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Review article

Efficacy tumor therapeutic applications of stimuli-responsive block copolymer-based nano-assemblies

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ABSTRACT

Block copolymers are composed of two or more blocks or segments with different chemical properties via various chemical bonds, which can assemble into nanoparticles with a "core-shell" structure. Due to the benefits of simple functionalization, superior drug-loading capacity, and good biocompatibility, various nano-assemblies based on block copolymers have become widely applied in the treatment of cancers in recent years. These nano-assemblies serve as carriers for anti-tumor bioactive, enhancing drug stability and prolonging their circulation time in vivo, which can reduce the toxic side effects of drugs and improve the therapeutic effect. However, the complex and heterogeneous tumor microenvironment poses challenges to the therapeutic efficacy of these nano-assemblies, having the result in the occurrence of drug resistance and the recurrence of tumors. Consequently, a diverse array of stimuli-responsive nano-assemblies has been devised in order to surmount these obstacles. This article provides a comprehensive overview of the utilization of stimuli-responsive nano-assemblies derived from block copolymers in the context of tumor treatment. The review summarizes block polymers responsive to internal stimuli (like ROS, redox, pH, and enzymes) and external stimuli (like light, and temperature), and discusses current challenges and prospects in this field, aiming to provide novel insights for clinical applications.

1. Introduction

Cancer is a serious disease that poses a significant health threat to humans. The main treatment methods for tumors include surgery, chemotherapy, radiation therapy, and immunotherapy. In recent years, Nanomedicine has played an important role against cancer due to its excellent drug-loading capacity and good biocompatibility [1]. There are several nanomedicines on the market, such as the liposomal doxorubicin Doxil, and nab-paclitaxel Abraxane [2]. Nanomedicine is commonly developed based on polymers, lipid materials, protein macromolecules, and inorganic materials. The block copolymer is synthesized by distinct polymer chains with different chemical properties via chemical linkages. When entering an aqueous solution, they could self-assemble into a "core-shell" nano-assemblies. The hydrophobic core can encapsulate various hydrophobic drugs, thereby enhancing drug solubility. The hydrophilic shell forms a protective barrier that reduces protein absorption in blood circulation and clearance by the reticuloendothelial system, ultimately prolonging the half-life of drugs [3,4]. By changing the variety and structure of blocks and the chemical bonding, we

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can regulate the physical and chemical properties of nano-assemblies, such as the particle size, shape, charge, and targeting. In recent years, it has been widely applied in anti-tumor therapy. The nano-assemblies can preferentially accumulate within the tumor tissue due to the enhanced permeability and retention (EPR) effect. The EPR effect arises from the increased vascular permeability in tumors due to the abnormal and leaky vasculature. Moreover, the impaired lymphatic drainage in tumors further prolonged the circulating of nano-assemblies within the tumor, which makes nano-assemblies serve as drug delivery systems for cancer treatment. Currently, there are three polymeric micellar nanomedicine drugs based on block copolymers available on the market: Genexol®PM, Nanoxel®M, and Paclical®. Genexol®PM. Genexol®PM is the first paclitaxel-loaded polymeric micelle based on the block copolymers mPEG-poly-D, L-lactide (PDLLA), approved for sale in breast and lung cancer. A phase II trial of Genexol®PM and gemcitabine that precise target patients suffer from advanced non-small-cell lung cancer(NCT00912639) and a phase II trial of doxorubicin and Genexol®PM in patients with advanced breast cancer(NCT01784120) were completed. Phase III trial to evaluate the efficacy and safety of Genexol®-PM compared to Genexol® in subjects with recurrent or metastatic breast cancer(NCT00876486) were completed. Nanoxel® M, a docetaxel PM formulation based on mPEG-PDLLA, was approved in 2012 against advanced breast cancer. Paclical received approval in Russia in 2015 for the treatment of ovarian cancer. Furthermore, several novel polymeric micellar nanomedicines based on block copolymers are currently undergoing various stages of clinical trials, such as NK012 based on Polyethylene glycol-polyglutamic acid (PEG-PGlu), and NK105 based on the Polyethylene glycol-poly(aspartic acid)(mPEG-*b*-P (Asp)).

However, the complex and highly heterogeneous tumor microenvironment poses significant challenges to the highly efficient delivery and therapeutic effect of nano-assemblies, leading to the occurrence of drug resistance and recurrence [5,6]. The tumor microenvironment (TME) refers to the internal environment that forms during tumor growth, incorporating tumor cells, surrounding fibroblasts, immune and inflammatory cells, glial cells, intercellular stroma, microvessels, and infiltrating biomolecules. The TME is closely associated with tumor development, progression, metastasis, and drug resistance. Additionally, it has emerged as a therapeutic target. The tumor microenvironment exhibits various characteristics, including hypoxia, redox, acidic microenvironment, abnormal tumor blood vessels, high interstitial pressure, lymphatic drainage obstruction, and remodeling of the extracellular matrix [7]. Firstly, the abnormal tumor blood vessels in the tumor microenvironment may hinder the efficient transport of nano-assemblies to the tumor cells. The high interstitial pressure and the high density of tumor cells also limit their penetration into the tumor tissue. Moreover, the vascular leakage, poor lymphatic drainage, and the remodeling of extracellular matrix such as fibrosis and hardening, seriously hinder the movement and diffusion of nano-assemblies, leading to insufficient penetration within the tumor and greatly compromising treatment efficacy [8]. Moreover, the acidic, hypoxia, and redox tumor microenvironment can cause nano-assemblies degradation, promote the invasion and metastasis of tumor cells, and increase their resistance to radiotherapy and chemotherapy. In addition, the acidic environment and abundant immune suppressive factors can weaken the immune system activation effect of nano-assemblies and inhibit the activity of immune cells, which reduces their ability to kill tumor cells and promote the invasion and metastasis of tumor cells [9]. Based on the characteristics of the tumor microenvironment, the stimuli-responsive block copolymer-based nano-assemblies have been designed as a promising method against tumors [10–12].

The block copolymer-based nano-assemblies are designed in response to the endo-stimuli such as redox, pH, enzyme, and hypoxia, and to the exo-stimuli such as Light, and temperature, in order to achieve effective drug release in specific sites and improved therapeutic effect [13]. The stimuli-responsive nano-assemblies have the following advantages. First, these nano-assemblies can undergo structural and physicochemical changes such as cleavage of chemical bonds and hydrophilic-hydrophobic transition in response to stimulation, which results in the instability of these nano-assemblies, followed by the targeted and highly efficient release of the drug in tumor sites. This also increases the killing efficiency of the tumor and reduces the toxicity and side effects. In addition, Due to the dense extracellular matrix of tumor tissue and elevated interstitial fluid pressure, the nano-assemblies cannot sufficiently penetrate the tumor tissue. Therefore, the nano-assemblies are designed to undergo size reduction or a positive/negative surface charge conversion, in order to let the nano-assemblies enter more easily into the tumor tissue and accumulate in the tumor cells. Moreover, some nano-assemblies achieve better biocompatibility and reduced clearance by the mononuclear phagocytosis system (MPS) in the blood circulation through the modification of hydrophilic blocks, such as polyethylene glycol (PEG), polybetaine, poly(2-oxazoline), and others. The stimuli trigger induced hydrolysis of the modification, resulting in a cascade that exposes biological molecules with specific targeting abilities, thus achieving effective tumor killing.

Our review displays the latest progress of stimuli-responsive nano-assemblies developed by block copolymers against tumors. These nano-assemblies have overcome challenges from the tumor microenvironment to achieve high selectivity, enhance cellular uptake and permeability within tumor cells, improve cytotoxicity, and combine multiple cancer treatment modalities while reducing toxicity and drug resistance.

2. Endo-stimuli-responsive nano-assemblies

2.1. Redox- responsive nano-assemblies

Studies demonstrate that the production of oxygen species (ROS) in tumor cells is higher than that in normal cells due to their abnormal metabolism [7]. The elevated ROS levels in the tumor microenvironment not only damage biomacromolecules like DNA, RNA, and proteins but also trigger lipid peroxidation. Tumor cells induce oxidative stress and engage multiple signaling pathways, such as NF-κB, TGF-β, JAK2-STAT1, and PI3K/Akt/ERK, to trigger the activation of oncogenes and suppression of tumor suppressor genes. This phenomenon further facilitates tumor occurrence, development, and metastasis. Meanwhile, to reduce ROS-induced damage, tumor cells generate a large amount of reducing substances, mainly glutathione (GSH). The concentration of GSH in the cytoplasm of tumor cells ranges from 2 to 10 mmol/L, which is approximately 1000 times higher than the extracellular GSH

concentration (2–20 μmol/L). The level of GSH in tumor cells is several times higher than that in normal cells [14]. Recent studies have found that the high concentration of GSH enhances the antioxidant stress response and drug resistance of tumor cells. Based on the characteristics of high ROS and high GSH in the tumor microenvironment, some redox-responsive nano-assemblies based on block copolymers have been constructed to regulate the oxidative-reductive imbalance of tumor cells and improve the effectiveness of tumor treatment.

The block copolymers are mainly designed to contain specific functional groups or linkages, which could be selectively cleaved or undergo structure change when exposed to the reductive environment in the tumor. ROS-responsive functional groups introduced into block copolymers include thiol-ketone (TK), polysulfide, boronic acid ester [15], anthocyanin, hoof, and ferrocene [16–18]. GSH-responsive chemical bonds include disulfide bonds [19–21], thioether bonds, diselenide bonds [22], selenium ether bonds [23, 24], sulfur-ketone bonds [25,26], and succinimide-thioether bonds [27]. The block copolymers-based nano-assemblies undergo structure changes upon exposure to redox, delivering drugs rapidly and efficiently in specific tumor sites. Afterward, the accumulation of anti-cancer drugs in tumor cells and efficacy increases [28]. As an example, Feng Xu and co-workers synthesized redox-responsive micelles self-assembled of the amphiphilic block copolymers poly(N-acryloylmorpholine)-*block*-poly(2-acryloyloxyethyl ferrocene-carboxylate) (PACMO) (PACMO-*b*-PAEFC). The reductive ferrocene groups of hydrophilic blocks can be quickly oxidized to hydrophilic ferrocenium in response to mild oxidation, which increases hydrophilicity and leads to swelling of the micelles, followed by the targeted release of the encapsulated Paclitaxel in tumor sites (Fig. 1) [16]. Another study exhibits a quinone propionic acid (QPA)--containing amphiphilic Copolymer Micelles polyQPA-mPEG 750, which undergoes solubility reversal and destabilized due to the release of pendant QPA groups exposed to the redox environment in cancer [29]. Runhai Chen et al. constructed nanoparticles that respond to both reactive ROS and GSH based on amphiphilic block copolymer with disulfide-linked phenylboronic ester groups. The particles show on-demand drug (DOX) release, effective killing effect against tumors, and lower side effects in the presence of ROS and GSH [15].

There are some problems to be addressed. Firstly, the redox-responsive block copolymers should be designed to remain relatively stable in the physiological redox environment while selectively responding to the tumor's redox conditions. Achieving this fine balance of stability and responsiveness can be challenging and requires extensive optimization. Furthermore, the intracellular redox condition within tumors can significantly differ from the extracellular environment. Designing redox-responsive block copolymers that can efficiently penetrate cell membranes and effectively respond to the intracellular compartment adds further complexity. Incorporating additional external or intracellular responsive moieties to redox responsive block copolymers has been a novel solution to overcome the challenges. Furthermore, the redox conditions in tumors can dynamically change over time due to various factors, including treatments and the tumor's adaptive responses. This dynamic nature of the tumor microenvironment poses challenges in maintaining the desired response of the redox-responsive copolymers over prolonged periods.

2.2. *pH-responsive nano-assemblies*

The increasing metabolic activity in tumor cells causes the elevated level of lactic acid and carbonic acid, contributing to an acidic tumor microenvironment. The acidic tumor microenvironment is one of the important characteristics of a solid tumor microenvironment, with a range of approximately 6.0–7.0, while the pH of normal tissues and blood vessels is around 7.4 [7]. The acidic tumor microenvironment can inhibit immune cell activity, weaken the immune system's killing effect, enhance tumor drug resistance, and influence tumor metastasis and invasion [30]. To overcome these challenges, it is of great significance to construct pH-responsive nano-assemblies based on block copolymers to promote treatment efficacy. These block copolymers frequently undergo

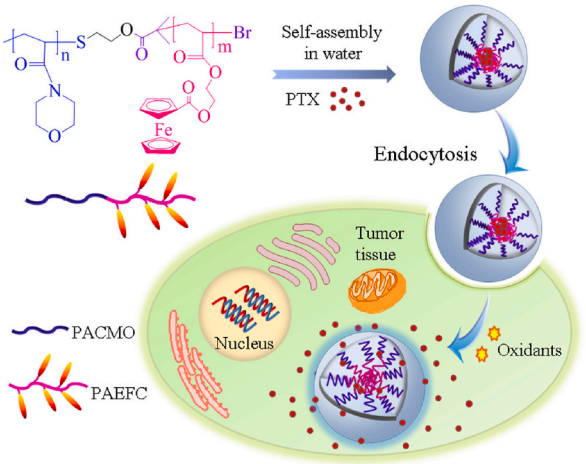


Fig. 1. Cumulative paclitaxel release from typical PTX-loaded $PACMO_{95}$-b-$PAEFC_{25}$ copolymer micelles at a temperature of 37 °C triggered by (A) three different oxidants, H_2O_2, NaClO, and $KMnO_4$, at pH 5.8 and (B) H_2O_2 with various concentrations at pH 7.4 and 5.8. (reprinted with permission from Ref. [16] Copyright 2017, American Chemical Society).).

conformational changes or exhibit pH-dependent solubility, enabling effective drug release within the lower pH environments of tumor cells and organelles like lysosomes. It helps the reduction of side effects and improvement of the efficacy of the drugs.

The most commonly used strategy is to introduce ionizable or acid-cleavable groups to block copolymers. Acid-cleavable linkages such as Acetal, ketal, Schiff-base, or orthoester linkages are widely used to synthesize pH-responsive block copolymers [31,32]. These acid-cleavable linkages remain stable at physiological pH but degrade when exposed to acidic conditions, resulting in the structural changes of nano-assemblies and drug release. For example, a study constructed pH-responsive amphiphilic diblock copolymers containing imine linkage. It exhibited effective and rapid release of encapsulated drug at the acidic pH of 5.5 [33].

In addition, some block copolymers are functionalized with ionizable chemical groups such as carboxylic, amino, and nitrogen, which can undergo positive and negative charge conversion in acidic environments. The commonly used anionic polymers involve polyurethane and sulfonamide, poly(acrylic acid) (PAA), polyethylenimine (PEI), poly(β-amino ester) (PAE), chitosan, and polyhistidine. Xiaoqing Cai et al. designed pH-sensitive biodegradable polymer PAE-containing block copolymers. The size of self-assembled micelles was decreased and zeta potential varied in pH 5.5 due to the protonation of PAE, which improves the release and retention time of encapsulated drugs in tumor cells [34]. Jie Kong and partners constructed a pH-responsive amphiphilic block copolymer composed by the polymers the poly(2-(diisopropylamino) ethyl methacrylate) (PDPA) and poly(2-(dibutylamino) ethyl methacrylate) (PDBA) with high sensitivity to pH from 7.4 to 6.3, which could transit from hydrophobic to hydrophilic. Vitro and in vivo studies confirmed the increased efficiency of drug release [35].

Moreover, the acid-cleavable groups mainly respond to intracellular acid environment such as the endosomal/lysosomal pH. Studies have demonstrated that maleic acid amide derivatives can be cleaved at the acidity of a tumor (pH ≈ 6.5–7.0) [36]. Xian-Zhu Yang et al. constructed pH-responsive nanoparticles S-NP based on PEGylated anionic block copolymers $mPEG_{45}$-*b*-$PAEP_{75}$--Cya-DMMA containing the maleic acid amide bond(Fig. 2A). Upon entering in tumor tissue, the pH-responsive linkages cleave that leading to the deshielding of the PEG layer from S-NP and transition of charged surface. The cellular uptake of nanoparticles is highly improved(Fig. 2B) [37]. He Wang et al. utilized acid-cleavable dimethylmaleic anhydride (DA) protection group to modify the block copolymers-based nano-assemblies, which prolong its circulation in the blood and increase its accumulation into the tumor sites. Upon acidic extracellular environment of the tumor (pH ≈ 6.5), the DA-conjugated amides undergo hydrolysis that leads to the charge reversal of nano-assemblies with mitochondria-targeting, which prolongs the circulation of nano-assemblies in the blood and increases its accumulation into the tumor sites [21]. A study fabricated a dual-pH responsive block copolymer-DOX conjugate with reactive aldehyde functionality. The nano-assemblies combined extracelluar acid microenvironments(pH 6.5)-induced charge conversion caused by protonation of PDPA block and pH-triggered cleavage of imine bond in tumor cells, which improved the cell internalization of nano-assemblies and the drug release of DOX in tumor site [38].

However, the pH levels in tumors exhibit variations both between different tumor types and within distinct regions of the same tumor. This heterogeneity poses a challenge for pH-responsive block copolymers, as they may not be able to effectively respond to all

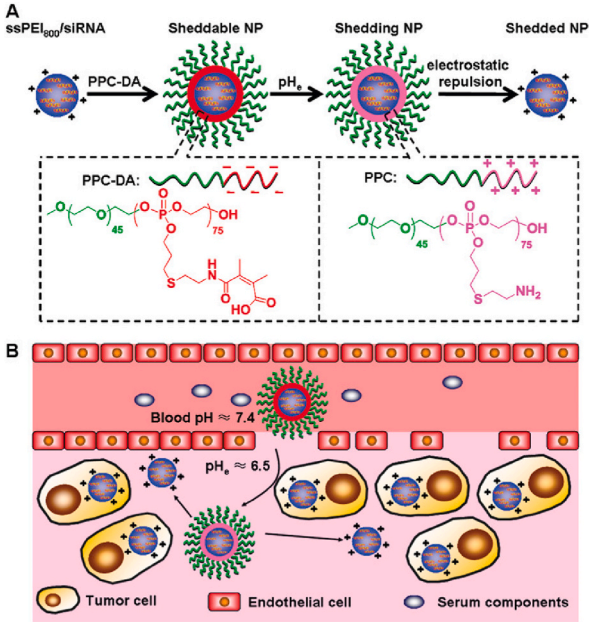


Fig. 2. (A) Shielding and deshielding of the positively charged ssPEI800/siRNA nanoparticles by the PEG shell in the acidic environment of the tumor. The ssPEI800/siRNA nanoparticles are coated with the PEGylated anionic polymer PPC-DA to form the sheddable nanoparticles (NP). At the extracellular pH (pHe) of tumor tissue, the sheddable NPs deshield the degraded PEGylated polymer layer (PPC) and re-expose the ssPEI800/siRNA nanoparticles (shedded NP). (B) Schematic illustration of the stealth property and promoted tumoral cell uptake of sheddable nanoparticles. The sheddable NPs minimize nonspecific interactions with serum components and deshield the PEG layer at the tumor site to re-expose the positive charges, leading to promoted cell internalization. (reprinted with permission from Ref. [37], Copyright 2012, American Chemical Society).).

the acidic environments within the tumor, leading to variations in drug release and targeting efficiency. In addition, the stability and release properties of the pH-responsive block copolymers-based nano-assemblies are crucial for their performance in vivo. The challenge depends on how to achieve a balance between their stability and the ability to respond to acidic pH conditions within the tumor environment.

2.3. Enzyme- responsive nano-assemblies

Compared with normal cells, tumor cells secrete excessive enzymes, such as hyaluronidases. Studies confirmed that the growth, invasion, and spreading of tumor cells are associated with these overexpressed enzymes. Various enzyme-responsive nano-assemblies constructed by block copolymers have been studied.

The commonly used strategy is to construct block copolymers containing blocks that can interact with enzymes specifically, thereby inducing structural changes under enzyme stimulation and achieving targeted drug release to precisely kill tumor cells. Firstly, the nano-assemblies are often designed with enzyme-sensitive linkers that can be selectively cleaved by tumor-associated enzymes or enzymes overexpressed in cancer cells [39]. The cleavage of these linkers results in the disassembly or degradation of the copolymer, facilitating therapeutic agents delivery. Ashutosh Barve et al. developed amphiphilic block copolymers composed of PEG, matrix-metallo proteinase-2 (MMP-2)-responsive linker, and cholesterol. The self-assembled nano-assemblies can be degraded by MMP-2, causing the improved release of encapsulated cabazitaxel and cellular uptake [40]. Lesan Yan and co-workers synthesized block co-polymers containing trimethyl-locked benzoquinone diol groups, assembling to nano-micelles and delivering anti-tumor drugs doxorubicin (DOX). Upon exposure to quinone oxidoreductase 1 (NQO1) overexpressed in tumor cells, the nano-micelles underwent disintegration and effective drug release. In vitro studies showed the specific drug release of the nano-assemblies in the presence of NQO1 enzymes [41]. In addition, enzymes trigger induced hydrolysis of the modification of the nano-assemblies based on the block copolymers and cascade to expose biological molecules with a specific target ability to improve cell internalization and achieve effective tumor killing. For instance, Wendong Ke and co-workers constructed enzyme-responsive nano-assemblies with peptide-linked and PEGylated block copolymers. The peptides can be cleaved in response to MMP-2, leading to the dePEGylation and exposure of RGD ligands on the surfaces of the nano-assemblies to enhance cellular internalization and improve drug delivery efficiency [42]. Moreover, some block copolymers functionalized by moieties specifically hydrolyzed by enzymes can undergo charge transition when exposed to specific enzymes, which will improve transcytosis ability of nano-assemblies and lead to deep tumor penetration. A study manufactured aminopeptidase (APN)–responsive block copolymer-drug conjugates to deliver anti-tumor drugs, which can be specifically hydrolyzed by the APN in tumors and that leads to positive charges transition of the polymer. The enzyme-triggered charges transition helps improve the transcytosis, accumulation, and deep penetration of nano-assemblies in tumors [43].

Enzyme-responsive nano-assemblies based on block copolymers have emerged as promising methods to kill tumors. However, there are still some problems that remain to be solved. Firstly, some enzymes specifically highly expressed in tumors are also found in normal tissues. Ensuring safety and reducing side effects of enzyme-responsive nano-assemblies based on block copolymers is of great significance. Strategies such as multi stimuli-responsiveness or cascade-responsiveness may be required to address this challenge. Moreover, tumors exhibit heterogeneity in enzyme expression, both between patients and within the same tumor. Designing personalized enzyme-responsive nano-assemblies based on block copolymers that can accommodate this variation is challenging.

2.4. Hypoxia- responsive nano-assemblies

The oxygen levels in tumors are lower than normal tissue levels caused by rapid proliferation of tumor cells and abnormal blood vessel networks that oxygen is difficult to diffuse [44]. Hypoxic tumor cells are usually distant from blood vessels, making it difficult for them to reach them. Hypoxic environments also promote the invasion and metastasis of tumor cells and increase their tolerance to radiotherapy and chemotherapy [45]. To enhance the effectiveness of tumor treatment, many studies have designed hypoxia-responsive nano-assemblies based on block copolymers to regulate tumor oxygen levels.

Commonly used strategy involves introducing hypoxia-sensitive functional groups or moieties to the block copolymers. These moieties often undergo redox reactions in response to low oxygen levels, resulting in changes in polymer conformation or degradation. These moieties include nitroimidazoles, quinones, and disulfide bonds. By incorporating these moieties, the polymer can respond to hypoxia by triggering effective drug release. As an example, Qinhao Zhou and co-workers utilize hypoxia-responsive nitroimidazole linkages to combine anti-tumor drugs camptothecin (CPT) and block copolymers PEG-*b*-P(CPTNMA-*co*-TPPMA). The nitroimidazole linkages can be cleaved under low oxygen, followed by the release of free CPT. The in vitro and in vivo studies displayed that hypoxia-responsive release of free CPT efficiently suppresses the growth of HeLa tumors [46].

In addition, some hypoxia-responsive block copolymers are designed to contain prodrugs of anticancer drugs that are selectively activated under hypoxia, exerting an antitumor effect while remaining non-toxic to normoxic regions. Zhishen Ge et al. fabricated a hypoxia-sensitive block copolymer prodrugs, based on PEG-b-PLG with metronidazole (MN) derivative. The in vivo studies exhibited a high antitumor efficacy for hypoxia-specific radiotherapy and chemotherapy [47]. Jianyang Zhao and co-workers constructed hypoxia-responsive nano-assemblies based on block copolymers grafted with Tirapazamine derivatives((TPZD) that can be activated and show anticancer cytotoxicity in low levels of oxygen. The in vitro study exhibited higher cytotoxicity to hypoxic cancer cells than to normoxic cancer cells [41].

Tumor hypoxia levels can vary within tumor tissues. The heterogeneous distribution limits the therapeutic efficacy. Recent studies have developed methods to settle the problems. The main strategy is combining hypoxia-activitable prodrugs chemotherapy and photodynamic therapy (PDT) which can consume oxygen in tumor sites to induce a hypoxia environment. Zhangting Xu et al. utilize

PDT of chlorine e6 (Ce6) to further amplify the hypoxia condition within the tumor. The study constructed Ce6-loaded linear-dendritic block copolymer poly [(ethylene glycol) methyl ether methacrylate] (POEGMA) -Dox prodrug. Improved killing effect and restrained transfer of tumor cells were observed in vivo studies [48]. Based on the hypoxia-responsive azobenzene-centered copolymers, the self-assembled nano-assemblies release DOX in response to hypoxia, leading to improved antitumor efficacy [49]. Moreover, the external X-ray stimulus helps to improve hypoxia condition in tumor site to activate TPZ-containing block copolymers prodrugs, which enhance tumor killing and reduce side effects. However, physiological hypoxic microenvironment exists in a variety of normal tissues. Stimuli-responsive systems respond only to hypoxic regions while maintaining stability in normal tissues is a significant challenge.

3. Exo-stimuli-responsive nano-assemblies

3.1. Light- responsive nano-assemblies

Due to the easy availability and remote precise control of light stimulation, it has been widely utilized as a common external stimulus. In recent years, various kinds of light-responsive nano-assemblies are devoted to research. The nano-assemblies undergo changes in morphology and physiological characteristics (such as redox potential, solubility, etc.) when the photosensitive molecules of block copolymers respond to light stimulation with specific wavelength, intensity, and irradiation time. The light-responsive nano-assemblies bring the advantages of effective drug release at targeted tumor sites to improve the accumulation and tumor-killing effect of the nano-assemblies.

The main strategy is to introduce specific photosensitive structures into block copolymers which can undergo isomerization and dissociation under ultraviolet (UV) or visible light stimulation. Photosensitive Structures frequently observed in these light-responsive block polymers include *o*-nitrobenzyl (ONB) esters, azobenzene, etc. As an example, Nagendra Kalva et al. constructed light-responsive nano-assemblies using block copolymers functionalized with light-responsive ONB ester group. In vitro, studies show the improved cellular accumulation and intracellular drug release in colon tumor cells [50]. Yu-Lun Lo and co-workers synthesized block copolymers containing adjacent UV light-sensitive ONB ester, which can be cleaved at 365 nm UV light and following lead to the improved release of DOX [51].

The antitumor effect depends on penetration depth of light in tumor tissues. UV lights have difficulties in penetrating deeply into the tissue due to scattering and absorption by the skin and fatty tissue, which limits its application as a light stimulus. Near-infrared (NIR) light has the advantages of strong tissue penetration and minimal tissue damage compared to ultraviolet and visible light. The NIR-responsive nano-assemblies based on block copolymers are well-explored over recent years. However, most photosensitive moieties-containing block polymers cannot be activated by NIR light. Therefore, doping reagents that can in situ convert NIR to UV radiation seems a solution to this problem. Many studies introduce upconverting nanoparticles (UCNPs) into block copolymers-based nano-assemblies to convert near-infrared (NIR) light to UV light, which could further activate photosensitive moieties (Fig. 3) [52,53]. For example, Lifang Wang et al. synthesized photosensitive block copolymers PCL-ONB–SS–PMAA in which novel core–shell UCNP and cancer drugs DOX were encapsulated. The core–shell UCNPs can emit UV light at 350 nm, leading to the cleavage of the ONB linkage and degradation of nano-assemblies by NIR irradiation at 980 nm to improve the drug release at the tumor site for enhanced antitumor efficacy. In vivo studies in A549 tumor-bearing mice confirmed that the UCNPs and DOX-containing nano-assemblies had a significant inhibitory effect on tumor growth under 980 nm diode laser [52].

Moreover, Ruthenium (Ru) complexes emission is in the visible or NIR region and exhibits an antitumor effect. Ru complexes have been utilized to construct NIR responsive block copolymers-based nano-assemblies [54,55]. For example, Guangli He et al. synthesized tetrahydrocurcumin Ru-based photocage (THCRu)-containing block copolymers which were photoactivated upon exposure to 760 nm NIR light. The self-assembled nanoparticles exhibited light-responsive release and improved efficacy of anticancer treatment [55]. Ru complexes-containing block copolymers have advantages of strong photostability, high generation of $^1O_2$, and high two-photon absorption characteristics, which shows promising methods for light-responsive antitumor treatment. However, NIR-responsive block copolymers-derived nano-assemblies are limited by slow drug release kinetics and introduction of cytotoxic UCNP and Ru, which

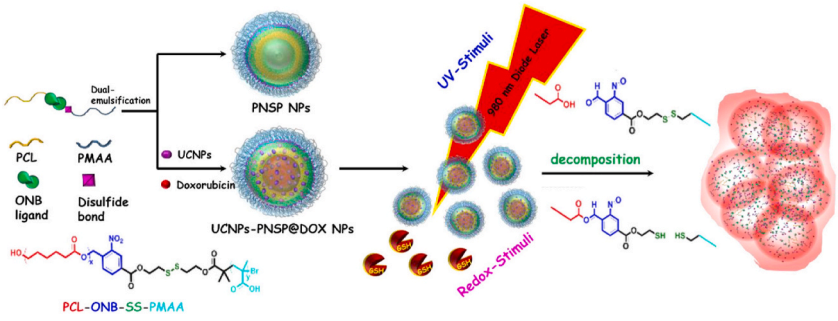


Fig. 3. Illustration of Poly(ε-caprolactone)-ONB–SS–poly(methacrylic acid)-formed Polymersome Nanoparticles (PNSP NPs) Encapsulated with Core–Shell Upconversion Nanoparticles (UCNPs) and Doxorubicin (DOX) (UCNP-PNSP@DOX NPs) and Responsiveness to External Stimuli. (reprinted with permission from Ref. [52], Copyright 2021, American Chemical Society).).

remain further research in the future.

3.2. Temperature- responsive nano-assemblies

Temperature is one of the common external stimuli, and in recent years, many temperature-responsive nano-assemblies have been developed. By using block copolymers containing thermos-responsive structures that have adjustable phase transition temperatures, the nano-assemblies can undergo temperature-responsive drug release and targeted killing of tumor cells [56]. Commonly used temperature-sensitive polymers include poly(N-isopropylacrylamide) (PNIPAM), poly(γ-benzyl-*l*-glutamate) (PBLG), and elastin-like protein polymers [57,58]. They undergo reversible hydrophobic-hydrophilic changes during a lower critical solution temperature (LCST) transition, allowing the block copolymers-derived nano-assemblies to undergo reversible expansion-contraction or disintegration, enabling controlled drug release. Surapaneni SG and co-workers constructed temperature-responsive nano-assemblies based on block copolymers containing poly(N-vinylcaprolactam) (PVCL) with a transition temperature of 41 °C. It was observed that nano-assemblies permeability was increased at 41 °C. The in vitro studies observed that the cellular uptake of DOX-loading nano--assemblies significantly increased at hyperthermia condition of 41 °C [58]. In addition to temperature, external stimuli such as light, magnetic fields, or ultrasound can be utilized to trigger or enhance the temperature-responsive behavior of the copolymers. This can offer spatiotemporal control over drug release and improve targeting capabilities. Zihao Zhou's group manufactured temperature and light dual responsive block copolymers by crosslinking PNIPAM with propyleneacylalkyl-4-azobenzoate (PAzoHPA) and the LCST reach 37 °C near normal body temperature. These dual-responsive can lead to a targeted and precise release of PTX and improved anticancer activities [59]. However, the copolymers should exhibit a sharp phase transition at the desired temperature, facilitating rapid drug release upon heating. Achieving a fast and reversible response to temperature changes is vital for efficient drug delivery.

4. Dual(muti)-stimuli-responsive nano-assemblies

Block copolymers with single responsiveness face challenges in achieving desired therapeutic effects in complex physiological microenvironments and heterogeneous tumor microenvironments in some cases. Consequently, block copolymers-based nano-assemblies with dual or multiple responses have been designed for individual and precise antitumor treatment [60]. The block copolymers with multi-stimuli-responsiveness contain two or more functional moieties that respond to specific stimuli. The response of muti-stimuli can be designed as simultaneous or cascade degradation, resulting in synergistic triggering in order to improve the sensitivity and specificity of anticancer treatment [61]. Moreover, it can combine different treatment methods and construct a multi-functional platform for diagnosis and treatment. For instance, Jiajia Tan et al. construct the amphiphilic block copolymers-based nanoparticles when encountered external stimuli light, endo trigger GSH and esterase (Fig. 4a) [62]. Upon stimulation, nanoparticles

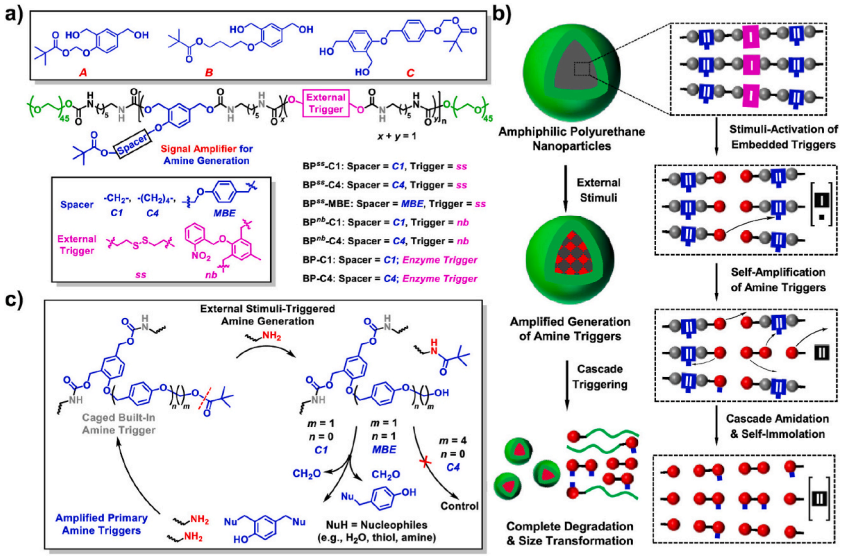
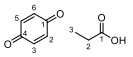
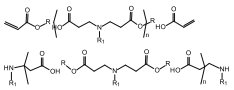
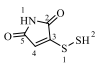
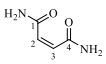
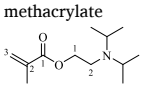
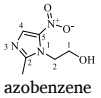
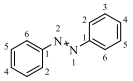


Fig. 4. Accelerated backbone degradation of amphiphilic polyurethane nanoparticles in physiologically relevant aqueous media via external stimuli-triggered activation and cascade self-amplification of built-in trigger signals (i.e., primary amine moieties). (a) Chemical structures of monomers A–C and amphiphilic block copolymers (BCPs) with the hydrophobic polyurethane block containing stimuli-sensitive linkages (ss and nb) and signal-amplifying units. (b) Upon triggering with external stimuli including reductive milieu, UV light, and esterase, core–shell micellar nanoparticles of these BCPs exhibit accelerated degradation features driven by activation and cascade self-propagation of embedded primary amine triggers. (c) Proposed mechanism of signal amplification in a positive feedback manner upon external stimuli-triggered liberation of reactive primary amines, which undergo further amidation reactions with pivalate ester linkages; the subsequent self-immolative elimination process leads to backbone scission and generates 2-fold primary amines. (reprinted with permission from Ref. [62], Copyright 2021, American Chemical Society).).

undergo a series of degradation events, that particles size become smaller and surface properties convert from hydrophobic to hydrophilic (Fig. 4b). Consequently, the delivered bioactive agents could be lastingly released and accumulated in cancer cells, which produces selective killing effect. Fig. 4c displays the self-propagating degradation behavior of the nanoparticles self-assembled by

Table 1
Characteristics of stimuli-responsive block copolymer-based nano-assemblies.

Stimuli		Sensitive Moiety	Block copolymers	Cargo	Ref
Endo-Stimuli	Redox	ferrocene groups 	PACMO-b-PAEFC	PTX	16
		disulfide linkage S–S	PEG-b-PBS	DOX	15
		quinone propionic acid 	polyQPA-PEG$_{750}$	PTX	29
	pH	PAE 	Cur-P123-PAE	Curcumin	34
			PEG-b-poly(DPA-*co*-DTM), PEG-*b*-poly(DBA-*co*-DTM)	DOX	35
					
		maleic acid amide bond. 	mPEG45-b-PAEP75-Cya-DMMA	siRNA	37
		poly(2-(diisopropylamino)ethyl methacrylate 	PDPA-b-P(FPMA-co-OEGMA)	DOX	38
	Enzyme	MMP2-responsive peptide(PLGVRK)	cholesterol-PLGVRK-PEG$_{2000}$, cholesterol-PEG$_{3000}$-DUPA	Cabazitaxel	40
		NQO1-responsive trimethyl-*p*-benzoquinone 	PEG-PTU-PEG	DOX	41
	Hypoxia	nitroimidazole 	PEG-b-P(CPTNMA-co-TPPMA)	CPT	46
		Metronidazole 	PEG-b-P(LG-g-MN)	DOX	47
		azobenzene 	POEGMA-b-PCL-Azo-PCL-b-POEGMA	DOX and chlorine e6	49
Exo-Stimuli	Light	*o*-nitrobenzyl 	PCL-ONB–SS–PMAA	DOX and UCNP	52
		acetonitrile	MPEG-b-PCPH- THCRuCl	Ru-based photocage	55
	Temperature	poly(N-vinylcaprolactam) 	PVCL-b-PLL	Dox	58
		poly(N-isopropylacrylamide) 	(P(NIPAM-co-DMAA)-b-PAzoHPA)	PTX	59

amphiphilic copolymers in the presence of external stimuli light and endo trigger GSH and esterase. In vitro studies observed efficient internalization of micellar nanoparticles in 4T1 and NIH3T3 cells. Xu Jie et al. fabricate the pH-responsive, GSH-responsive, and ROS-responsive nano-assemblies Poly(ferrocenes) (BP ^{nbs}-Fc). Acidic pH triggers polymer chain's degradation, followed by the release GSH-reactive moieties and aminoferrocene, which can synergistically enhance cellular oxidative stress and chemodynamic therapy (CDT) efficacy. In vivo studies observed the elevated tumor accumulation, sustaining tumor retention of nano-assemblies at tumor site, and high therapeutic effect. At day 28 of treatment, only 40% of the mice survived in the control group and 100% in the BP ^{nbs}-Fc group [63]. However, these multi-stimuli-responsive block polymers are designed with complex structures and multiple mechanisms, which pose challenges of difficult synthesis and poor controllability to different stimuli. Besides, the levels of specific stimulus may vary within individuals and tumors during the course of antitumor treatment. Therefore, it is of great importance to construct multi-stimulus-responsive block copolymers that can be dynamically regulated to achieve precisely controlled drug delivery.

5. Conclusions and perspectives

Stimuli-responsive nano-assemblies based on block copolymer are increasingly used for targeting killing cancer cells, offered a new delivery strategy for various bioactives, such as chemotherapeutic drugs, active gene fragments, and immune enhancers. Paclitaxel, vincristine, and camptothecin are frequently used phytoconstituents loaded by nano-assemblies for cancer therapy [26,41,46,48,58]. Phytoconstituents are natural bioactive compounds extracted from plants, such as alkaloids, terpenoids, polyphenols, curcuminoids, and quinones. While these phytoconstituents-load nano-assemblies hold promise as cancer treatments, further research and clinical studies are needed to explore their antitumor effect, optimize dosages, and evaluate their efficacy and safety in specific cancer types.

The review concentrates on a summary of latest progress in stimuli-responsive block copolymer-based nano-assemblies against tumors. These nano-assemblies are triggered by the tumor microenvironments and external stimuli such as light and temperature. Typical tumor microenvironments, characterized by weak acidic pH, redox condition, overexpression of specific enzymes, and low oxygen level, are utilized for fabricating stimuli-responsive nano-assemblies. Table 1 summarizes the strategies employed for stimuli-responsive nano-assemblies from block copolymers. These systems enable triggered targeted release of anticancer drugs, improved penetration ability into tumors, and enhanced antitumor efficacy.

However, there are still some problems to be processed for the application of the stimuli-responsive nano-assemblies from block copolymers in clinic. Firstly, the heterogeneity of tumor tissues to some extent brings about uncertainty in antitumor effects and significant differences in efficacy between individuals and tumors. It is important to the composition of block copolymers regarding the characteristics of tumors in order to achieve precise targeted killing of tumor cells. Additionally, there has been extensive research in recent years on block copolymers with multiple stimuli. However, the synthesis of the block copolymers with specific properties and regulation of the self-assembly process is complex and challenging. The delivery, biodistribution, biodegradation, and therapeutic mechanisms of the block copolymers remain to be explored. Ensuring the uniformity and repeatability of nano-assemblies and decreasing fabrication costs is crucial. Further research is crucial to address these challenges and maximize the potential of stimuli-responsive nano-assemblies from block copolymers in clinical practice.

Data availability statement

No data was used for the research described in the article.

CRediT authorship contribution statement

Jie Zhou: Writing – review & editing, Writing – original draft, Data curation, Conceptualization. **Rui Yang:** Writing – review & editing, Writing – original draft, Data curation, Conceptualization. **Yu Chen:** Writing – review & editing, Writing – original draft, Funding acquisition, Conceptualization. **Daozhen Chen:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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