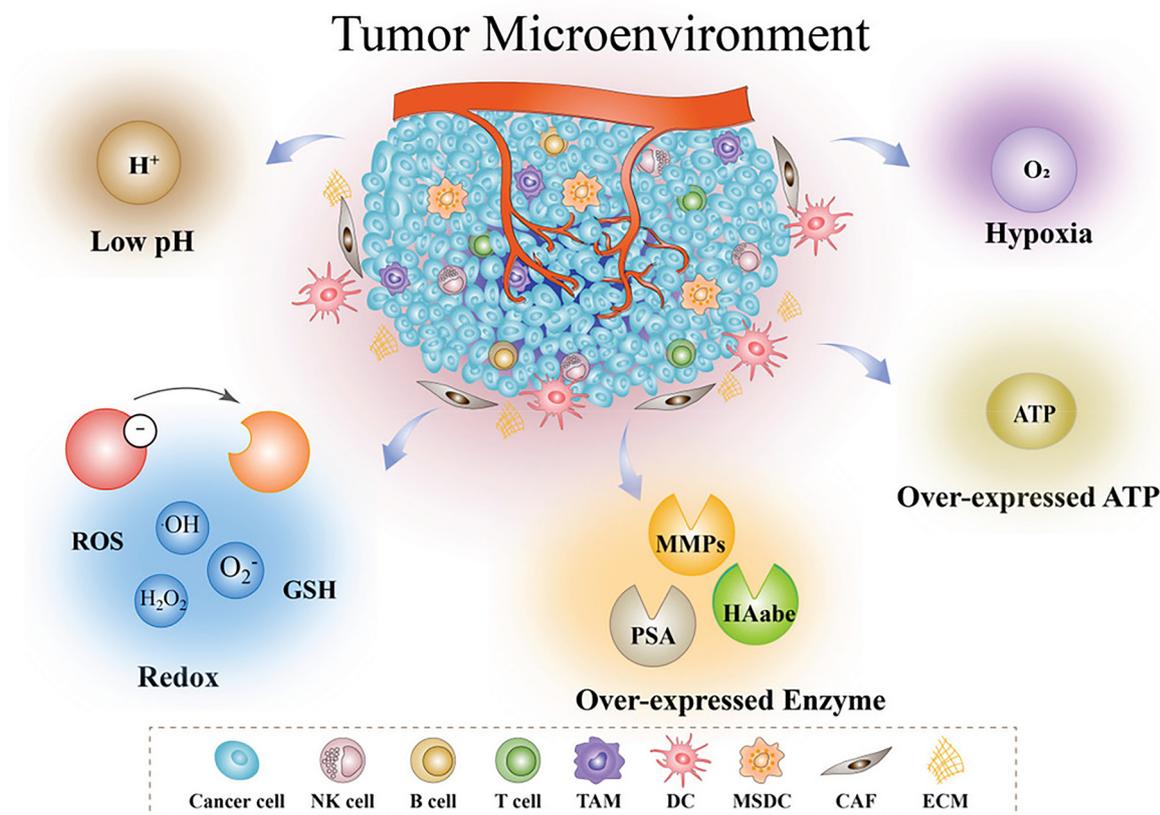
Figure 2: Characteristics of the TME include hypoxia, low pH, redox, overexpression of enzymes, overexpression of ATP, and an immune-suppressive microenvironment. Reproduced with permission from Peng et al. [79]. Copyright 2022, Wiley-VCH GmbH.

which further synergized with RSL-3 to promote ferrogenesis at the tumor site, producing an efficient anti-tumor immune response.

In addition, Ding and Nie group developed a stimuli responsive DNA based nanovaccine for cancer immunotherapy [109]. Antigens and multiple adjuvants were accurately loaded on the nanodevice to stimulate tumor-specific T cell responses that efficiently inhibited tumor growth. With a size suitable to efficient draining to and retention in draining lymph nodes, the nanodevice achieved enhanced delivery to antigen-presenting cells (APCs) and exposed its active payloads in a pH responsive manner. Moreover, Liang and Li group developed a proton-driven nanotransformer-based vaccine that could induce a strong immune response [34]. In an acidic environment, the particles transformed into bigger structures, which caused endosomal membrane disruption and thus transported antigenic peptides (APs) to the cytoplasm. As well as promoting cytosolic delivery and cross-presentation of APs, this nanovaccine could activate the NLRP3-inflammasome pathway and thus strengthen antitumor immunity.

Enzyme responsive polymeric nanomedicines

Enzymes have essential roles in current nanotechnology because of their excellent biorecognition abilities and preeminent catalytic properties [88, 110, 111]. The abnormal enzyme expression observed in the TME facilitates strategies using enzyme responsive polymeric nanomedicines for precise delivery and triggered release of therapeutic agents at the tumor site to enhance cancer therapy [87, 112–119].

For example, cathepsin B is a proteolytic enzyme secreted and overexpressed in the TME of many solid tumors including breast cancer, colorectal cancer, melanoma, and, prostate cancer [120]. The use of cathepsin B responsive linkers in construction of nanomedicines for effective treatment of tumors has been widely explored [121–124]. Pu and Huang group reported a semiconducting polymer nano-proteolysis targeted chimeras (SPNpro) with phototherapeutic and activatable protein degradation abilities for photo-immunometabolic cancer therapy [125]. SPNpro was specifically activated by cathepsin B to trigger
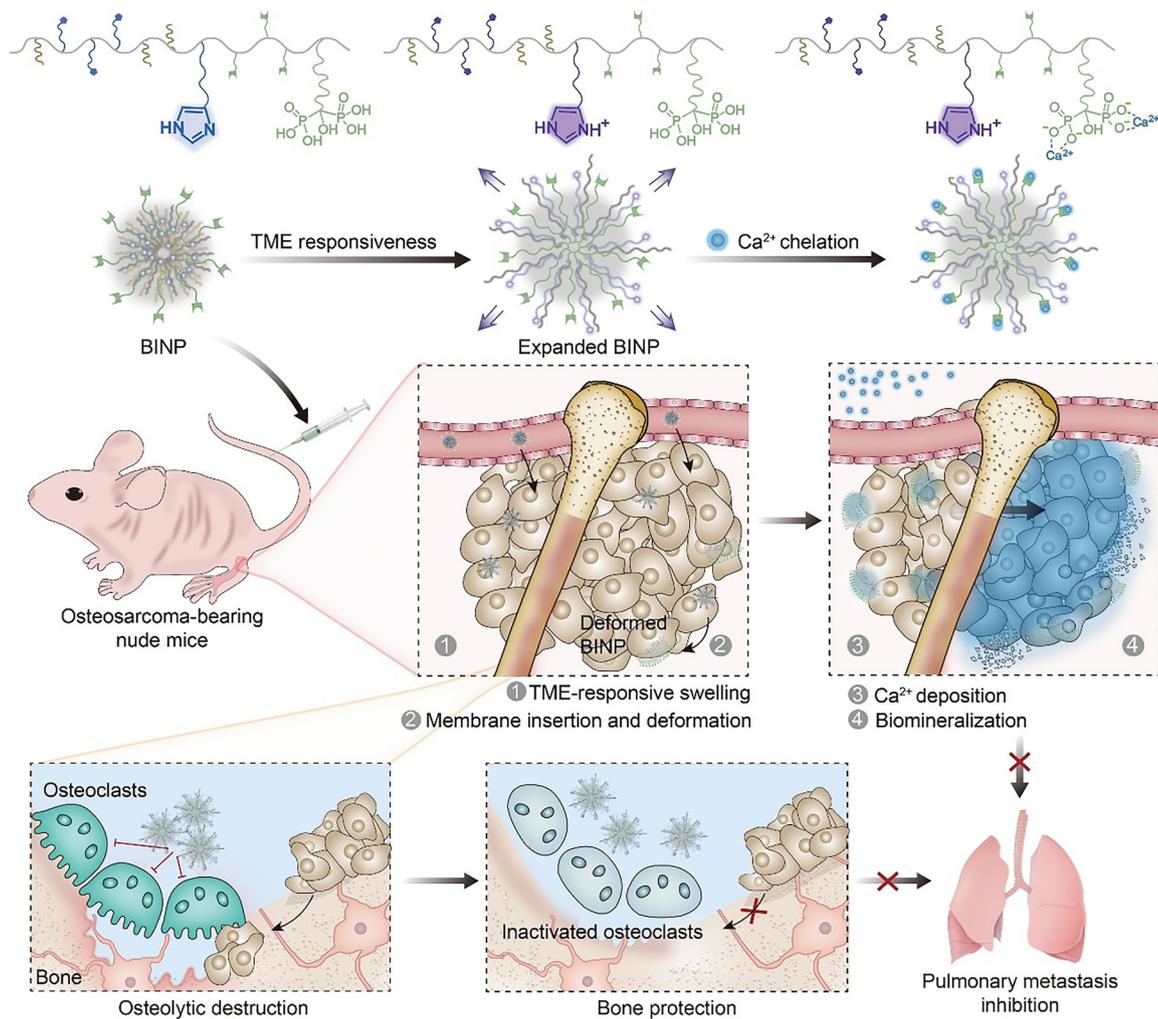
Figure 3: Schematic illustrating the TME responsive BINP for osteosarcoma therapy. Reproduced with permission from Liu et al. [12]. Copyright 2022, Wiley-VCH GmbH.

targeted proteolysis of immunosuppressive indoleamine 2,3-dioxygenase in tumor-bearing mice, thereby promoting the activation of effector T cells. Furthermore, Luo group synthesized poly (OEGMA)-PTX@Ce6 (NPs@Ce6) composed of a photosensitizer, chlorin e6 (Ce6), and a cathepsin B responsive polymer-paclitaxel (PTX) prodrug (Figure 5) [126]. The hydrophilic fragment of the polymer prodrug was prepared by reversible addition fragmentation chain transfer polymerization of OEGMA, and PTX was covalently linked to the polymer backbone through a cathepsin B responsive tetrapeptide Gly-Phe-Leu-Gly (GFLG). The combination of PTX-based chemotherapy with PDT upregulated oxidative phosphorylation and ROS production, blocked the cell cycle and proliferation, and downregulated genes associated with tumor progression, invasion, and metastasis.

Overexpression of various MMPs has been reported in multiple types of tumors, and MMP-2 and MMP-9 in particular have been explored with respect to applications in enzyme responsive drug delivery [127, 128]. For instance, Yu and Li group designed an enzyme activatable prodrug vesicles (EAPVs) for combination photodynamic immunotherapy [129]. To construct the TME sheddable prodrug vesicles, PPa was conjugated with methoxy poly(ethylene glycol) (mPEG-NH$_2$) *via* an MMP-2-liable peptide spacer to obtain mPEG-GALGLPG-PPa. EAPV-mediated PDT resulted in an immune-promoting environment with enhanced intratumoral infiltration of IFN-γ-positive T cells, inhibited tryptophan degradation in the tumor tissues, and finally reduced infiltration of intratumoral Tregs.

Many nanomedicines have been designed based on enzymes responsive structures. These nanomedicines not only kill tumor cells but also prevent excessive activation of fibroblasts, thereby reducing drug resistance and tumor metastasis. For instance, Shen group designed an esterase
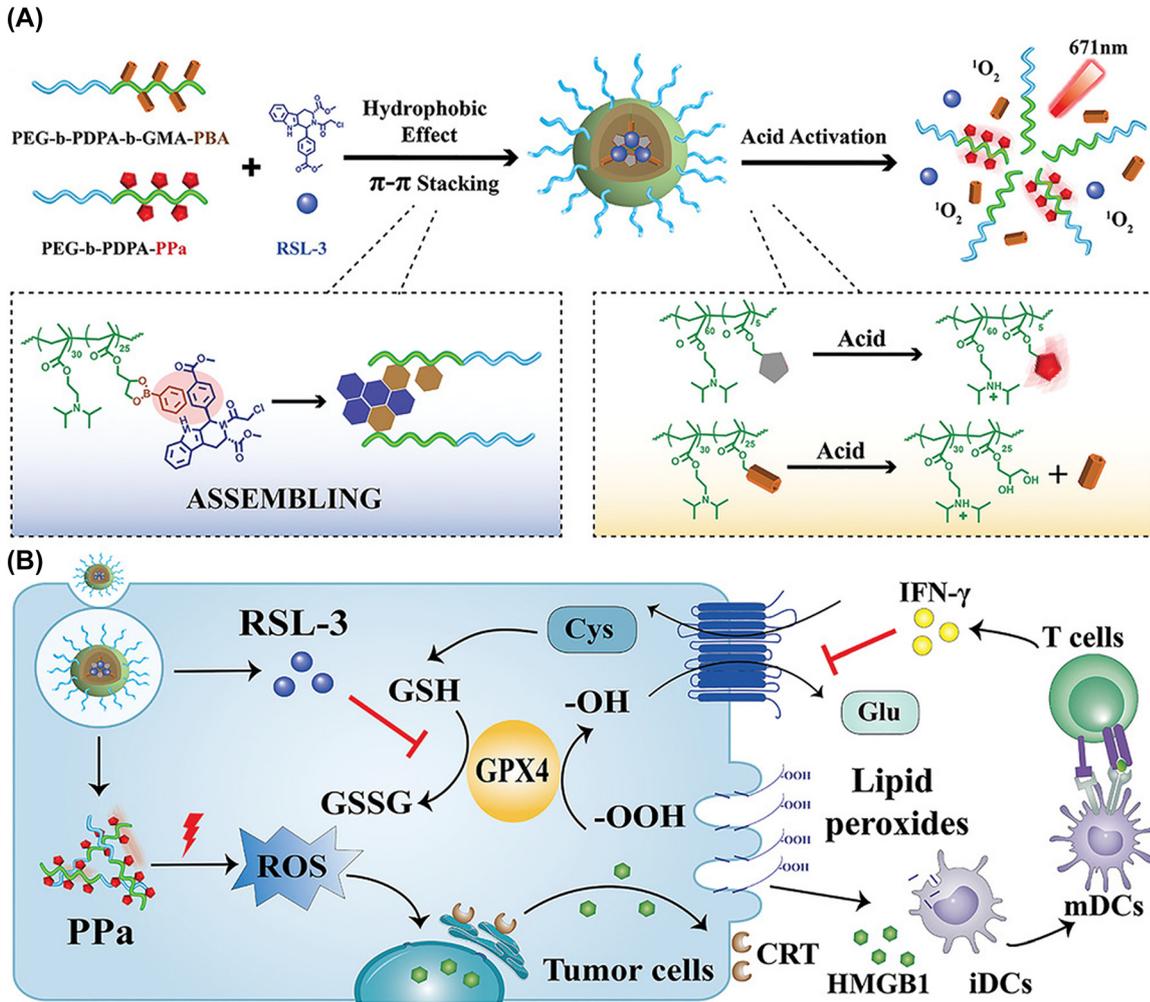
Figure 4: Schematic illustration of the induction of immunogenicity by pH responsive nanomedicines. (A) Preparation and activation of PPa-conjugated nanoparticles. (B) Boosting of ferroptotic death by nanoparticles. Reproduced with permission from Song et al. [108]. Copyright 2021, Wiley-VCH GmbH.

responsive charge-reversal polymer (ERP) [87]. Alkyl esters are stable and difficult to hydrolyze even in the presence of enzymes, whereas phenolic acetates are easily hydrolyzed by esterase. Hence, 4-acetoxybenzyl esters were employed as triggers for ester-catalyzed charge reversal. The ERP polyplexes showed selective gene expression in cancer cells with high levels of esterase but conserved fibroblasts owing to their low esterase activity. Such polyplexes effectively induced apoptosis of HeLa cells but did not activate fibroblasts to secrete WNT16B which caused the surviving cancer cells to be drug resistant and metastatic, enabling potent anticancer activity with few side effects (Figure 6).

Hypoxia responsive polymeric nanomedicines

The unlimited proliferation and metabolism of tumor cells leads to hypoxia in the TME, which causes drug resistance

and tumor metastasis [130]. Malignant tumors are difficult to cure and prone to relapse after surgery, largely owing to the hypoxic TME. Therefore, changing the hypoxic environment at the tumor site is an important aspect of tumor treatment [131]. In addition, to utilize tumor hypoxia, various hypoxia responsive nanomedicines have also been proposed. There are three main strategies to treat hypoxic tumors: improving the hypoxic TME [132], hypoxia responsive nanomedicines [133], and hypoxia activated prodrug [134].

You group reported a multifunctional nanomedicine co-loaded with hemoglobin and doxorubicin (DOX) to change the hypoxic TME and enhance the therapeutic effect of chemotherapy medicines [135]. This nanomedicine could be efficiently loaded with oxygen and deliver oxygen and chemotherapeutic drugs to the tumor site, causing them to accumulate at the tumor site. It not only reversed the hypoxia of the TME but also improved the utilization rate of
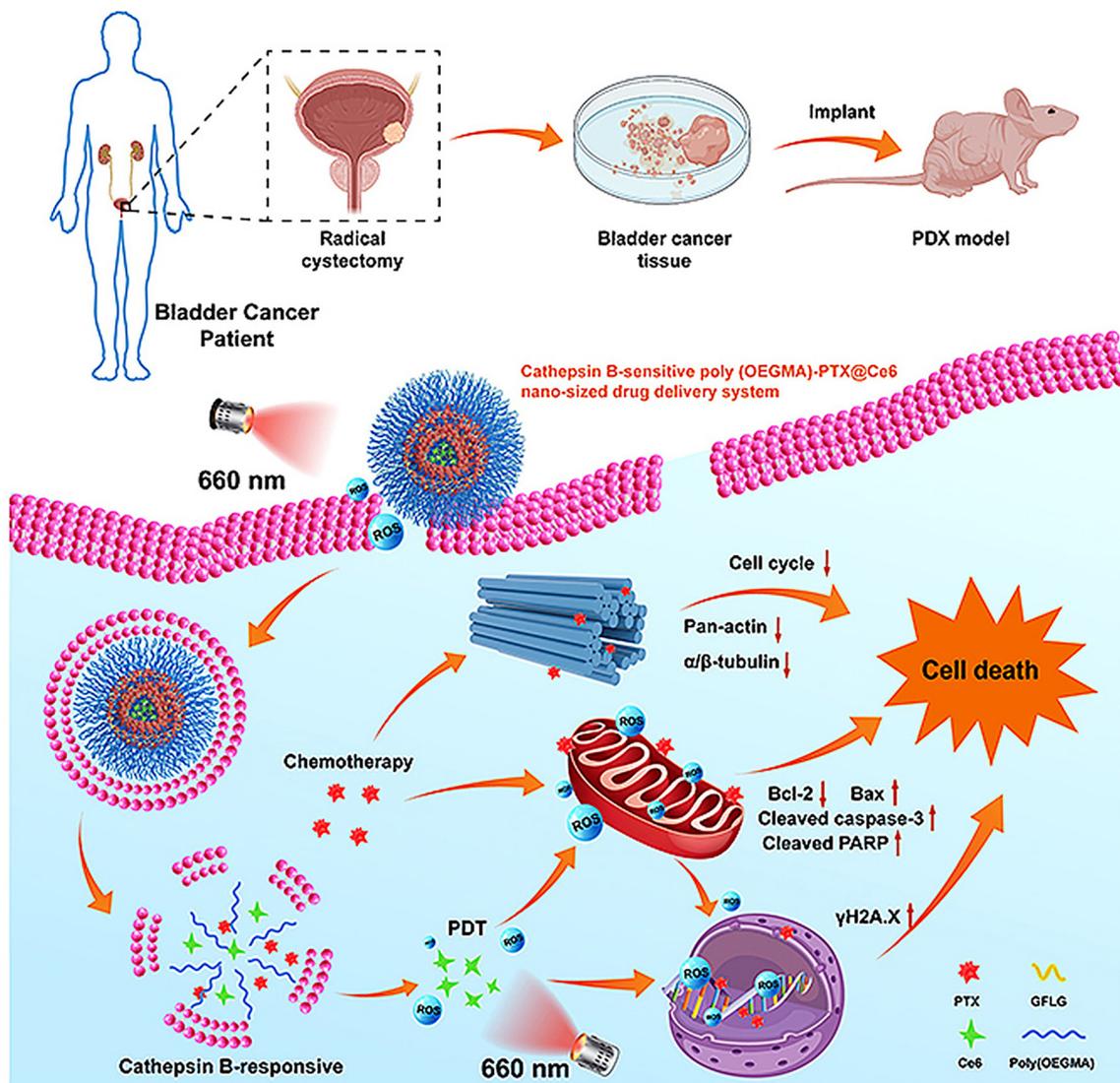
Figure 5: Schematic illustration of the cathepsin B responsive PTX prodrug. Reproduced with permission from Tan et al. [126]. Copyright 2021, Elsevier.

chemotherapy drugs. Compared with commonly used oxygen delivery strategies, such as hyperbaric oxygen and perfluorinated carbon nanoparticles, this hemoglobin and DOX co-loaded nanomedicine overcame the problems of limited oxygen-loading capacity and inefficient drug delivery to hypoxic tumors.

Abnormal proliferation of tumor cells, an inadequate blood supply, and insufficient endogenous oxygen lead to hypoxia of tumor tissues [136]. A common strategy is to engineer hypoxia responsive release through hypoxia-sensitive linkages [137]. Guo group reported a calixarene based hypoxia responsive molecular container called CAC4A, which showed strong binding to a range of chemotherapy medicines [138]. Formation of a complex with CAC4A significantly improved the solubility and stability of drugs, and, more importantly, the host-guest complex dissociated easily under low oxygen conditions. Under these conditions, the reduction of the azo group of CAC4A led to a decrease in the affinity between the drug and calixarene, with eventual targeted release of the medicine within the tumor.

Hypoxia responsive prodrug have been designed primarily for combination with PDT and vascular occlusion to enhance the therapeutic effect of the prodrug [131, 139]. With increasing tumor volume and continuous proliferation, many blood vessels are established near the tumor, which indicates a new way to alter the TME [140]. Disruption of the established tumor vasculature effectively blocks the blood supply to the tumor, thereby preventing exponential
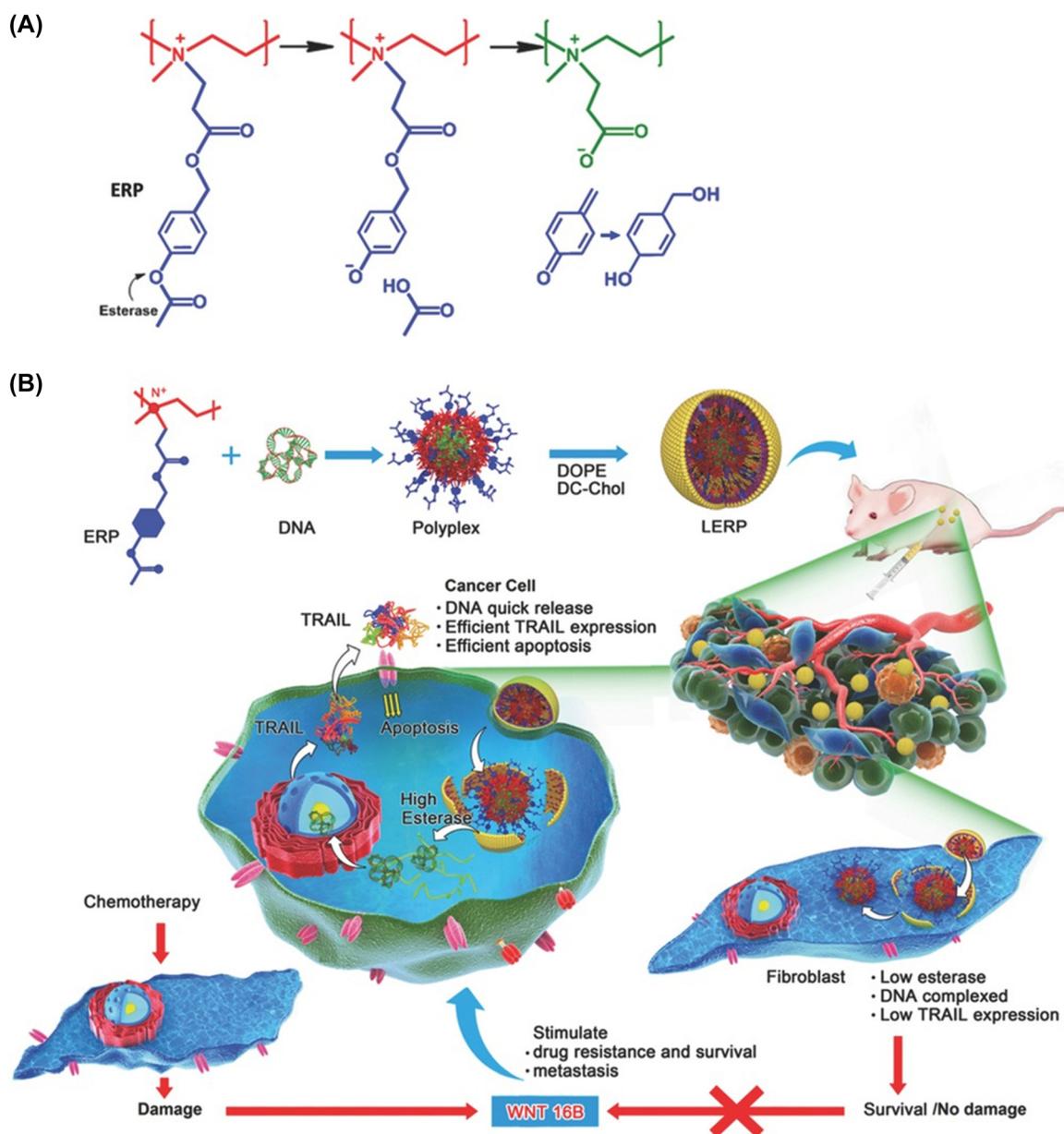
Figure 6: Schematic illustration of esterase responsive nanomedicines for cancer gene therapy. (A) The charge-reversal mechanism of ERP in the presence of esterase. (B) Application of the ERP mechanism in cancer gene therapy. Reproduced with permission from Qiu et al. [87]. Copyright 2016, Wiley-VCH GmbH.

tumor growth and metastasis [141]. Jing group reported a PTX prodrug that could be activated in a hypoxic environment [142]. They first modified the photosensitizer Ce6 in the peptide copolymer and then encapsulated the PTX autolytic medicine (PTX2-Azo) in the copolymer (Figure 7). This design achieved the precise release of PTX under the tumor hypoxic environment.

Cancer stem cells (CSCs) are highly resistant in the hypoxic region of tumors and are also highly carcinogenic; these are the main causes of tumor proliferation and recurrence [143]. Mo group reported a nanomedicine loaded with differentiation inducer all-trans retinoic acid (ATRA) and chemotherapy medicine camptothecin (CPT) [144]. First, ATRA was released in the hypoxic TME, and the nanoparticles dissociated. Then, ROS levels increased in the vicinity of tumor cells, leading to the release of CPT. This strategy not only achieved controlled drug release but also reduced CSC-related drug resistance.
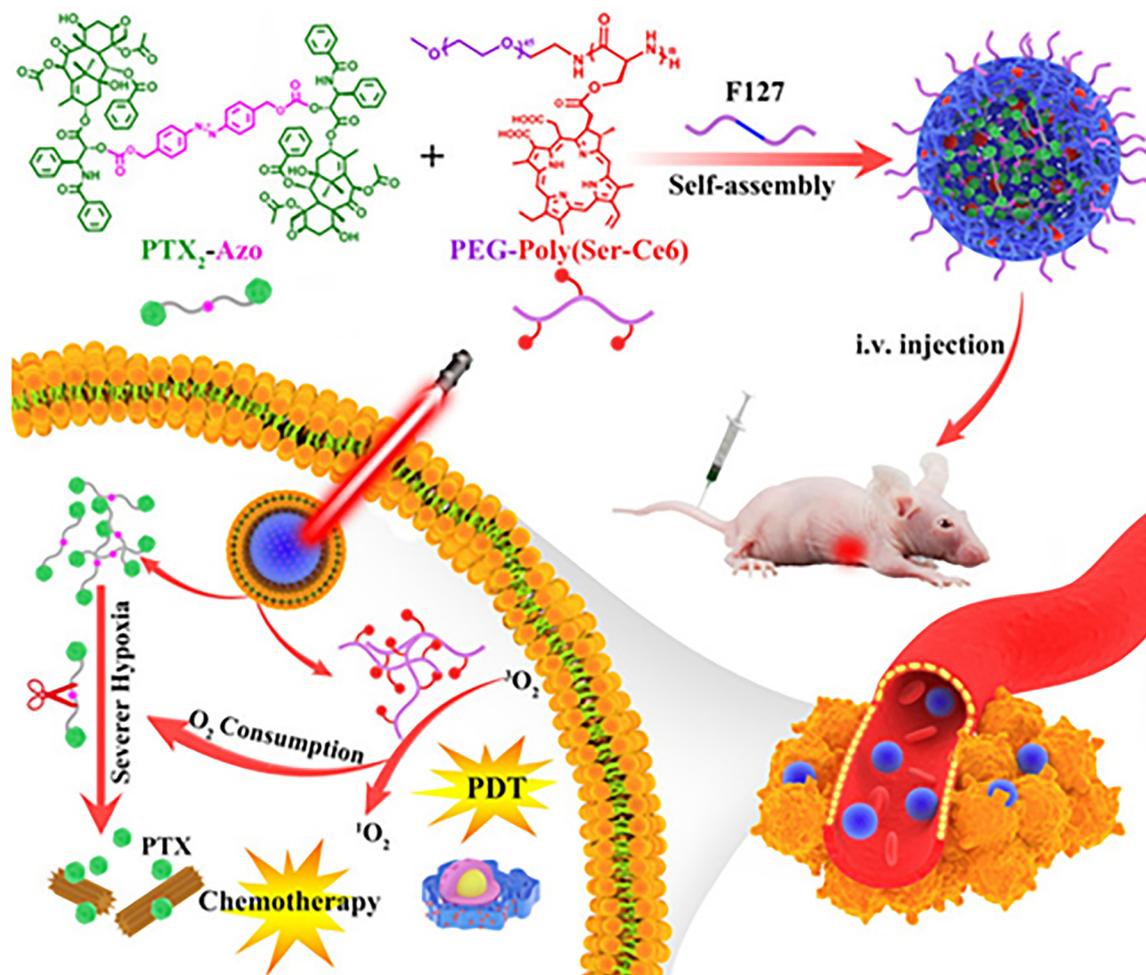
Figure 7: Design of hypoxia responsive nanomedicine Ce6/PTX2-Azo NP and its release under hypoxic conditions *in vivo*. Reproduced with permission from Zhou et al. [142]. Copyright 2020, Wiley-VCH GmbH.

Redox responsive polymeric nanomedicines

ROS is a general term for oxygen-containing chemically reactive substances, including singlet oxygen ($^1O_2$), hydrogen peroxide (H_2O_2), superoxide anion (O_2-), and hydroxyl radical (–OH) [145]. There are many mechanisms by which cells produce ROS, but endogenous ROS are mainly generated through mitochondrial metabolism, or by peroxidases and members of the transmembrane NaDPH oxidase family [81]. Owing to the activation of oncogenes, tumor suppressor function is lost and mitochondrial activity is changed, resulting in significantly higher levels of ROS in tumor cells compared with normal tissue cells. The process of tumor spread further increases the production of ROS [146]. Therefore, ROS responsive nanomedicines can achieve more precise drug delivery at the tumor site [147, 148].

Chen group reported a ROS responsive nanomedicine consisting of β-lapafenone (Lap), ferric ions, and a ROS responsive PEG-*block*-poly thioketal DOX prodrug. Lap catalyzed the generation of H_2O_2, which killed tumor cells by producing toxic –OH through the Fenton reaction [97]. DOX was released in response to a high concentration of ROS levels when the nanomedicine entered the TME. Furthermore, Ding group reported a TME responsive composite gel consisting of a temperature responsive hydrogel and a ROS responsive nanogel, which enabled precise drug release while enhancing nanomedicine targeting and immune system activation [149]. Regorafenib (REG) was preferentially released from the hydrogel after *in situ* formation, generated ROS and inhibited tumor growth. Subsequently, excess ROS enabled LY3200882 (a selective TGF-β inhibitor) to be released on demand, thereby reversing the tumor proliferation and immune escape of tumor cells induced by TGF-β (Figure 8).
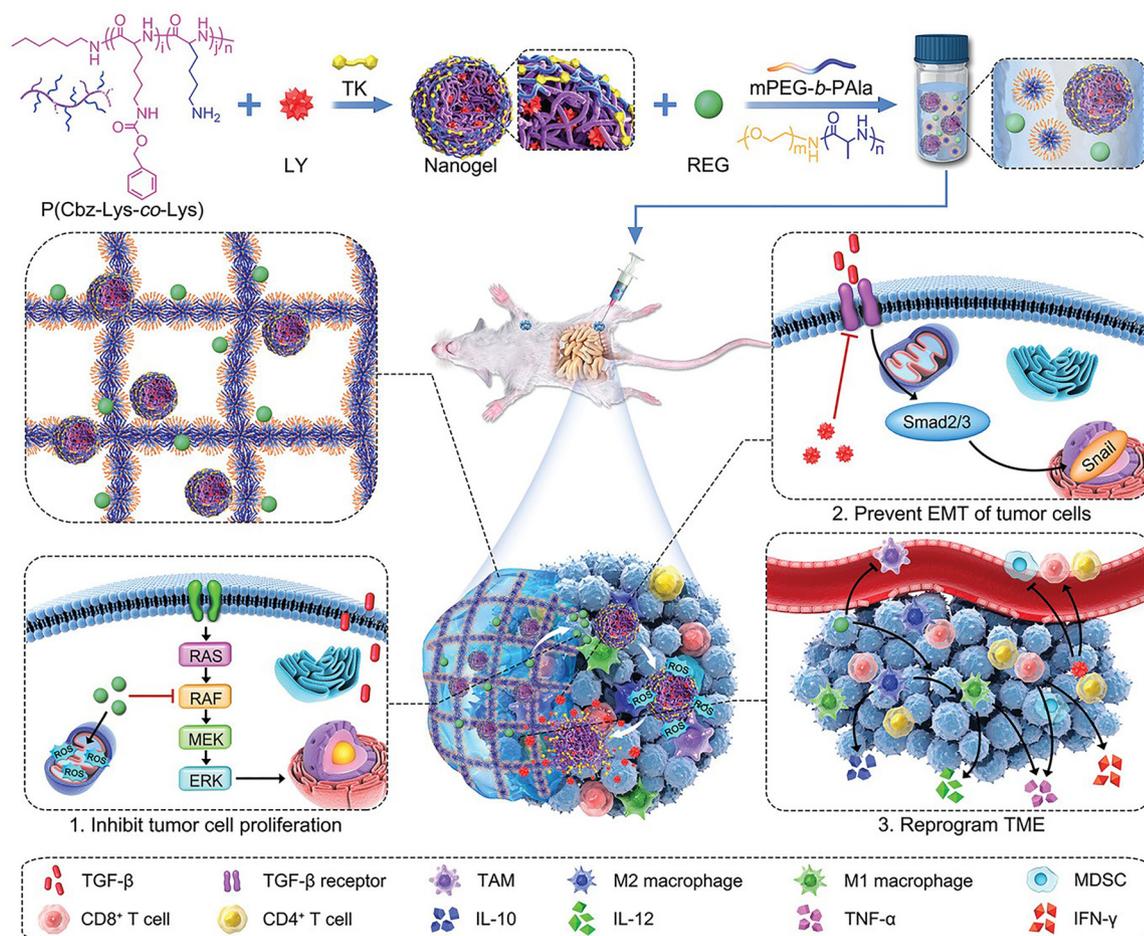
Figure 8: Schematic illustration of the preparation and *in vivo* antitumor effects of gel/(REG+NG/LY). After hydrogel formation *in situ*, REG and LY are released sequentially to induce ICD and enhance immune effects. Reproduced with permission from Li et al. [149]. Copyright 2022, Wiley-VCH GmbH.

Shuai group reported a ROS responsive nanomedicine in which oleic acid was modified with manganese oxide and incorporated with temozolomide (TMZ) into polyethylene glycol-polyethyl methacrylate polymer micelles containing internalized arginine-glycine-aspartic acid (iRGD) [150]. iRGD enhanced the targeting and tumor penetration of the nanomedicine. TMZ, Mn^{2+}, and O_2 were released in the TME after aggregation of the nanomedicine within glioma. Large amounts of Mn^{2+} caused intracellular oxidative stress and killed tumor cells through toxic ·OH generated by the Fenton reaction. TMZ induced immunogenic cell death (ICD) and O_2 generation, which changed the hypoxic TME. In summary, this nanomedicine exerts a promising anti-tumor effect through synergistic effects on multiple pathways.

Kataoka group reported a strategy to construct reactive nanomedicines based on multi-ion composite vesicles by incorporation of ROS responsive groups into a cross-linked membrane network [151]. After H_2O_2 exposure, the ROS reactive linkers were gradually split, and the vesicle structure underwent stable expansion. Owing to the decrease in membrane cross-linking density, the membrane changed from hydrophobic to hydrophilic, leading to the swelling of vesicles and therefore an increase in the permeability of the membrane.

Song group reported a nanomedicine constructed using host-guest interactions between poly-([N-2-hydroxyethyl]-asparagine)-Pt(IV)/β-cyclodextrin, CpG/polyamidoamine-thioketal-adamantane, and methoxy poly(ethylene glycol)-thioketal-adamantane [152]. The nanomedicine accumulated around the tumor after intravenous injection and released antigens and immunoadjuvant CpG upon stimulation with high levels of ROS. This resulted in the activation and antigen presentation of APCs and generated a potent anti-tumor immune response.

GSH removes excessive ROS and maintains the redox balance in the vicinity of cells. However, the presence of excessive levels of GSH in the vicinity of tumor cells disrupts the balance of redox homeostasis [153]. Levels of GSH in tumor cells can be as high as 2–10 mM, about 100–1000 times

higher than that in the ECM (2–10 μM) and 7–10 times higher than that in normal tissues [83]. This makes GSH a preferred target for endogenously responsive nanomedicines.

To date, various GSH responsive nanomedicines have been developed, including nanoparticles containing disulfide bonds (S-S), diene bonds (Se-Se), carbon diselenoic bonds (C-Se), and sulfonyl groups [154]. GSH react with these bonds, leading to the cleavage of nanoparticles and the precise release of chemotherapy drugs at the TME [155]. Wang group reported a GSH responsive nanomedicine (sNP@G/IR) synthesized with a disulfide containing polymer (poly[CHTA-*co*-HD]-PEG) that enhanced the tumor permeability of the drug and inhibited the growth of bacteria inside the tumor [156]. The outer shell of the nanomedicine was degraded by hyaluronidase in the ECM near the tumor, and the small size of the nanoparticles facilitated deep penetration into the tumor. Subsequently, the drug was released in the tumor under the action of GSH (Figure 9). The dead intratumoral bacteria (killed by the drug) led to the maturation of DCs and activation of CD8⁺ T cells. Furthermore, GSH responsive nanomedicines can also be designed to disrupt tumor vasculature to block tumor blood supply [157]. Chen group reported a GSH responsive polymer, PEGylated poly(alpha-lipoic acid), conjugated with vascular blocker Combretastatin A4 [158]. The selective release of Combretastatin A4 was induced by the high concentration of glutathione at the tumor site, cutting off the supply of blood (and therefore of nutrition and oxygen) to the tumor tissue, leading to tumor internal necrosis.

ATP responsive polymeric nanomedicines

In tumor tissues, large amounts of intracellular ATP are released from cells owing to the influence of inflammation, necrosis, hypoxia, and other factors. This results in an increased concentration of ATP in the TME, which has a non-negligible impact on tumor proliferation, invasion, and metastasis [159, 160].

Owing to the high ATP concentration inside tumors, ATP responsive nanomedicines delivering therapeutic drugs have
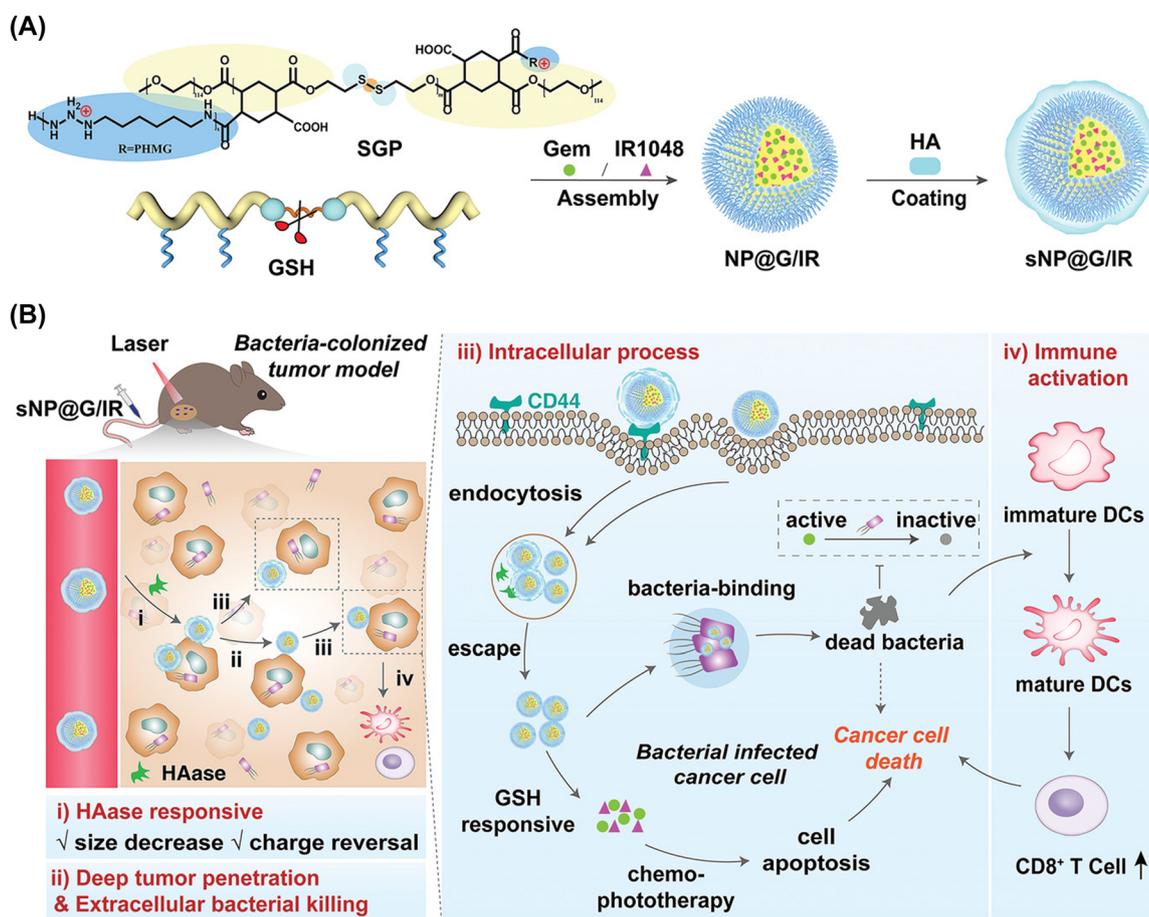
Figure 9: Schematic illustration of the synthesis of GSH responsive nanomedicines as well as their actions *in vivo*. (A) Preparation of responsive nanomedicines with core–shell structure. (B) Nanomedicines inhibited bacteria-colonized tumor growth by killing of intratumoral bacteria and precision drug release. Reproduced with permission from Kang et al. [156]. Copyright 2022, Wiley-VCH GmbH.

been designed. As intracellular and extracellular ATP concentrations are very different (1–10 mM intracellularly; 0.4 mM extracellularly), using ATP could be a practical way to modulate medicine release [161]. Kataoka group reported an ATP responsive nanomedicine in which mRNA was complexed with a phenylboronic-acid-derived poly(ethylene glycol)-poly(cationic block copolymer) and polyol by spontaneously formed phenylboronic acid esters [66]. The phenylboronic acid ester bound to high concentrations of mRNA released in response to ATP, and the released mRNA compensated for the aberrant expression of oncogenes around tumor cells. This strategy represents a new approach to designing ATP responsive nanomedicines. Moreover, Deng group developed ATP responsive nanomedicines (IR@ZIF-RGD) that affected tumor ATP metabolism and modulated the TME [65]. IR@ZIF-RGD was synthesized by self-assembly of a short interfering RNA/polyethylenimine complex, followed by electrostatic adsorption of indocyanine green and surface coating of RGD-modified polylactic acid-hyperrambrated polyglycerol. This nanomedicine depleted intracellular ATP and inhibited ATP synthesis (Figure 10). IR@ZIF-RGD released the drug in response to ATP, elicited robust ICD, and promoted intratumoral infiltration of effector T cells, thereby enhancing anti-tumor immune response.

Exogenous stimuli responsive polymeric nanomedicines

Photo responsive polymeric nanomedicines

Photo responsive polymeric nanomedicines make use of photochemical reactions or photothermal effects and can be used in photoisomerization-mediated therapy [162]. Benefiting from spatiotemporal adjustability, photo responsive nanomedicines allow site-specific non-invasive delivery of therapeutics [163–165].

Near-infrared light has advantages including high tissue permeability and low side effects. Qian group reported a thioketal bond linked CPT and photosensitizer-2-(1-hexyloxyethyl)-2-devinyl pyropheophorbide-a, constituting a photo responsive platinum nanoenzyme (PtNP) [166]. Under 660 nm laser irradiation, ROS were produced by PtNP, which effectively enhanced PDT and controlled the release of CPT. Furthermore, PtNP effectively catalyzed the decomposition of H_2O_2 into O_2 to alleviate hypoxia in the TME and inhibit tumor growth.

Photoisomerization is a change in the conformation of a molecule that allows the structure to open upon absorption of light energy to trigger drug release. Light irradiation can induce reversible photoisomerization of selected organic compounds, including spiropyran and azobenzene [162]. Feng group reported a strategy for the integration of photochromic spiropyran into biocompatible cationic polymers, which involved the assembly of nucleic acids into functional nanoparticles without the introduction of other photosensitizers and imaging agents [167]. Upon UV irradiation, Borrelia bound copolymers changed from hydrophobic to hydrophilic, which facilitated controlled release of the drug. In addition, the production of ROS during light exposure could also alleviate hypoxic TME.

The ability to control changes in the physical and chemical structures of nanomedicine carriers plays a key part in drug delivery. Wang group reported a photo responsive donor-acceptor Stenhouse adduct and folic acid units conjugated to form a polymeric nanomedicine [168]. Drug release could be precisely controlled under light irradiation (λ = 550 nm). The photo responsive property led to simultaneous swelling and opening of nanoparticles to release the drug. In addition, the ROS produced due to light also helped to kill tumor cells and relieved the hypoxic TME. Furthermore, Xiao group reported co-assembly of a semiconductor polymer (PSP) and an amphiphilic polymer (PEDOX) with DOX conjugated through a thioketal bond [169]. Irradiation at 808 nm resulted in rapid release of DOX, and the sacrificial degradation of PEDOX and PSP by intracellular GSH resulted in dissociation of the nanomedicine (Figure 11). Furthermore, light at 808 nm induced tumor ICD and increased tumor immunogenicity. As a result, infiltration of DCs and cytotoxic T lymphocyte (CTLs) increased in the TME, and M2 macrophages were converted to M1 macrophages, resulting in the release anti-tumor cytokines and generating a potent anti-tumor immune response.

Thermal responsive polymeric nanomedicines

Thermal stimulation has the advantages of a wide temperature control range and precise control of the action area [170]. Thermal responsive polymeric nanomedicines are relatively stable at a certain temperature, but undergo structural changes when the temperature increases or decreases [171]. Therefore, thermal responsive polymeric nanomedicines can be prepared for controlled drug release. In addition, it is possible to promote the release of drugs after elevation of temperature by adding thermally unstable materials to the carrier [172].

The thermal response characteristics of polymeric nanomedicines are usually determined by the upper critical solution temperature (UCST) or lower critical solution temperature (LCST) of the material [173]. When the ambient temperature is lower than the UCST of the material or higher
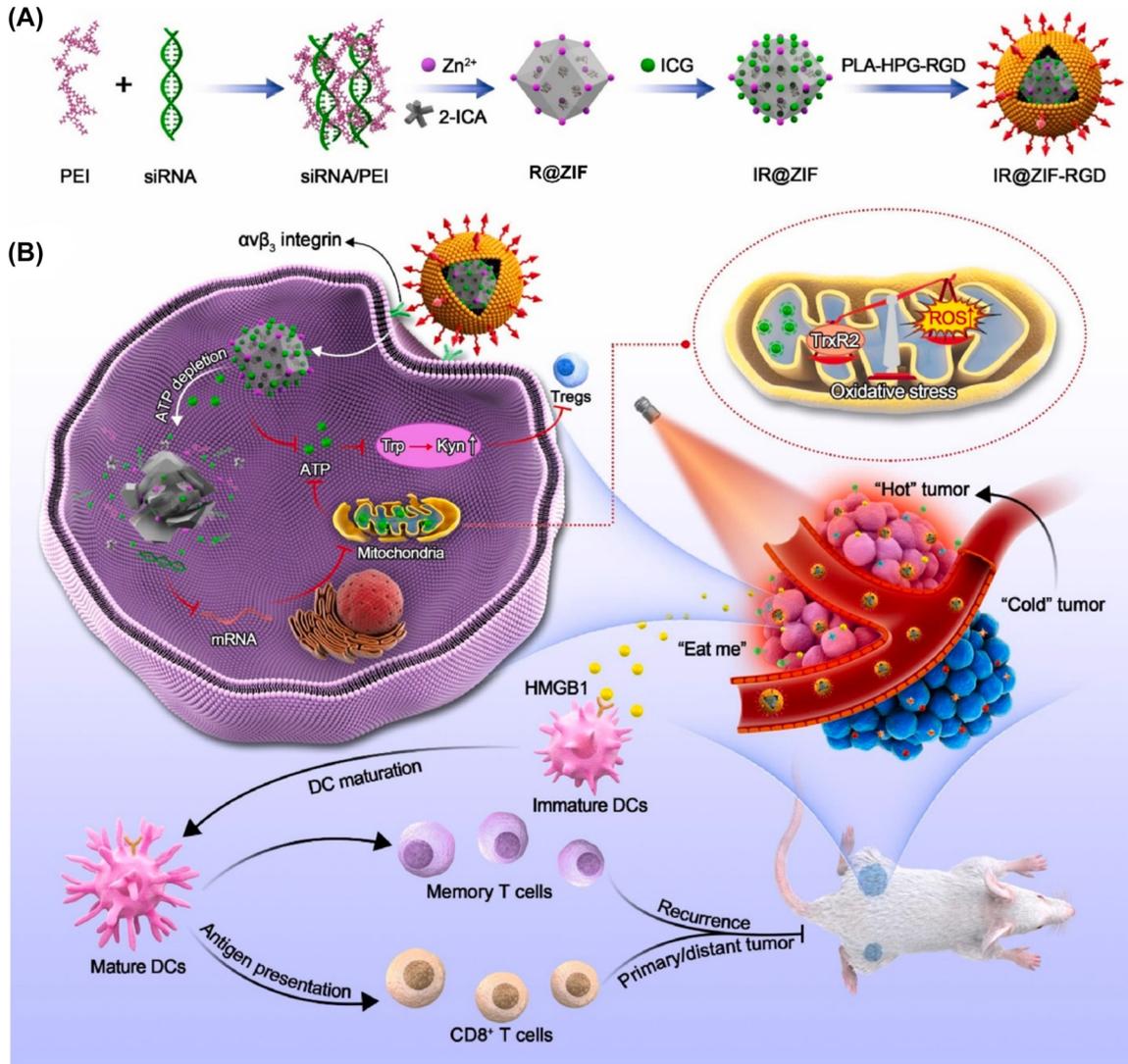
Figure 10: Schematic synthesis of IR@ZIF-RGD with ATP responsive properties, nanoparticle-mediated intratumoral metabolic intervention and immune response. (A) Preparation of IR@ZIF-RGD. (B) IR@ZIF-RGD mechanisms that mediate metabolic remodeling and enhance photoimmunotherapy in the TME. Reproduced with permission from Yu et al. [65]. Copyright 2022, Elsevier.

than its LCST, the carrier will change from a hydrophilic state to a hydrophobic state, thereby facilitating drug loading or release [174]. For example, Alem group reported a nanoparticle with a core–shell structure consisting of Fe_3O_4, 2-(2-methoxy) ethyl methacrylate (MEO_2MA) and oligo (ethylene glycol)-methacrylate (OEGMA) [175]. By adjusting the ratio between the MEO_2MA and OEGMA blocks, a polymer with a LCST of 41 °C was obtained and successfully loaded with the hydrophobic drug DOX. *In vitro* studies found that almost all of the DOX was released within 52 h at a temperature slightly higher than the LCST of the polymer. At an ultra-low DOX concentration of 0.07 μg mL^{-1}, the killing rate of the nanomedicine against human ovarian cancer SKOV-3 cells was more than 70%; in addition, long-term drug

infiltration of the TME was achieved, the immune escape of tumor cells was prevented.

Du group reported a thermal responsive and liver tumor cell-targeting peptide A54 modified polymer [176]. The A54--poly(ethylene glycol)-*g*-poly(acrylamide-*co*-acrylonitrile) could self-assemble into an 80 nm micellar form, which exhibited thermal responsive behavior with an UCST of 43 °C. DOX and magnetic nanoparticles (MNPs) were co-encapsulated at temperatures below 43 °C. There was greater accumulation on the tumor under navigation with the A54 targeting peptide. The temperature increased due to the thermal effect of the MNPs not only activated drug release within tumor cells but also increased the effectiveness of thermal therapy. The thermal treatment also caused ICD of
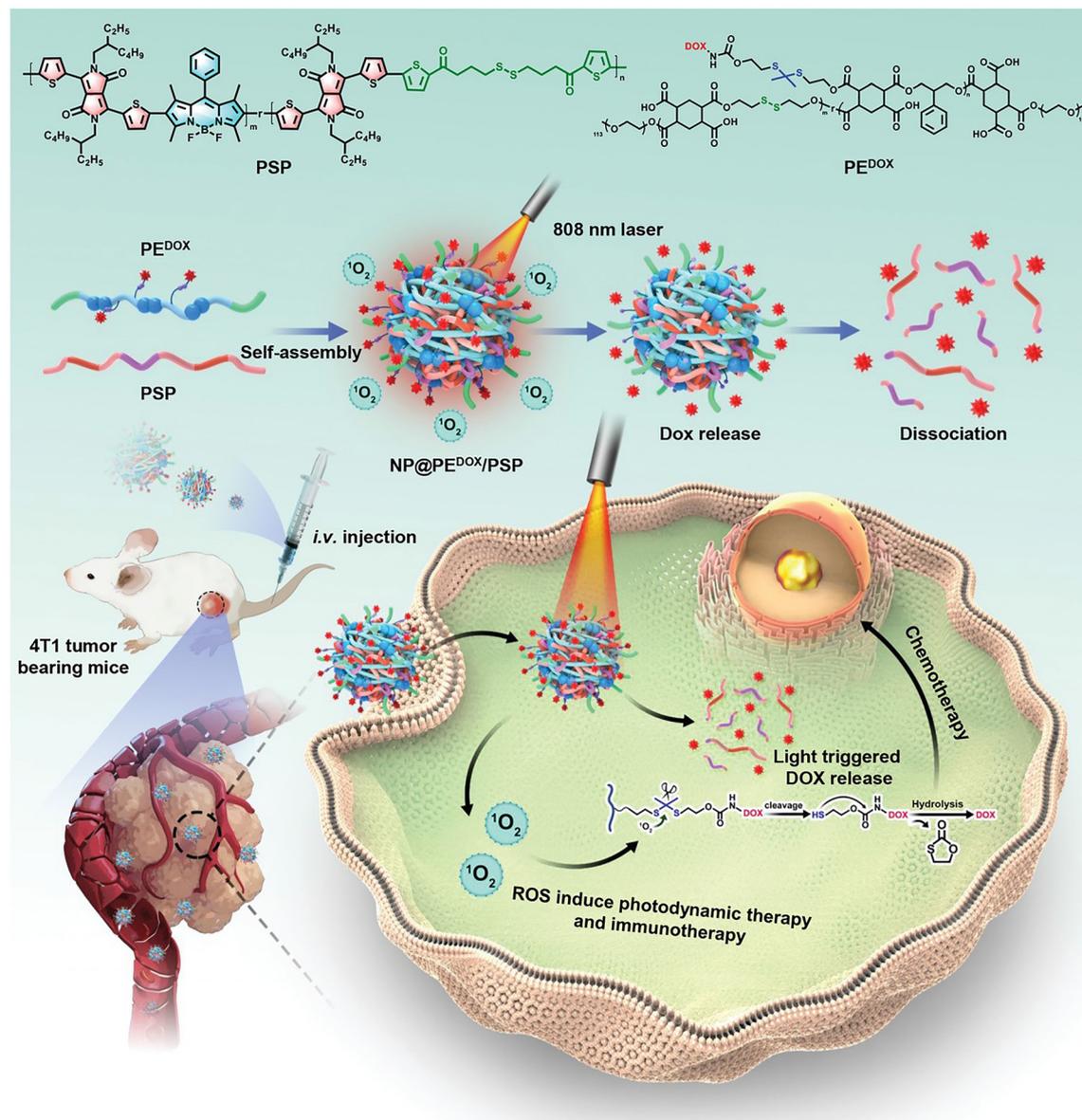
Figure 11: Schematic illustration of NP@PEDOX/PSP and the mechanism of the photo responsive release of the drug by the nanoparticles *in vivo*. Reproduced with permission from Tang et al. [169]. Copyright 2022, Wiley-VCH GmbH.

tumor cells, exposed large numbers of antigens, accelerated DC maturation, and regulated the TME. Similarly, Hu group reported multifunctional polypyrrole (PPy) nanoparticles, the inner core with UCST characteristics was loaded with CPT, whereas the outer corona was connected to the heat-lytic DOX prodrug, with a further *in situ* coating of PPy to obtain CPT@DOX-UCST/PPy nanoparticles (Figure 12). Upon 808 nm continuous laser irradiation, the PPy absorbed light to generate a large amount of heat, which lead to DOX prodrug cleavage and a considerable size increase, and facilitated simultaneous release of both drugs, thereby triggering the combined activation of PTT

and chemotherapy. The drug was maintained tumor infiltration for a long period of time (more than 24 h) and the tumor remained in a state of long-term immune activation, which was more conducive to DC maturation and T cell activation [70].

Ultrasound responsive polymeric nanomedicines

In recent years, ultrasound responsive polymeric nanomedicines have attracted considerable attention owing to
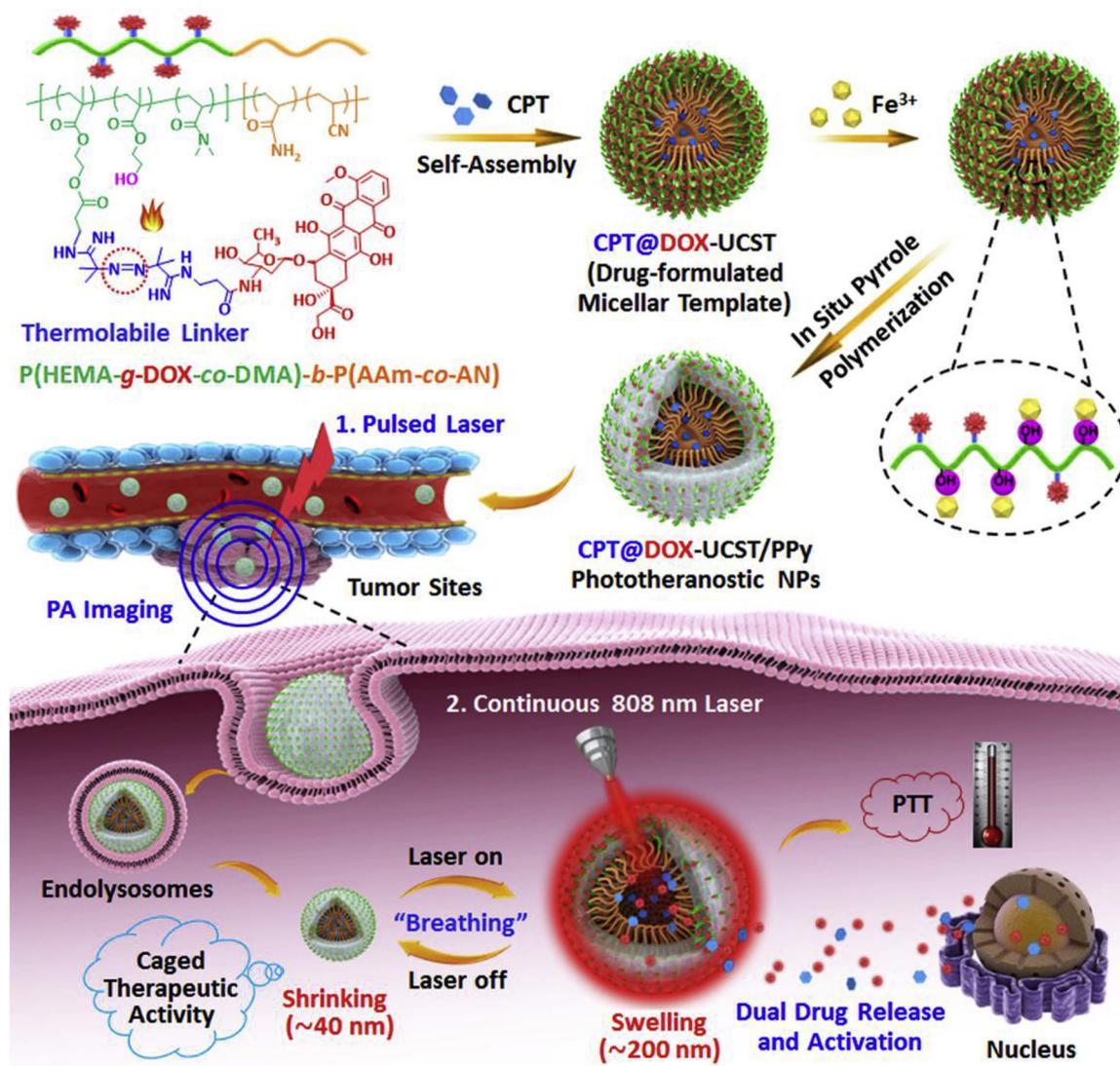
Figure 12: Schematic illustration of polymeric nanomedicines for photothermal synergistic therapy of cancer. Reproduced with permission from Yang et al. [70]. Copyright 2018, Elsevier.

their non-invasiveness, high tissue penetration depth, and spatiotemporal controllability [177]. Such systems typically encapsulate drugs in ultrasound responsive nanomedicines, making them stable in physiological environments before accumulating at tumor sites through the EPR effect. Then, under the action of ultrasound, the drugs are released to kill tumor tissues selectively [178–180]. For instance, Pu group reported a series of semiconducting polymers as sonosensitizers. Then they conjugated anti cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) antibodies onto the surface of the nanoparticles that delivered sonosensitizers. Under the action of ultrasound, nanomedicines elevated the level of $^1O_2$ in TME and induced ICD. Increased $^1O_2$ also promoted the release of anti-CTLA-4 antibodies conjugated to the polymers so that triggered

checkpoint blockade [181]. Jiang group developed a polymer for ultrasound responsive ultrasound therapy through the Stella coupling reaction and used it to prepare a nanomedicine based on 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-(carboxy[polyethylene glycol]-2,000). Catalase was coupled to the surface of the nanomedicine to relieve hypoxia in the TME. The polymeric nanomedicine converted H_2O_2 into $^1O_2$ under ultrasound and effectively inhibited tumor growth. This strategy simultaneously addressed the issues of poor tumor site penetration and hypoxia, thereby enhancing cancer therapy [182].

In addition, Du group synthesized a triblock dual-response copolymer using atom transfer radical polymerization on the basis of their previous research (Figure 13) [75, 183]. The 2-(diethylamino)ethyl methacrylate segment could be
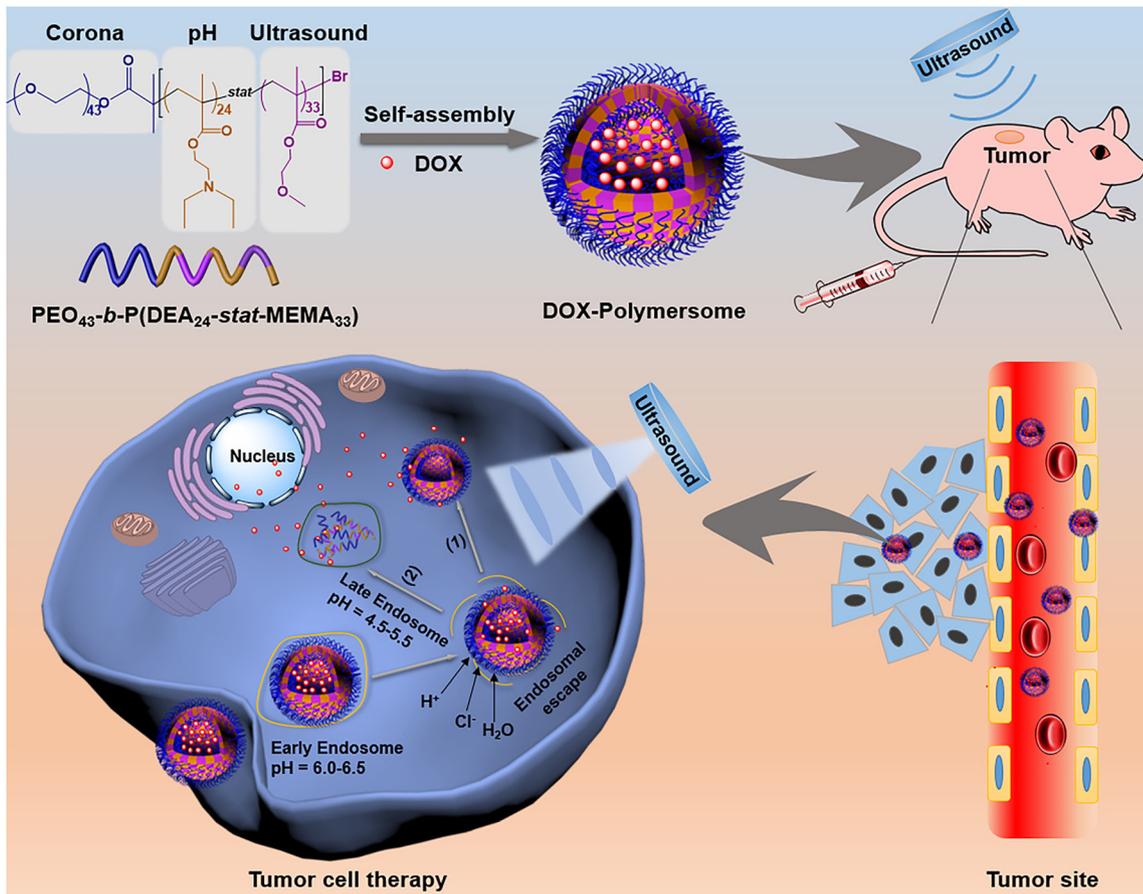
Figure 13: *In vivo* mechanism of ultrasound responsive polymeric nanomedicines. Reproduced with permission from Wei et al. [75]. Copyright 2020, Elsevier.

protonated under acidic conditions to enhance the endosome escape ability, and the methoxyethyl methacrylate segment was hydrophobic and ultrasound responsive. *In vivo* anti-tumor experiments showed that under the action of ultrasound, the loaded DOX was released from the polymeric nanomedicines at an accelerated rate and achieved tumor-inhibiting efficiency of more than 95%, which further confirmed the applicability of ultrasound responsive polymeric nanomedicines in the field of tumor treatment. Ultrasound triggered drug release from the DOX-multimers and promoted drug release in the tumor, which led to more drug diffusing into the surrounding or deeper tumor tissues. Ultrasound treatment increased vascular permeability and promoted drug accumulation in tumors.

Other types of responsive polymeric nanomedicines

Magnetic responsive polymeric nanomedicines have also been used to modulate the TME. Charushin group reported a magnetic responsive nanomedicine consisting of ([3-triethoxysilyl]propyl)succinic acid-polyethylene-glycol and silica co-modified Fe_3O_4 magnetic nanoparticles, which were loaded with DOX [76]. DOX was released under an alternating magnetic field at a frequency of 230 kHz at 0.27 kOe, which resulted in a 2.5-fold increase in the cytotoxic effect of the nanomedicine against 4T1 tumor cells within 1 h.

Begum group reported a pH and magnetic field responsive casein-calcium ferrite hybrid biopolymeric carrier conjugated with biotin for the lung carcinoma treatment [184]. Cinnamaldehyde (CNA) reached 85.5% release within 4 h in response to magnetic field stimulus. The nanomedicine significantly increased the anticancer potential of CNA with an 18-fold reduction in the IC50 value compared with the pure drug against A549 cell lines.

X-ray have also been used as stimuli to trigger drug release [185, 186]. Chen group reported a smart nanomedicine formed by crosslinking methoxy poly(ethylene glycol)-*block*-poly(L-glutamic acid-*co*-γ-2-chloroethyl-L-glutamate) (mPEG-*b*-P[LG-*co*-CELG]) with a Se-Se bond [187]. Polypeptide nanogels loaded with DOX (PNG/DOX) showed accelerated drug release
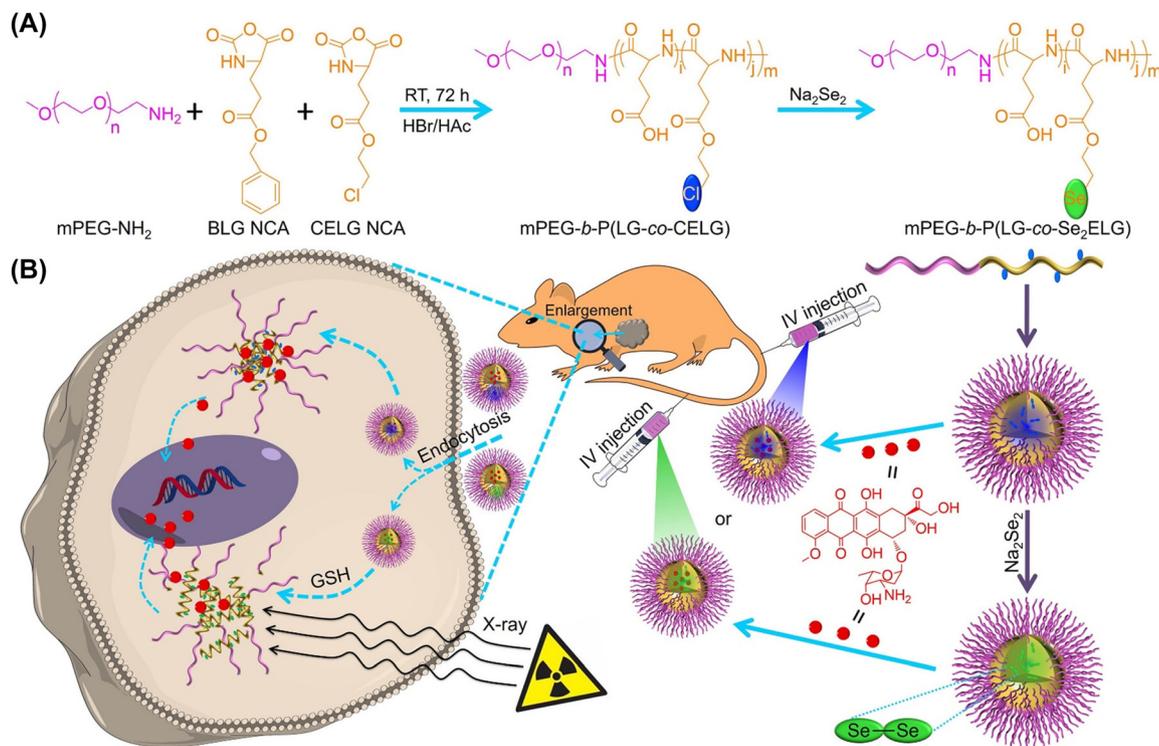
Figure 14: Preparation and *in vivo* metabolism of mPEG-*b*-P(LG-*co*-CELG) micelle and mPEG-*b*-P(LG-*co*-Se₂ELG) nanogel. (A) Synthesis of mPEG-*b*-P(LG-*co*-CELG) and mPEG-*b*-P(LG-*co*-Se₂ELG). (B) Responsive release of DOX at the TME. Reproduced with permission from Wang et al. [187]. Copyright 2021, Elsevier.

due to degradation of Se-Se bonds when exposed to X-ray irradiation (Figure 14).

Multimodal responsive polymeric nanomedicines

In order to achieve better control for delivery of anti-tumor drugs, multiple responsive polymeric nanomedicines with high efficiency, intelligence, and collaborative therapeutic effects were developed; these conferred the ability not only to accurately control the release of different drugs under different conditions but also to reduce the dosage of different drugs while maintaining a synergistic effect [188].

PDT and magnetothermal combination have synergistic anti-tumor activity and induce ICD, resulting in tumor-specific immune response. Dong group synergistically enhanced the anti-metastatic efficacy of immunotherapy by combining immunogenic-nanoparticle-mediated PDT with magnetic hyperthermia [189]. Based on bullet magnetic mesoporous organic silica nanoparticles (M-MONs) embedded with photosensitizer Ce6, mesoporous organic silica rods with disulfide bonds grew asymmetrically on Fe_3O_4 nanospheres. The obtained M-MON@Ce6 nanoparticles were further coated

with breast cancer cell membranes to generate CM@M-MON@Ce6 for effective PDT and magnetothermal therapy. This treatment effectively triggered a strong anti-tumor immune response, which inhibited the distant metastasis combined with CTLA-4 checkpoint blockade.

Shi group developed upconversion nanoparticles (UCNP) as intelligent pH/ROS-responsive polymeric nanomedicines (Fe^{2+}@UCM-BBD) [190]. The acidic microenvironment of tumors induced DOX release and subsequent apoptosis of tumor cells and promoted the production of H_2O_2. Furthermore, the UCNP could convert 980 nm light to ultraviolet/visible light, which activated Ce6 and produced $^1O_2$. The ROS responsive diallyl sulfur olefins were cleaved by $^1O_2$, resulting in the release of Fenton reagent. Moreover, Guo group reported GSH and hypoxia dual-responsive nanomedicines. Hypoxia responsive dimeric azocalixarene (D-SAC4A) was mixed with GSH responsive disulfide-linked CPT (D-CPT) in equal proportions in water to assemble a polymeric nanomedicine (DSPNs) [191]. The tumor suppression rate of 16.7% with CPT alone was increased to 87.2% with this nanomedicine. Therefore, this GSH and hypoxia dual responsive nanomedicine greatly improved the anti-tumor efficiency of the chemotherapeutic drug (Figure 15).

Lei group designed a polymeric nanomedicine based on *Ganoderma lucidum* polysaccharides with pH and redox
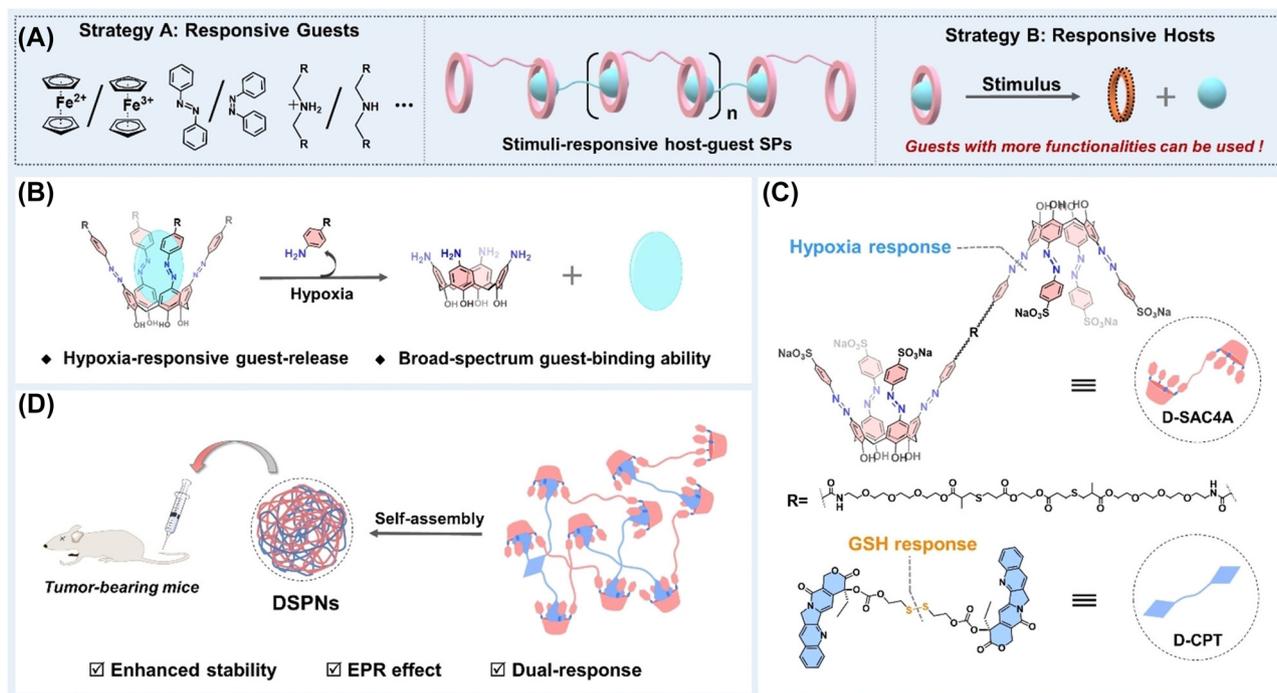
Figure 15: The design of dual responsive nanomedicines. (A) Two strategies for constructing nanomedicines. (B) Hypoxia responsive release behavior of azocalixarenes. (C) Structural formula of hypoxia responsive D-SAC4A and GSH responsive D-CPT. (D) Self-assembly of anti-tumor dual responsive DSPNs. Reproduced with permission from Yao et al. [191]. Copyright 2022, Wiley-VCH GmbH.

dual responsiveness [192]. In acidic environments, rutin was released to inhibit the activity of MMP. Dihydroartemisinin and 10-hydroxy CPT were released in a redox environment with a high concentration of GSH. The nanomedicine effectively suppressed tumor growth with reduced side effects.

With the development of precision nanomedicine, responsive polymeric nanomedicines have increasingly been used to remodulate the complex TME. In the future, polymeric nanomedicines will be designed more precisely to achieve high levels of targeting and hypersensitive responsiveness while modulating multiple TME components to achieve efficient cancer therapy and avoid toxicity to normal tissues.

Conclusions

The TME plays a key part in tumor progression by contributing to tumor growth, metastasis, immunosuppression, and resistance to multiple therapies. Therefore, modulation of the TME is crucial for tumor therapy. In this review, we have summarized the stimuli responsive polymeric nanomedicines developed in recent years to modulate the TME for improved cancer therapy, aiming to promote the design and innovation of polymeric nanomedicines for cancer therapy. As understanding of the TME increases, we expect that more potent polymeric nanomedicines will enter clinic settings in the future, providing new opportunities for cancer therapy.

Author contributions: Yuanzhen Su: Conceptualization, Investigation, Writing – Original Draft, Validation, Writing – Review & Editing. Guanyu Jin: Investigation, Validation, Writing – Review & Editing. Huicong Zhou: Investigation, Validation, Writing – Review & Editing. Zhaofan Yang: Writing – Review & Editing. Lanqing Wang: Writing – Review & Editing. Zi Mei: Writing – Review & Editing. Qionghua Jin: Writing – Review & Editing. Shixian Lv: Conceptualization, Writing – Review & Editing, Supervision, Project administration, Funding acquisition. Xuesi Chen: Conceptualization, Writing – Review & Editing, Supervision, Project administration, Funding acquisition.

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