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REVIEW

Advances of Stimuli-Responsive Amphiphilic Copolymer Micelles in Tumor Therapy

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Abstract: Amphiphilic copolymers are composed of both hydrophilic and hydrophobic chains, which can self-assemble into polymeric micelles in aqueous solution via the hydrophilic/hydrophobic interactions. Due to their unique properties, polymeric micelles have been widely used as drug carriers. Poorly soluble drugs can be covalently attached to polymer chains or non-covalently incorporated in the micelles, with improved pharmacokinetic profiles and enhanced efficacy. In recent years, stimuli-responsive amphiphilic copolymer micelles have attracted significant attention. These micelles can respond to specific stimuli, including physical triggers (light, temperature, etc). chemical stimuli (pH, redox, etc). and physiological factors (enzymes, ATP, etc). Under these stimuli, the structures or properties of the micelles can change, enabling targeted therapy and controlled drug release in tumors. These stimuli-responsive strategies offer new avenues and approaches to enhance the tumor efficacy and reduce drug side effects. We will review the applications of different types of stimuli-responsive amphiphilic copolymer micelles in tumor therapy, aiming to provide valuable guidance for future research directions and clinical translation.

Keywords: polymer micelles, stimuli-responsive, tumor therapy, delivery system

Introduction

Malignant tumor remains one of the leading causes of death in the 21st century[1] regardless of tremendous developments in recent years. Surgical resection serves as the cornerstone for the treatment of malignant solid tumors, complemented by chemotherapy, radiation therapy, phototherapy, and immunotherapy to enhance therapeutic efficacy. However, the clinical benefit is still unsatisfactory due to the limited therapeutic efficacy and severe side effects. For example, chemotherapy primarily relies on systemic drug administration, resulting in non-specific biodistribution of the chemotherapeutics within the body, indiscriminately targeting both tumor and healthy tissue cells.[2] As such, treatment outcomes are often disappointing due to severe side effects. Besides, biopharmaceuticals such as proteins, antibodies, and nucleic acids are often deactivated and degraded before reaching their intended disease site.[3,4] Additionally, intrinsic or acquired multidrug resistance (MDR) in certain types of cancer cells further diminishes therapeutic effectiveness.[5,6]

The integration of nanotechnology with biomedicine has led to the emergence of novel drug delivery systems designed to improve therapeutic outcomes while minimizing damage to normal tissues. These nanoparticles have some common advantages including enhanced solubility of poorly soluble anticancer drugs, prolonged circulation time and decreased uptake by the reticuloendothelial system (RES). Besides, the nanoparticles can protect the encapsulated drugs from enzymes and metabolic processes in the blood. Moreover, they can selectively accumulate at tumor sites[7] through the enhanced permeability and retention (EPR) effect and active targeting via ligand modification, thus enhancing therapeutic efficacy and minimizing adverse effects. And varieties of nanogranule-based delivery systems have been ingeniously crafted and have achieved successes across a spectrum of outcomes. These systems are capable of delivering multiple drugs simultaneously to the tumor site. Moreover, therapeutic nanomedicines can carry both therapeutic agents and diagnostic agents, enabling both antitumor efficacy and imaging capabilities.[8] These advancements span a wide array of pioneering platforms, such as

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liposomes, micelles, exosomes, inorganic particles and amphiphilic block copolymers. For example, liposomes have demonstrated promising potential due to their biocompatibility and proficiency in penetrating biological barriers, and some liposome-based delivery system has been approved to treat cancer.[9,10] And inorganic particles, distinguished by their adaptable physical and chemical characteristics along with the potential for multifunctional modifications, signify yet another frontier in the landscape of advanced delivery systems.[11,12]

Amongst the above mentioned nanocarriers, amphiphilic block copolymers, featuring an assortment of hydrophobic and hydrophilic segments—commonly including polyethylene oxide—exhibit the capability to self-assemble in aqueous environments into structures akin to micelles or niosomes. Amphiphilic block copolymers can form polymer micelles (PMs) or polymer vesicles (polymersomes). Taking polymersomes as an example, they boast a surface area-to-membrane thickness ratio that is notably lower than that of most nanoparticles, hence imparting them with superior flexibility and reduced surface tension. As a consequence, they are more deformable and can more easily pass through the constricted barriers.[13] Polymersomes can emerge through the self-assembly process of a variety of amphiphilic block copolymers, encompassing diblock and triblock copolymers with diverse architectures such as ABA, BAB, or ABC configurations. Here, A and C denote hydrophilic blocks with distinct chemical compositions, B signifies the hydrophobic block, and complex multiblock copolymers with linear or grafted blocks are also included. The attributes of polymersomes, including size and morphology, are finely tunable by manipulating the hydrophobic/hydrophilic ratio. These characteristics evolve in response to variations in the molecular weight of the block copolymers and alterations in surface functionality, thereby modulating the bilayer thickness, the scale of the polymersome, and the chemical nature of the polymersome wall. This adaptability renders polymersomes suitable for a broad spectrum of applications.[14,15] Similar to polymersomes, PMs have several outstanding features over other nanoparticle-based delivery systems. These include high stability at very low critical micelle concentrations (CMCs), which we refer to their stability under controlled conditions, when the micelles are in a relatively stable environment and above their CMC; ease of covalent or non-covalent fixation of microstructures for enhanced stability, various self-assembling morphologies for targeted delivery, adjustable nanoparticle size, and the potential for additional functionalities such as stealth characteristics, endosomal escape, and stimuli-triggered assembly or disassembly for programmed release.[16,17] PMs are thermodynamically stable colloidal solutions with a size range of 10–100 nm and a unique core-shell structure.[18] And the hydrophobic core allows for the encapsulation of hydrophobic drugs in the micellar core.[19,20] as most anticancer drugs are inherently hydrophobic,[21] while the hydrophilic corona effectively protects the hydrophobic core and its entrapped therapeutic from the external biological environment during circulation, thus reducing nonspecific protein adsorption.[22,23] Moreover, their small size makes them less recognizable by the liver and RES, thus preventing rapid renal clearance of anticancer drugs and prolonging their circulation time to maintain biological activity and function in vivo. Additionally, modifying the hydrophilic segment to confer specificity can control the release of drugs at tumor sites, thereby enhancing therapeutic efficacy and minimizing adverse effects.

Despite the remarkable stability of self-assembled PMs, they face significant challenges when applied as promising drug delivery in therapeutic settings, which severely limit their full potential.[24,25] After intravenous injection, polymeric micelles loaded with therapeutics encounter high dilution and shear stress.[26,27] These conditions can lead to premature disassembly of micelles when their concentration falls below the CMC before reaching the target site, causing early drug release and shortening the effective duration of the nanomedicine, which diminishes the therapeutic outcomes and causes a series of adverse effects.[28,29] More challenging still, even if polymer micelles maintain relative stability in the bloodstream, their diffusion in the tumor microenvironment unexpectedly slows down the rate of drug release. This delayed release not only fails to achieve sufficient drug concentrations inside tumor cells but may inadvertently induced drug resistance in these cells.[30] Therefore, to overcome these limitations, polymer micelles must ensure rapid drug release at tumor sites or within tumor cells while maintaining exceptional stability in the circulatory system. This ensures that therapeutic agents act efficiently and precisely on targets, maximizing treatment outcomes while avoiding potential issues of drug resistance.

Although passive targeting strategies (via the EPR effect) and active targeting strategies (through affinity ligand conjugation and receptor-specific cell uptake) have been developed, the true benefit of receptor-specific targeting in enhancing the accumulation of nanocarriers within tumor tissue requires further validation. Therefore, researchers have tried alternative strategies to control the drug delivery in a site-specific manner utilizing the distinct features in tumor microenvironment (TME) or external stimuli to improve therapeutic efficacy.[31] Contrary to normal tissues, the tumor

microenvironment exhibits distinct characteristics such as a slightly acidic pH, hypoxic conditions, reduced catalase activity, an abundance of hydrogen peroxide (H_2O_2), and a notably high concentration of glutathione (GSH). Additionally, some external stimuli have been utilized to regulate the behaviors of nanoparticles, such as light. By rationally designing the chemical composition, chain topology, and self-assembled nanostructure of polymer micelles, stimuli-triggered presentation of ligands on the nanoparticle surface and controlled release of activators through assembly/disassembly can be achieved.

pH has been the most extensively studied internal trigger for stimulus-responsive drug delivery, not only in oncological treatments (owing to the acidic nature of the tumor microenvironment), but also in other pathological settings like ischemia,[32] bacterial biofilms,[33] and inflammation,[34] where the pH is lower compared to healthy tissues. Moreover, the decreased pH within endosomal compartments post-endocytosis can be harnessed to enhance endosomal escape (eg, via the proton sponge effect), facilitating intracellular drug release and access to the target site.[35] Other stimuli, including temperature,[36] redox conditions,[37] and more recently, enzymes,[38] have also emerged as intriguing triggers for drug release (Figure 1). These stimuli capitalize on hyperthermia, the reductive intracellular milieu, and the upregulation of enzymes at disease sites, respectively.[39] Under these endogenous and exogenous stimuli, the physical and chemical properties of these polymer micelles undergo noticeable changes. This transformation triggers micelle disassembly or expansion, which enables rapid drug release at the predetermined site, thus optimizing therapeutic outcomes and reducing drug-related side effects. Such stimuli-responsive systems offer the potential for precise spatiotemporal control over drug release, minimizing systemic side effects and maximizing therapeutic efficacy. Therefore, stimuli-responsive block copolymer assemblies can increase targeting efficiency and enhance the effective concentration of drugs in tumor tissue and cellular environments.

In this review, we provide an overview of the latest advances in PMs responsive to physical, chemical, and physiological stimuli for cancer treatment. We will briefly introduce the mechanism and different strategies to fabricate the stimuli-responsive nanocarriers. Then we will give some examples of stimuli-responsive PMs and highlight their potential in drug delivery, such as enhancing treatment efficacy by targeted delivery and improved penetration, reducing side effects through decreased non-specific binding and controlled release rates, and prolonging drug action through sustained release. Furthermore, we will provide an outlook on the emerging field of stimuli-responsive amphiphilic copolymer micelle combinations for tumor-related applications, with an emphasis on the current challenges of stimuli-responsive PMs in clinical use.

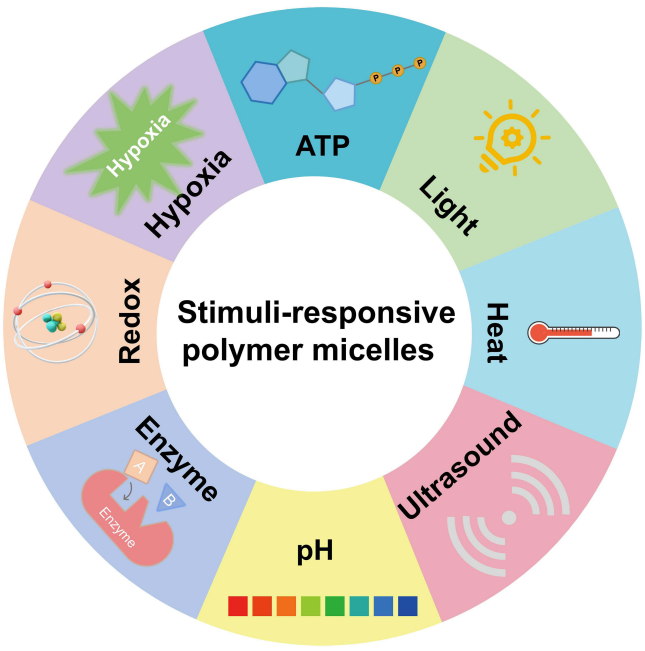

Figure 1 Overview of the stimuli-responsive polymer micelles in cancer treatment.

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Chemical Stimuli-Responsive Micelles

pH-Responsive Micelles

The acidity of diseased tissues such as cancer, bacterial infections, and inflammation is lower than the normal tissues, and thus this naturally diverse pH environment has been harnessed to fabricate pH-responsive DDSs, which selectively release drugs into these diseased tissues. The pH in physiological conditions ranges from 7.2 to 7.4, while the elevated glucose metabolism in cancer cells leads to an accumulation of H^+ ions, which in turn decreases the pH in the tumor microenvironment.[40] The pH in tumor tissue is approximately 6.5–6.8, and the pH in tumor cell is around 5.0–5.5. The nucleoli and lysosomes of cancer cells are even more acid, with pH of 5.0–6.0 and 4.0–5.0,[41] respectively. Therefore, pH-responsive nanoparticles have become an effective anti-tumor drug delivery system, capable of selectively and rapidly releasing anti-cancer drugs in acidic tumor tissues and cells.

A pH-sensitive amphiphilic diblock polyphosphate was synthesized using a one-pot condensation method, forming self-assembled micelle structures in aqueous solution. It contained acid-labile P(O)-O-C and C(O)-O-C linkages, which can be selectively cleaved in the acid environment. The hydrophilicity of the copolymer was enhanced by incorporating lactate. Copolymers with a lactate content of 10.7% exhibited a drug loading capacity of (3.2 ± 0.3)% and an encapsulation efficiency of (57.4 ± 3.2)%. Copolymers with a lactate content of 41.8% showed a drug loading capacity of 1.63% and an encapsulation efficiency of 45.8%. The drug loading and encapsulation efficiency tests of doxorubicin (DOX) indicated that hydrophobic drugs can be delivered via the copolymer. At physiological pH of 7.4, the DOX-loaded micelles exhibited a sustained release profile with a cumulative release percentage below 35% over a period of 48 hours, indicative of their high retention capacity. Conversely, under acidic conditions at pH 5.0, the release kinetics of DOX markedly accelerated, achieving over 70% drug release within 24 hours and exceeding 90% by 48 hours, which was notably swifter than the release rate observed at pH 7.4. This accelerated release can be attributed to the expedited hydrolysis of phosphoester bond present in the hydrophobic segments of the micelles under acidic milieu, leading to the disassembly of the micellar structure and the enhanced liberation of DOX. The results demonstrated that the poly [alkylpoly(ethylene glycol) phosphate-b-alkylpoly(ethylene glycol)lactate phosphate] DOX system possessed pH-responsive capabilities, enabling selective accumulation of DOX in acidic tumor environments.[42]

Kahveci et al fabricated a novel amphiphilic block copolymer, named poly(2-deoxy-2-methacrylamido-d-glucose-co-2-hydroxyethyl methacrylate)-b-poly(β-amino ester) [P(MAG-co-HEMA)-b-PBAE], which exhibited both active cancer cell targeting potential and pH responsiveness. Poly(β-amino ester) (PBAE), one of the pH-responsive polymers harboring tertiary amine moieties with a pK_b value of approximately 6.5, becomes protonated when the pH decreases below its pK_b and transformed into a cationic species with high aqueous solubility.[43] Such cationic polymers readily interact with negatively charged molecules like DNA and RNA, forming complexes known as polyplexes. Capitalizing on the protonation and deprotonation of the tertiary amine groups, PBAE is regarded as a promising pH-sensitive material for tumor-targeted drug delivery. To confirm the pH-responsive behavior of PBAE and the block copolymer P(MAG-co-HEMA)-b-PBAE, they concurrently executed acid-base titrations and monitored changes in optical density. Their results demonstrated that P(MAG-co-HEMA)-b-PBAE formed stable micellar structures at physiological pH 7.4 and exhibited a pH-sensitive hydrophobic-to-hydrophilic transition within the tumor microenvironment's acidic milieu, particularly around pH 5.5. Therefore, this block copolymer, endowed with a PBAE segment, presented itself as a potent contender for an effective carrier in the targeted delivery of anticancer therapeutics.[44]

Another example is provided by Zhang et al, who synthesized the amphiphilic copolymer $mPEG_{2000}$-PBAE via Michael addition reaction. PBAE is one of the pH-responsive polymers containing tertiary amine groups with a pKb value around 6.5. As pH decreases below the pKb, the tertiary amines are protonated, transforming PBAE into a cationic polymer that exhibits increased solubility in aqueous environments. This change triggers the disassembly of micelles and the subsequent release of encapsulated drugs. Using the thin film dispersion method, polymeric micelles loaded with paclitaxel (PTX) and triptolide (TPL) (TPL/PTX-PMs) were prepared.[45] These PMs boasted a distinctive core-shell structure, with a hydrophobic core enveloped by a hydrophilic coating, which facilitated the encapsulation of hydrophobic drugs within the polymeric micelles.[19] Furthermore, by chemically modifying the hydrophilic segments to impart specificity, the release of drugs from PMs at tumor sites could be controlled, thereby mitigating adverse drug reactions.

The TPL/PTX-PMs exhibited an average particle size of 97.29±1.63 nm, with a loading content (LC%) of 6.19±0.21% and an encapsulation efficiency (EE%) of 88.67±3.06%. In vitro release studies demonstrated that under acidic conditions (pH 5.5), TPL/PTX-PMs underwent ionic disassembly, facilitating an abrupt release of the entrapped drug. Notably, within the initial six-hour timeframe, these micelles released approximately 65.57% of their encapsulated drug load. Subsequently, between the 6 and 12 hour interval, the release rate of the drug reached its apex, indicating heightened activity in the liberation of the pharmaceutical agent during this period. They disassembled in the acidic tumor microenvironment to facilitate targeted drug release, effectively eradicating breast cancer cells.

In a separate study, a pH-responsive amphiphilic block copolymer, PEOz-PCL, was employed to engineer a targeted drug delivery system for delivering gambogic acid (GA) to MDA-MB-231 cells, which effectively induced cell death.[46] Here, the tertiary amide group promptly attached to hydrogen ions in solution and engaged in hydrogen bonding with other tertiary amide groups of the PEOz molecule. Under acidic conditions, the increase of these hydrogen bonds led to the disruption of the core-shell structure, compromising the stability of the polymer micelles and thereby releasing the entrapped drug.[47] Metabolomic analysis revealed that the nanoparticles may suppress triple-negative breast cancer (TNBC) cells by interfering with amino acid synthesis, nucleotide metabolism, glucose metabolism, and impairing their energy production pathways.

Researchers have proposed the incorporation of quinine-functionalized monomers (Q) into block polymer structures to form self-assembled micelles for efficient gene delivery. Incorporating Q into the core and/or shell of the micelles led to intercalative binding with the genetic payload and the formation of larger micelle-DNA complexes (micelle complexes) due to the hydrophobicity of Q in the shell. These factors enhanced the resistance of the micelle complexes to serum and resulted in more sustained protein expression post-transfection. When incorporated into the core, the micelles exhibited pH responsiveness to facilitate endosomal escape. When incorporated into the shell, the micelles bound to DNA through intercalation in addition to electrostatic interactions. Studies have shown that under acidic conditions, incorporating Q into the micelle core led to pH-dependent disassembly, resulting in differences in transfection efficiency between pH-responsive micelles and non-pH-responsive systems across multiple cell lines. Most importantly, incorporating Q into the shell resulted in intercalative binding interactions with DNA and more hydrophobic particles, thereby improving serum stability and prolonging the transfection effect.[48]

Effective endosomal escape is crucial in the development of siRNA-based therapeutics. Li et al synthesized a series of quaternary ammonium-based amphiphilic triblock polymers with a pH-sensitive hydrophobic core (Figure 2). Under the acidic environment of endosomes (pH 6.5–6.8), the optimized polymer $mPEG_{45}$-P(DPA_{50}-*co*-$DMAEMA_{56}$)-PT_{53} nanomicelles (PDDT-Ms) and PDDT-Ms/siRNA polyplexes rapidly disassembled, thereby promoting the release of siRNA and enhancing silencing activity. Through colocalization and gene silencing analysis, they demonstrated that PDDT-Ms/siPLK1 complexes could effectively escape from endosomes, and significantly inhibited tumor growth in HepG2 xenograft models and highly malignant patient-derived xenograft models.[49] This research provided guidelines for the design of nucleic acid delivery systems and laid a solid foundation for the development of siRNA-based cancer therapeutics.

ROS-Responsive Micelles

ROS, including singlet oxygen ($^1O_2$), superoxide ($O^{2-}\cdot$), hydroxyl radicals ($\cdot OH$), and hydrogen peroxide (H_2O_2), participate in a myriad of physiological processes, such as regulation of protein function, hormone synthesis, modulation of cellular signaling, mediation of inflammation, and elimination of pathogens.[50,51] However, these ROS are highly reactive, and may lead to oxidative stress and induce various biological damages when present in excess. The pathogenesis of inflammatory diseases is often accompanied by an overproduction of ROS.[52] Excessive ROS generation contributes to a wide range of biological injuries and is implicated in numerous disorders such as cancer, inflammatory and thrombotic complications, as well as neurodegenerative diseases. Therefore, taking advantage of the excessive ROS in diseased sites, varieties of ROS-responsive polymers have been devised to combat these diseases related to ROS and have shown great promise.

Several studies have highlighted that mitochondrial dysfunction in cancer cells markedly stimulates excessive generation of ROS. And the ROS level in cancer cells is approximately tenfold higher than that in normal cells.[53] Given the relatively weak DNA repair capacity within mitochondria, the delivery of mitochondria-targeted chemotherapeutics that can interact with mitochondrial DNA represents a potent strategy to reverse multidrug resistance (MDR) in cancer. Herein, the study reports a polyprodrug designed to sequentially target cancer cells and

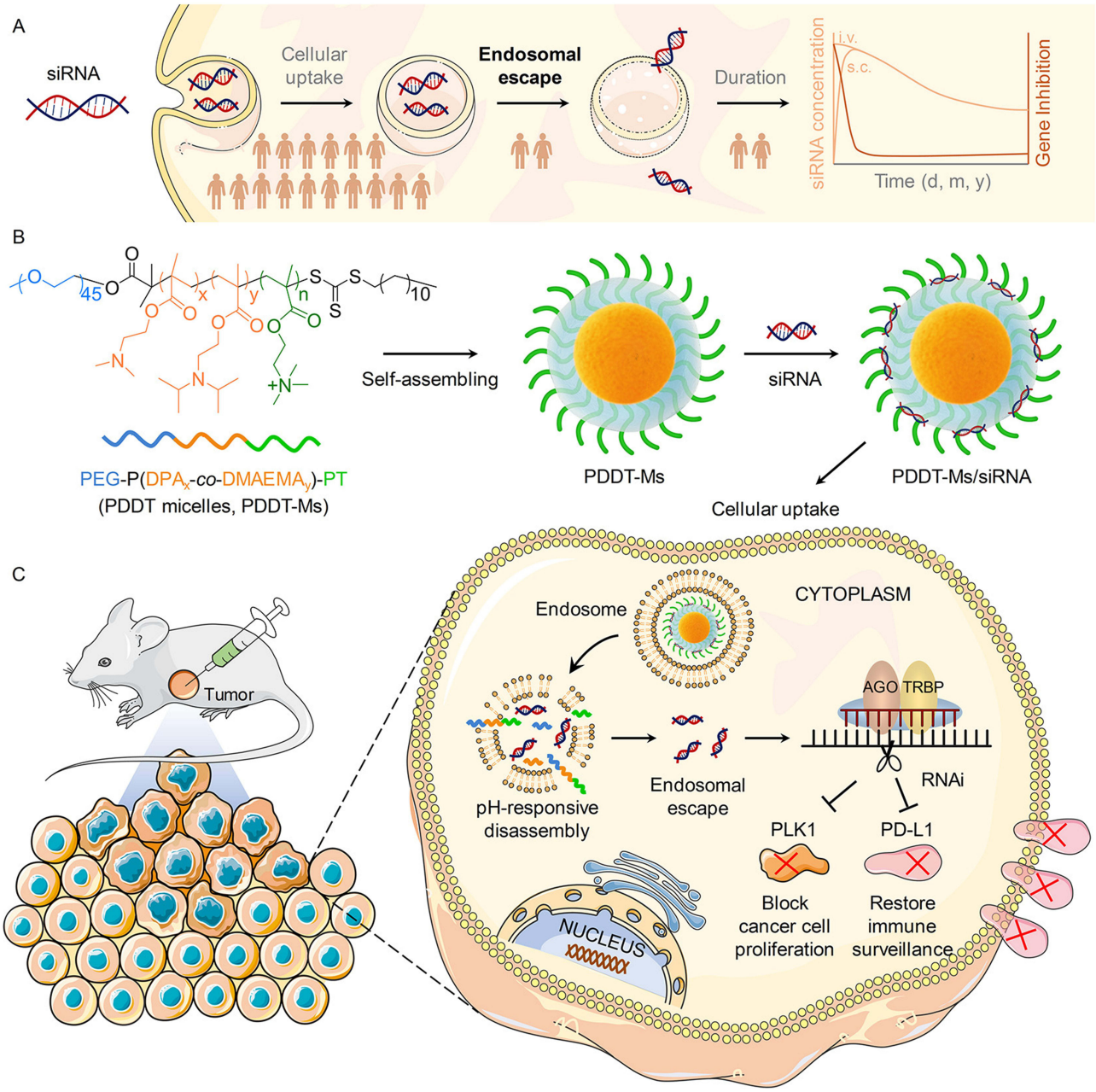

Figure 2 Schematic Illustration of the Core Concept of the Study (**A**) Processes of siRNA delivery and gene silencing, in which cellular entry, endosomal escape, and duration pattern of silencing activity are of importance for siRNA therapeutic development. Most people paid their attention to cellular entry in past decades. Increasing evidence proves that efficient endosomal escape of siRNA constitutes a determining factor of success or failure. (**B**) Chemical structure of proposed triblock polymer of PDDT and the preparing process of PDDT-Ms/siRNA polyplexes. (**C**) Cellular uptake and intracellular trafficking of PDDT-Ms/siRNA polyplexes. pH-responsive disassembling of the polyplexes will happen once they stay in the acidic endosomal environment. Two siRNAs targeting PLK1 and PD-L1 were employed in this study to achieve successful cancer treatment. Reprinted with permission from Li C, Zhou J, Wu Y, et al. Core role of hydrophobic core of polymeric nanomicelle in endosomal escape of siRNA. Nano Lett. 2021;21(8):3680–3689. Copyright (2021). American Chemical Society.[49]

mitochondria using folic acid (FA) and tetraphenylphosphonium (TPP), respectively. They were conjugated to the terminal groups of the amphiphilic block copolymer prodrugs composed of poly[oligo(ethylene glycol) methyl ether methacrylate] (POEGMA) and copolymerized monomers containing cinnamaldehyde (CNM) and doxorubicin (DOX). The synthesized polymer could self-assembled into micelles, which were termed as TF@CNM + DOX (Figure 3).[54] Upon internalization into tumor cells, the relatively low endosomal pH (~pH 5) triggered CNM release through the cleavage of acetal linker. CNM then accumulated in mitochondria, promoting the production of

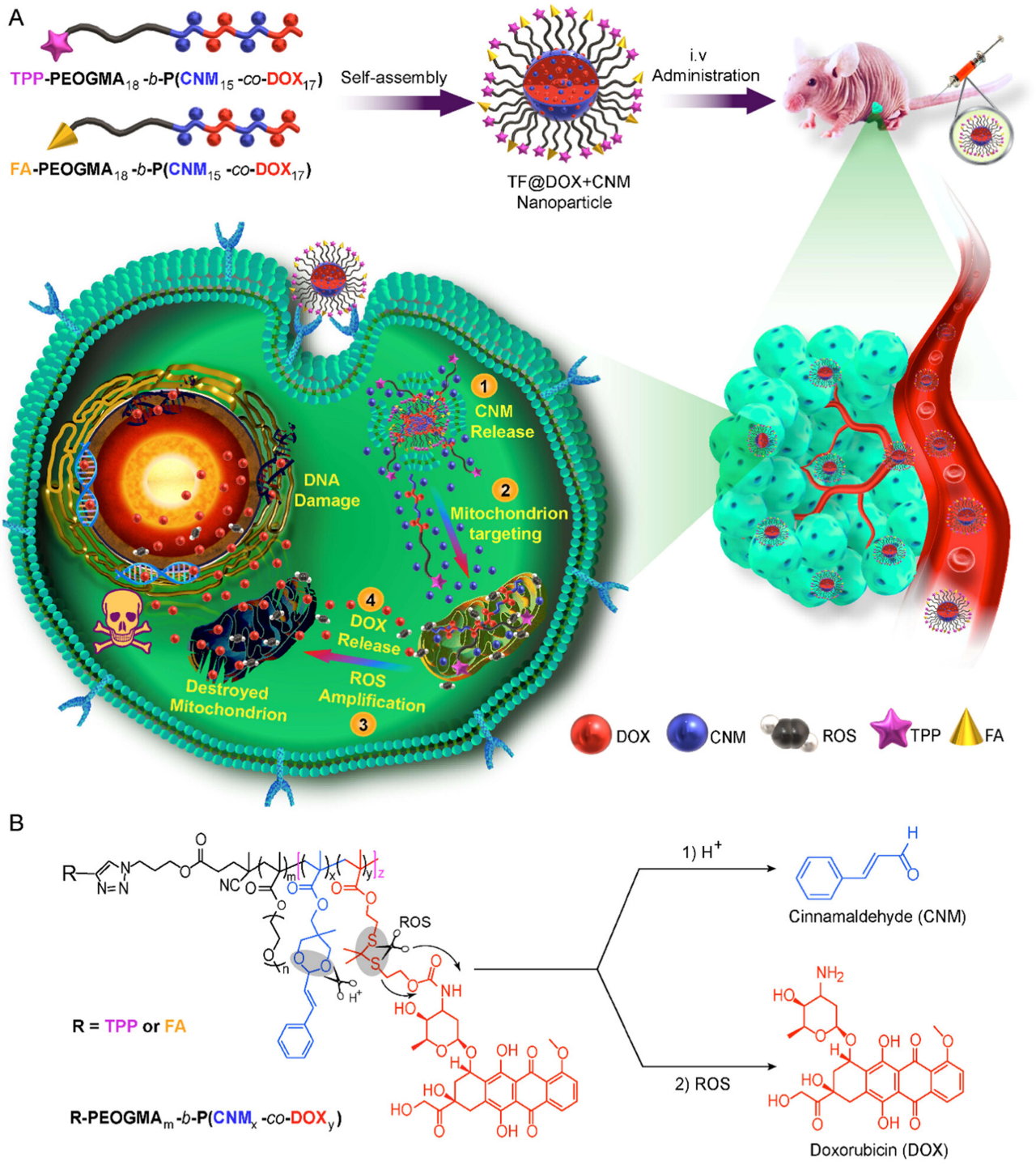

Figure 3 (**A**) Schematic illustration for the preparation of TF@CNM + DOX polyprodrug nanoparticles via self-assembly of a mixture of TPP-POEGMA-b-P(CNM-co-DOX) and FA-POEGMA-b-P(CNM-co-DOX) and their application to reverse multi-drug resistance; the proposed mechanism for TF@CNM + DOX nanoparticles; (1) cellular internalization of TF@CNM + DOX micelles via folate receptor-mediated endocytosis and CNM release at the endosomal pH 5.0; (2) excessive production of ROS in turn triggers the release of DOX mainly in the mitochondria through the cleavage of TK linkers. (**B**) pH and ROS-Responsive Release of CNM and DOX from the Polyprodrugs, Respectively. Reprinted with permission from Mukerabigwi JF, Tang R, Cao Y, et al. Mitochondria-targeting polyprodrugs to overcome the drug resistance of cancer cells by self-amplified oxidation-triggered drug release. Bioconjug Chem. 2023;34(2):377–391. Copyright (2023). American Chemical Society.[54]

excessive ROS. Subsequently, ROS induced DOX release in mitochondria via thioketal bonds (TK) cleavage, further amplifying oxidative stress. In addition to the ROS overproduction and amplified oxidative stress induced by CNM in the mitochondria, localized DOX release within mitochondria further enhanced cytotoxicity, thereby achieving

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heightened therapeutic outcomes. This approach demonstrated an augmented cytotoxic effect against doxorubicin (DOX)-resistant breast cancer cells (MCF-7 ADR), with no discernible adverse effects observed from the use of TF@CNM + DOX nanoparticles.

GSH-Sensitive Micelles

GSH is a reducing peptide that is widely present in human cells. The concentration of GSH in tumor tissues is generally at least twice higher than that in human plasma (typically 1–2 mm) and normal tissues (approximately 2–20 mm); in some cases, particularly in resistant tumors, overexpressed GSH can reach up to ten times higher. On the other hand, the much higher concentration of intracellular GSH (10 mm) determines the reductive microenvironment of the cytoplasm.[55] The oxidative environment in the extracellular space favors the maintenance of disulfide bonds, which are crucial for the structure and function of proteins outside of cells or in membranes.[56] Among these, disulfide bonds are most commonly utilized in redox-sensitive drug carriers. Disulfide bonds can exist in the main chain[57] and side chains of polymers, and can also serve as cross-linking bonds.[58] Under reductive conditions, disulfide bonds break down within minutes to hours through thiol-disulfide exchange reactions. The disruption of disulfide bonds alters the hydrophilicity and hydrophobicity of the polymer chains, leading to changes in the micelle structure, and can even cause the disintegration of micelles. This disruption facilitates the redox-responsive release of drugs.

Zhang et al developed a reduction-sensitive nanomicelle loaded with Anlotinib, cyclic RGD peptide (cRGDyk)-anlotinib-reduction sensitive micelles (cARM), as a tumor microenvironment-responsive delivery platform.[59] The micellar carrier was self-assembled from the reduction-sensitive amphiphilic copolymer DSPE-SS-PEG2k and the cRGDyk-functionalized DSPE-PEG2k. The micelle surface, modified with hydrophilic PEG, formed a hydration layer that hindered phagocytosis by the reticuloendothelial system (RES), thereby prolonging its circulation time in vivo. Following cRGD modification, the micelles displayed active targeting capabilities and bound specifically to αvβ3 integrin receptors, which are highly expressed in various tumor cells and neovascular endothelial cells but minimally in normal organs.[60,61] Therefore, the cARM showed better tumor accumulation than their unmodified counterpart. Moreover, the elevated GSH in tumor cells enabled the controlled drug release of the cARM via the clevage of disulfide bonds. The study demonstrated that the cARM significantly inhibited melanoma cell proliferation by blocking the VEGF/VEGFR-2 pathway.

In another study, Ibrahim et al developed a polymer prodrug micelle based on self-assembly of an amphiphilic block copolymer composed of polyethylene glycol (PEG) and a disulfide-linked camptothecin methacrylate monomer (CPTM) with 1-(1H-imidazole-4-yl)-2-(octylamino)-2-oxoethyl methacrylate (ImOAMA). After being internalized into cells via endocytosis, the PEG-b-P(CPTM-co-ImOAMA) micelles became entrapped within endosomes of tumor cells. Moreover, the high concentration of glutathione in the cancer cytoplasm triggered the release of active camptothecin (CPT) by cleaving the disulfide bond in PCPTM. In vitro results indicated that the PEG-b-P(CPTM-co-ImOAMA) micelles were effectively internalized into cells, followed by endosomal escape, which contributed to a significant enhancement in cytotoxic efficacy against cancer cells. Additionally, in vivo studies confirmed that PEG-b-P(CPTM-co-ImOAMA) micelles effectively suppressed tumor growth without noticeable toxicity.[62]

Hypoxia-Responsive Micelles

The robust proliferation of tumor cells leads to a significant consumption of oxygen, resulting in the establishment of a hypoxic microenvironment. While the oxygen pressure in healthy tissues is around 9.3 kPa, within tumors, it can plummet to merely 0.2 kPa.[63] The stark disparity in oxygen tension between normal tissues and tumors facilitates a more controlled release behavior of drugs from micellar structures.[64] Owing to the hypoxic state of tumors, levels of various reductases and reductive molecules, such as nitroreductase, NADPH, azoreductase, DTD (dithiothreitol-dependent disulfide reductase), and methionine synthase reductase, are notably elevated.[65] Capitalizing on this distinctive feature, research endeavors have focused on the development of nanocarrier systems responsive to hypoxic conditions. These systems aim to enhance the delivery and efficacy of therapeutic agents specifically in the hypoxic tumor microenvironment.

Lu et al[66] developed a bio-reducible linker based on 2-nitroimidazole to connect paclitaxel (PTX) to other molecules. Under hypoxic conditions within cells, the 2-nitroimidazole could be enzymatically reduced, and subsequently, the bio-reducible linker rapidly released the bound PTX.

Physical stimuli-responsive micelles

Thermosensitive-Micelles

Temperature-sensitive polymer micelles undergo phase transitions around the critical dissolution temperature (CST), resulting in changes to their conformation, solubility, and hydrophilic-hydrophobic equilibrium. When heated, some polymers become soluble, exhibiting an upper critical solution temperature (UCST), while others become insoluble, displaying a lower critical solution temperature (LCST). Exceeding the critical temperature prompts the polymers to collapse, minimizing their interaction with the environment. This characteristic has found broad application in drug delivery and biotechnology. Drug release can be triggered either by an endogenous temperature rise that induces polymer collapse or by an externally applied heat stimulus.[67] Notably, solid tumors naturally possess a marginally higher temperature than the normal body temperature. By calibrating the LCST of thermo-responsive polymers to lie between physiological body temperature and the increased tumor temperature, drug delivery systems (DDS) can selectively concentrate within the tumor microenvironment.

In the majority of studies, temperature-responsive polymer micelles are fabricated using LCST polymers, which initiate a shrinkage and subsequent release of encapsulated drugs when the temperature is raised above a specified LCST. For example, Chen et al employed free radical random copolymerization to fabricate two thermos-responsive polymeric materials, designated as P(FAA-NIPA-co-AAm-co-ODA) and P(FPA-NIPA-co-AAm-co-ODA). By incorporating hydrophilic polymer monomers into Poly(N-isopropylacrylamide) (PNIPA), the modified polymer micelles can effectively deliver drugs to the target site at the normal human body temperature of 37°C. Upon localized heating, which triggers the collapse of the micelle structure, the loaded drugs are rapidly released within a short period. Following synthesis, the polymers underwent self-assembly to form micelles structures, which were investigated for their potential use in targeted drug delivery systems. At a physiological temperature of 37°C (under LCST), PFAAM exhibited reduced solubility in water, leading to a prolonged release profile of cyclopentanopropionate ester, requiring almost 600 hours to be fully released from the PFAAM segment. Conversely, fluorescein, being highly water-soluble, diffused out of the micellar structure rapidly and completely. When the temperature escalated to 43°C (above LCST), the release kinetics of both cyclopentanopropionate ester and fluorescein were markedly accelerated, attributable to the structural rearrangement and collapse of the micelles' amphiphilic architecture and hydrophilic core in response to thermal stimuli. Furthermore, paclitaxel (PTX), a potent chemotherapeutic agent, was encapsulated within these micelles, and to augment their tumor-targeting precision, folic acid—a recognized tumor-targeting ligand—was conjugated to the micellar surface. The investigators assessed the enhanced selectivity and targeting efficacy of the folic acid-conjugated, thermosensitive micelles toward tumor cells and tissues, along with their pronounced antitumor activity, across both cellular and animal models. The synergistic application of PTX@PFPAM micelles in conjunction with hyperthermic therapy emerges as a promising and targeted modality for the treatment of tumor.[68]

In addition to LCST polymers, UCST polymers have also demonstrated potential in thermosensitive drug release. In their study, Palanisamy et al[69] devised a self-assembled multilayer composite employing polyphenols and copolymers that exhibited an UCST behavior, with a polyamino acid component integrated into their structure. The copolymer, consisting of poly(ethylene pyrrolidone) and polyurea (ornithine-co-lysine), was synthesized through a ring-opening polymerization (ROP) process coupled with subsequent urea functionalization. The thermos-responsive properties of this copolymer were characterized by a UCST of 33°C, below which it self-assembled into micelles aggregates, whereas it disintegrated when the temperature surpassed this threshold. This temperature-induced transformation in the copolymer's morphology offers significant potential for application in stimuli-responsive systems.

Ultrasound-Responsive Micelles

Ultrasound, as a mechanical wave and a manifestation of energy, is distinguished primarily by its non-invasive nature. Drug release from micelles triggered by ultrasound stems from the oscillation of bubbles and their subsequent collapse within an acoustic field, a process known as sonoporation. To promote the drug liberation from polymeric micelles, an ultrasound threshold intensity must be attained. This ensures the generation of adequate shear force via ultrasonic cavitation, which disrupts unstable chemical bonds in the polymer matrix and leads to the disintegration of the micellar

structure. Ultrasound-driven drug release offers several key benefits: it is non-invasive, devoid of ionizing radiation, and allows for adjustable penetration depth into tissues.[70] High-frequency ultrasound can selectively target specific tissue areas, while minimizing damage to neighboring healthy tissues.

In a study, Lin et al reported a new class of High Intensity Focused Ultrasound (HIFU) responsive block copolymer self-assembled nanocarriers, which were capable of sequentially releasing the anticancer therapeutic dasatinib (DAS) and sonodynamic agent methylene blue (MB) following HIFU application. Initially, an ultrasound-responsive block copolymer was synthesized, incorporating an end-functional Eosin Y fluorophore, 2-tetrahydropyranyl acrylate (THPA), and acrylate mannose (MAN). Subsequently, the block copolymers self-assembled into micelles. The HIFU-induced selective cleavage of the hydrophobic THPA groups into hydrophilic methyl acrylate groups led to the disruption of the polymer micelles and the release of their cargo. To achieve targeted delivery, mannose was employed to form the hydrophilic block and acted as the targeting moiety within the system. The introduction of the mannose groups enhanced cellular uptake by human hepatocellular carcinoma (HepG2) cells. Their results demonstrated that the system, utilizing PMAN-b-PTHPA micelles loaded with DAS and MB, effectively inhibited tumor growth by inducing DNA damage in cancer cells and suppressing Src phosphorylation.[71]

Light-Responsive Micelles

Presently, light signals are widely harnessed for crafting photoreactive materials. This has sparked growing intrigue among researchers towards photoreactive micellar nanocarriers. Light serves as an external environmental cue without disrupting the body's physiological milieu. Its merits as a stimulus encompass non-invasiveness, absence of side effects, environmental friendliness. Compared with traditional environment-sensitive micelles, photosensitive micelles confer significant advantages. Through modulation of light intensity, the velocity of payload release can be finely tuned, permitting precise orchestration of the light stimulation's duration and dosage at a predetermined location and moment. As a result, photosensitive micelles can amplify drug utilization efficacy and mitigate toxicity towards healthy cells.

Li et al[72] reported a single-molecule oxygen-responsive micellar nanocarrier that expanded in size upon light exposure, thereby releasing the photosensitizer. Imidazole, a well-known scavenger of singlet oxygen ($^1O_2$), was conjugated to the backbone of mPEG-PAsp, which then self-assembled into micellar nanocarriers in aqueous medium. Taking advantage of the coordination interaction between the imidazole and Zn^{2+}, the photosensitizer chlorin e6 (Ce6) was encapsulated within the micelles. Upon irradiation, the generated $^1O^2$ facilitated the transformation of imidazole to urea. Urea possesses both hydrogen bond donor and acceptor properties (via the NH2 and C=O groups), which allows it to form extensive hydrogen bond networks with a large number of water molecules. Consequently, urea exhibited notable hygroscopic properties, effectively absorbing moisture from its surroundings, which disrupted the coordination complex and caused the rapid release and distribution of Ce6 within the cells. Compared to free Ce6, these single-molecule oxygen-responsive expandable nanocarriers promoted the enrichment of Ce6 in tumors.

The heterogeneous distribution of hypoxic regions inside tumors limits the therapeutic efficacy of photodynamic therapy (PDT) and hypoxia-responsive prodrugs. To overcome this dilemma, Zhou et al developed a well-defined polyprodrug amphiphiles for complementary photodynamic-chemotherapy. They harnessed nitroimidazole as a linker (CPTNMA) to copolymerize with camptothecin (CPT) prodrug methacrylate monomers, utilizing polyethylene glycol (PEG) as a macro-raft chain transfer agent. The synthesis was achieved through reversible addition-fragmentation chain transfer (RAFT) polymerization, yielding an amphiphilic hypoxia-responsive block copolymer precursor, PEG-b-P (CPTNMA-co-TPPMA) (Figure 4). Upon self-assembling into polyprodrug micelles (PPMs) and subsequent intravenous administration, PPMs accumulated in tumor tissues via extended circulation and the enhanced permeability and retention (EPR) effect. In oxygen-rich regions, upon light irradiation, the photosensitizer TPP converted oxygen to singlet oxygen ($^1O_2$) and induced apoptosis. Meanwhile, in the hypoxic tumor microenvironment, the nitroimidazole linker in polyprodrug micelles were responsive to the overexpressed nitroreductases for controlled release of free CPT. Moreover, oxygen consumption by PDT-aggravated hypoxia further accelerated CPT release. Ultimately, the synergistic action of released CPT combined with $^1O_2$ from PDT potently suppressed tumor growth.[73]

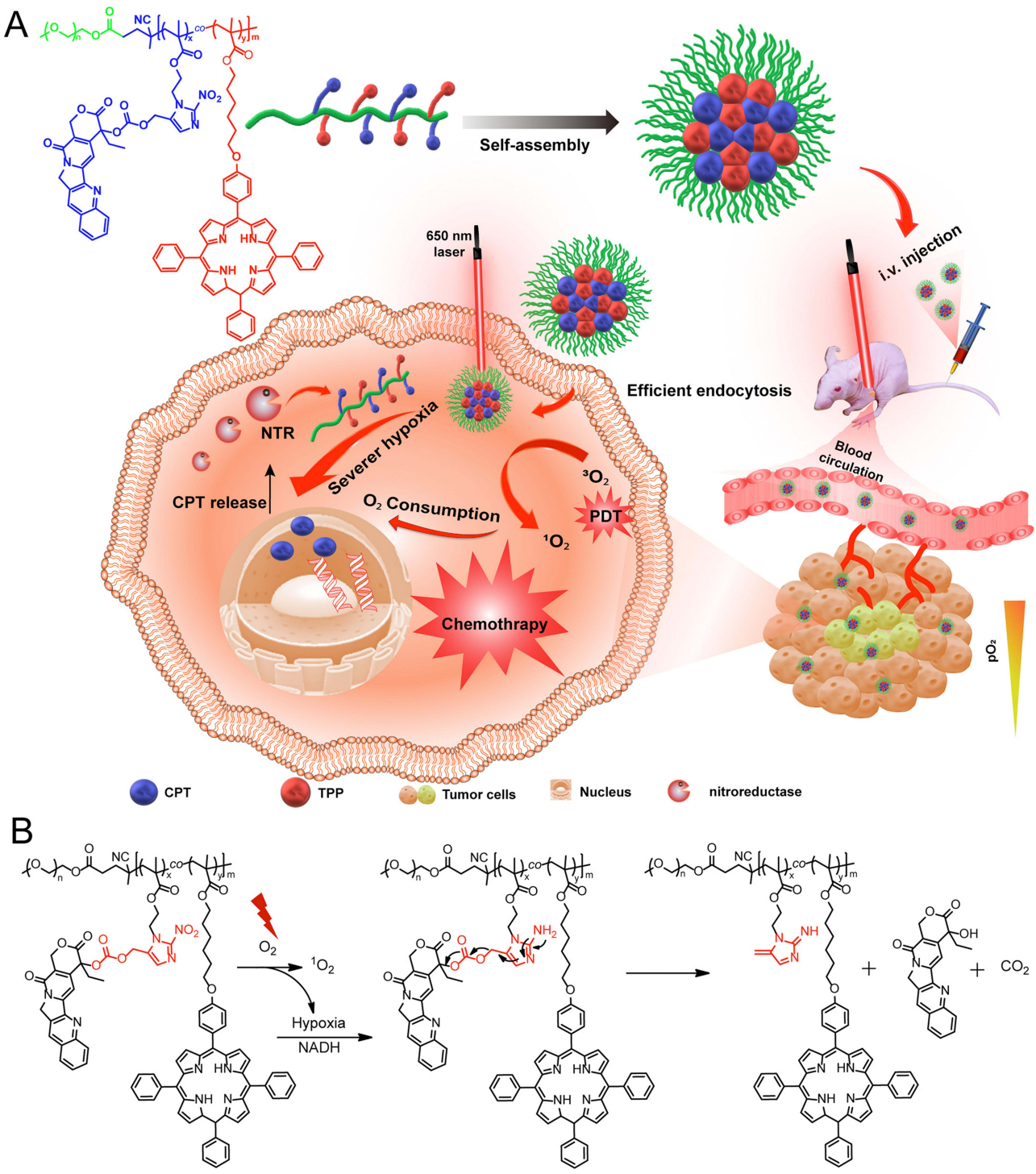

Figure 4 (**A**) Schematic illustration for the formation of polyprodrug micelles and the combination of PDT and light-boosted hypoxia aggravation for hypoxia-responsive self-immolative drug release inside tumor tissues. (**B**) The mechanism of PDT and hypoxia-responsive drug release from the polyprodrug. Reprinted with permission from Zhou Q, Mohammed F, Wang Y, et al. Hypoxia-responsive block copolymer polyprodrugs for complementary photodynamic-chemotherapy. *J Control Release*. 2021;339:130–142. Copyright (2021). Elsevier.[73]

Physiological Stimuli-Responsive Micelles

Enzyme-Responsive Micelles

The human body is replete with diverse enzymes, including hydrolases, proteases, and others, each playing pivotal roles in various biological processes. Certain enzymes can catalyze reactions that involve specific functional groups

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within polymers, such as phosphorylation, dephosphorylation, and oxidation-reduction reactions. Through enzymatic action, the physical and chemical characteristics of polymers are altered, resulting in significant transformations of polymeric micelles' shape, structure, and functionality.[74] Enzyme catalysis can also produce specialized molecules as byproducts of their catalytic activities, including hydrogen peroxide (H_2O_2), carboxylic acids, and other substances. These generated molecules subsequently interact with segments of the micelles, inducing structural changes and regulating the release of the encapsulated payload. Moreover, enzymatic reactions proceed under gentle conditions, showcasing remarkable specificity, making them ideal for targeted drug delivery mechanisms. And tailored enzyme-responsive micellar carriers can be engineered based on the specific types and concentrations of enzymes present in different tissues.

Enzyme-responsive polymers have emerged as a powerful tool in the development of targeted drug delivery systems, leveraging the unique enzymatic milieu present in diseased tissues. A prime example was NAD(P)H:quinone oxidoreductase-1 (NQO1), an enzyme overexpressed in certain tumor types.[75] NQO1 accomplished this through an intramolecular cyclization process that reduced the trimethyl-locked quinone propionic acid (QPA) moiety to lactone.[76] In a study by Jaehyun et al, an innovative amphiphilic block copolymer, QPA-P, was synthesized, incorporating a hydrophobic NQO1 enzyme-triggered depolymerizable QPA-locked PCL and hydrophilic poly(ethylene glycol) (PEG). The mechanism began with the quinone group of QPA-P being reduced by NQO1 to hydroquinone, which then underwent a nucleophilic attack on the carbonyl group of the amide bond, triggering the first cyclization process and releasing a lactone moiety. Subsequently, the exposed amine group initiates a second cyclization process by attacking the ester bonds along with the main PCL backbone, leading to the elimination of the lactam segment and triggering the release of anticancer drugs specifically at the target cancer cells.[77] The NQO1-mediated depolymerization of QPA-locked PCL through a cascade two-step cyclization process ultimately induced the dissociation of the micellar structure and the release of loaded drugs at the target site (Figure 5).

In another example, Barve et al developed a biodegradable, enzyme-responsive, and targeted polymer micelle system specifically designed for cabazitaxel.[78] The micelles were constituted by two amphiphilic block copolymers. The first copolymer comprised PEG linked to an enzyme-responsive peptide and cholesterol, while the second copolymer was made of a targeting ligand conjugated to PEG and cholesterol. The enzyme-sensitive peptide was cleavable in the presence of matrixmetaloproteinase-2 (MMP-2), which is overexpressed in the tumor microenvironment of prostate cancer. The MMP-2 responsive linker PLGVRK in the micelles was cleaved by MMP-2 present in the microenvironment of prostate tumors. This cleavage led to the disassembly of the micelle structure, releasing the encapsulated cabazitaxel into the tumor microenvironment, where it exerted its therapeutic effects. Significantly, the micelles demonstrated enhanced cellular uptake in prostate cancer cells compared to free cabazitaxel. Of paramount importance, the ligand-conjugated polymer micelles demonstrated superior inhibition of tumor growth in mice bearing prostate cancer xenografts relative to unmodified micelles and free cabazitaxel.

Another study highlighted the potential of enzyme-responsive polymers in immunotherapy. An amphiphilic diblock copolymer was fabricated featuring one segment bearing the hydrophobic Toll-like receptor 7 (TLR7) agonist 1V209, and another segment with a hydrophilic peptide serving as a substrate for matrix metalloproteinases (MMPs). The polymer design enabled the hydrophobic block, which formed the spherical micellar core, to encapsulate therapeutic agents, while the hydrophilic polymer block that constituted the micellar shell was composed of enzyme-responsive peptides. These hydrophilic peptides are substrates for MMPs, which are overexpressed in many tumors. Their results demonstrated that when the particles were loaded with the TLR-7 agonist 1V209, this targeted approach led to a significant reduction in tumor progression as well as a decrease in the number of lung metastases.[79] This strategy shows promise in selectively delivering immunotherapeutics to tumors and impeding their advancement and spread.

Recent researches on single-stimulus responsive micelles are presented above. And in Table 1, we summarize the single-stimulus responsive amphiphilic polymer micelles, focusing on the delivery system, model and stimulus responsiveness.

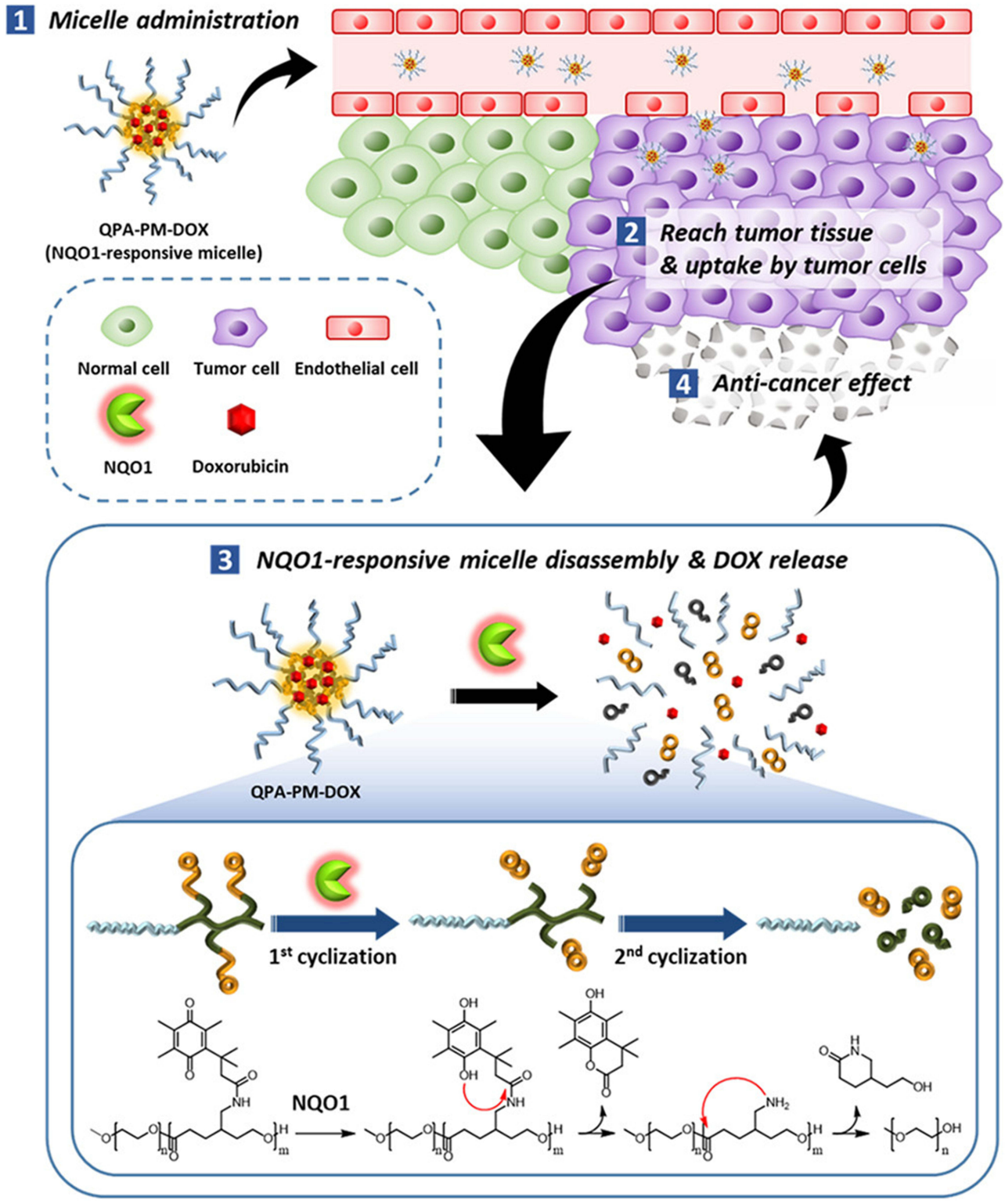

Figure 5 Schematic representation of NQO1-Responsive drug delivery system and their enzyme-triggered disassembly and drug release facilitated by NQO1 depolymerization and disassembly of the micellar structure. Reprinted with permission from Park J, Jo S, Lee YM, et al. Enzyme-triggered disassembly of polymeric micelles by controlled depolymerization via cascade cyclization for anticancer drug delivery. ACS Appl Mater Interfaces. 2021;13(7):8060–8070. Copyright (2021). American Chemical Society.[77]

Dual Stimuli Responsive Micelles

Responsive nanomicellar carriers are engineered to release their therapeutic payloads in response to diverse stimuli signals encountered both in vitro and within the living body. The chief aim of designing these responsive micelles is to

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Table 1 Summarizes of the Single-Stimulus Responsive Amphiphilic Polymer Micelles

Stimuli	Delivery Systems	Models	Drugs	Purpose	Reference
Ph	DOX-micelle	B-16 melanoma mice	Doxorubicin (DOX)	To release drugs specifically to diseased tissues	[42]
	P(MAG-co-HEMA)-b-PBAE	Glioblastoma cell line, u87-mg	Doxorubicin (dox)	To actively target cancer cells	[44]
	TPL/PTX-PMs	MDA-MB-231 cells	Paclitaxel (ptx) and triptolide (tpl)	To control the release of the drug at the tumor site, and passively target drugs to solid tumors	[45]
	PEOz-PCL	MDA-MB-231 cells	Gambogic acid (ga)	To enhance the ph-responsive ga loaded micelles accumulation in TNBC tissues and maintain structural stability in normal tissues	[46]
	DQ-BQ	A549 cells	PZSGREEN-n1 plasmid	To induce micelle disassembly and improve transfection efficiency by promoting endosomal escape	[48]
	mPEG45-P(DPA50-co-DMAEMA56)-PT53	HepG2 xenograft models	siRNA	To promote the release of siRNA and enhance silencing activity	[49]
ROS	TF@CNM + DOX	MCF-7 ADR	Cinnamaldehyde (cnm) and doxorubicin (dox)	To overcome the drug resistance through an orchestrated amplification of mitochondrial oxidative stress and ros-triggered drug release into the mitochondria	[54]
GSH	cARM	Melanoma cells	Anlotinib	To prolong its circulation time in the body and exhibit active targeting and binds to αvβ3	[59]
	PEG-b-P(CPTM-co-ImOAMA	H22 tumors	Camptothecin (cpt)	To facilitate endosome escape and trigger the release of active camptothecin	[62]
Temperature	PTX@PFPAM	MDA-MB-231 and A549 tumor models	Paclitaxel (PTX)	To actively target tumor	[68]
Ultrasound	DAS/MB@M	Human hepatocellular carcinoma (HepG2) cells	Dasatinib (DAS) and sonodynamic agent methylene blue (MB)	To enhance cellular uptake in human hepatoma (HepG2) cells	[71]
Light	MPEG-PAsp-IM	4T1 breast cancer model in mice	Chlorin e6 (Ce6)	To control the release of Ce6 under irradiation	[72]
	PPMs	HeLa tumor models	Camptothecin (CPT) prodrug methacrylate monomers	To enhance tumor accumulation	[73]
Enzyme	QPA-P	A549 tumor model	Doxorubicin hydrochloride (DOX)	To target cancer cells	[77]
	Enzyme-responsive polymeric micelles of cabazitaxel	Prostate cancer	Cabazitaxel	To enhance cellular uptake in prostate cancer cells	[78]
	Amphiphilic diblock copolymers containing hydrophobic Toll-like receptor 7 (TLR7) agonists and hydrophilic peptides	TLR-7 agonist 1V209	Mice bearing 4T1 breast cancer tumors	To enhance accumulation in tumors	[79]

prevent premature drug leakage during systemic circulation and to ensure secure transit until the medication reaches its designated target, whereupon it is promptly released. Although most stimuli-sensitive micellar nanocarriers are programmed to react to a single signal, certain complex situations demand a more nuanced approach. Responsiveness to a single stimulus alone may fall short in achieving finely tuned control over drug release. In light of this, researchers have innovated dual-responsive, triple-responsive, and even multi-responsive micellar carriers. These advanced micelles possess the capability to respond simultaneously or in sequence to multiple external stimuli, thereby augmenting the precise control over drug payload and targeted delivery. This multifaceted responsiveness not only enhances the therapeutic efficacy but also minimizes potential side effects by ensuring the drug is activated exclusively at the desired location.

pH- and ROS- Responsive Micelles

Su et al have synthesized a novel, multifunctional, and biodegradable amphiphilic block copolymer, PEG-poly(ω-pentadecalactone-co-N-methyldiethyleneamine sebacate-co-2,2'-thiodiethylene sebacate) (PEG-PMT), via lipase-catalyzed copolymerization.[80] The amphiphilic PEG-PMT copolymer readily transformed into stable micellar nanoparticles through self-assembly in aqueous media. Upon encountering the tumor microenvironment, particle dimensions dramatically increased due to protonation of thioether groups and oxidation of amines within the PMT micellar core, triggered respectively by acidic pH and high levels of reactive oxygen species (ROS). Their results showed that docetaxel (DTX)-loaded micelles were triggered synergistically by acidic pH and ROS stimuli to release over 85% of the anticancer drug. And the pH- and ROS-responsive micelles effectively prohibited the growth of CT-26 tumors in vivo.

pH- and Redox Responsive Micelles

Maghsoudian et al engineered a cleavable copolymer system utilizing 2-methylacryloyloxyethyl phosphorylcholine (MPC) and poly(ε-caprolactone) (PCL) as the shell, and gold nanoparticles (Au NPs) sensitive to pH and glutathione as their core. This design aimed to specifically deliver doxorubicin to human breast cancer cells while mitigating the adverse effects of free cytotoxic drugs. Upon exposure to ultrasound stimulation, the AuS NPs facilitated the cleavage of disulfide bonds within the nanoparticles through oxidation-reduction reactions with GSH, generating oxidized glutathione (GSSH) and thereby reducing GSH levels. This process led to an elevation in reactive oxygen species (ROS) production. Compared to other available nanosenstitizers like titanium dioxide, AuS-PM, when subjected to ultrasonic radiation (1.0 W/cm² for 2 min), markedly amplified cavitation effects and induced up to fivefold higher ROS generation. The study validated that the AuS-PM-TMTM-DOX micelles efficaciously enhanced cellular uptake and induced apoptosis of MCF7 and MDA-MB231 cell lines. In animal tumor models, these micelles demonstrated a high degree of tumor accumulation and minimized detrimental effects on healthy tissues, underscoring their potential for targeted and safe chemotherapy.[81]

In another innovative study, researchers developed dual redox/pH-sensitive star-shaped amphiphilic sucrose-oligo (butyl fumarate) (thioglycolic acid conjugate)–SS–poly(ethylene glycol) (Suc-OBF(TGA)–SS–PEG) copolymers and their self-assembled micelles for efficient intracellular delivery of doxorubicin. Sensitivity to pH was achieved by introducing carboxyl groups as ionizable moieties into the polymer structure. To endow the micelles with redox sensitivity, the arm connecting the hydrophobic polymer c (oligo(butyl fumarate) (OBF)) and the hydrophilic polymer (PEG) was designed to incorporate a disulfide bond. After micellization, the impact of varying the length of the hydrophobic chains on the micelle properties was investigated. The hydrophobic region was then utilized as a reservoir for the hydrophobic anticancer drug doxorubicin (DOX) to mitigate its limitations. Under acidic conditions with a pH of 5.0, the drug release rate from these micelles reached 80% over a period of 96 hours. Furthermore, compared to free drugs, the pH-responsive GA-loaded micelles were more effective in killing MDA-MB-231 cells and exhibited higher activity and targeting capabilities.[37]

Lo et al further expanded the scope of dual-responsive micellar systems by fabricating a poly(ε-caprolactone)-SS-poly (methacrylic acid) (PCL-SS-PMAA) diblock copolymer-based micelle system for the co-delivery of paclitaxel and cisplatin. The PCL-SS-PMAA was formulated into core-shell micelles (PSPm) in aqueous solution. Paclitaxel (PTX) was encapsulated within the core, while cisplatin (CDDP) was chelated onto the shell of the PSPm, enabling the stimuli-responsive release of both PTX and CDDP from PSPm (PTX/CDDP) under pH 5.5 and 10 mm GSH conditions. The cleavage of disulfide bonds

within the hydrophobic core of the micelles led to instability of the self-assembled structures, resulting in programmable drug release behavior. Remarkably, the PSPm(PTX/CDDP) exhibited synergistic cytotoxic effects and demonstrated superior anti-lung cancer activity compared to either single-drug loaded PSPm formulations or the free drug combination, highlighting its potential as an enhanced therapeutic strategy.[82]

Zhang et al ingeniously designed a distinctive multistage pH/redox-responsive polyprodrug to sequentially control the drug release. The prodrug was composed of a pH-sensitive diblock copolymer, poly(ethylene glycol) methyl ether-b-poly (β-amino ester), and the hydrophobic doxorubicin (DOX), which was conjugated via a redox-sensitive disulfide bond (mPEG-b-PAE-ss-DOX). This polyprodrug assembled into micelles (DOX-ss@PMs) at low concentrations, exhibiting high serum stability. In vitro findings revealed that DOX-ss@PMs accumulated extensively in tumor sites, and subsequently disassembled in response to acidity and efficiently penetrated into tumor cells. Then the DOX was released from the micelle in the presence of high GSH concentration, thereby inducing the apoptosis of tumor cells. Further in vivo investigations demonstrated that DOX-ss@PMs effectively inhibited tumor growth and prolonged the survival rate of tumor-bearing mice.[83]

Shetty et al constructed an amphiphilic block copolymer-based nanocarrier for controlled gene delivery.[84] The block copolymer was synthesized by atom transfer radical polymerization (ATRP), and contained an acid-labile acetal linkage at the block junction and a pendant disulfide group in the hydrophobic block. The hydrophobic HMssEt units in the nanocarrier promoted the condensation of the negatively charged dsDNA or dsRNA via electrostatic interactions. Moreover, the incorporation of acid-labile acetal linkage and disulfide group enabled both disulfide-core-cross-linking and dual-location dual-acid/reduction-responsive degradation (DL-DSRD). Their results showed that the nanocarrier were stable under physiological conditions and even in the presence of serum proteins. Besides, it demonstrated dual-location dual-acid/glutathione responses to accelerate the release of encapsulated dsRNA in the presence of glutathione and acidity. Moreover, the dual-acid/glutathione responsive carrier exhibited enhanced EGFP silencing efficiency in the presence of GSH, suggesting that cellular GSH-induced degradation can promote gene silencing in cancer cells.

A further advancement was achieved by a team that fabricated a PEGylated poly(α-lipoic acid) copolymer (mPEG-PαLA) as a dual-reduction/pH-responsive nanocarrier for the co-delivery of paclitaxel (PTX) and doxorubicin (DOX) in osteosarcoma therapy.[85] The prepared NP-PTX-DOX exhibited enhanced release of PTX and DOX under reductive and acidic stimuli. Following cellular internalization, protonation of carboxyl groups in mPEG-PαLA and primary amines in DOX within the acidic intracellular milieu weakened the electrostatic and hydrophobic interactions between mPEG-PαLA and the encapsulated drugs. Moreover, degradation of the disulfide-containing PαLA backbone in the reducing cytosolic environment led to the disintegration of the nanoparticles. Both mechanisms mediated the synergistic, dual-reductive/pH-triggered release of DOX and PTX inside cells. Their results indicated that NP-PTX-DOX presented improved biodistribution and demonstrated a cooperative antitumor effect in a murine K7 osteosarcoma model.

In another study, a triblock copolymer, poly(tertiary-butyl methacrylate)-b-poly(2-hydroxyethyl methacrylate)-b-poly (poly (ethylene glycol) methyl ether methacrylate) (4AS-PtBMA-PHEMA-PPEGMA), was synthesized via activator regenerated by electron transfer atom transfer radical polymerization (ARGET ATRP), followed by Michael addition reactions and hydrolysis, which subsequently self-assembled into three-layer disulfide-crosslinked stimuli-responsive cross-linked micelles (SCMs). The Michael addition herein involved the reaction of the double bond on the triblock polymer with the amino group of cystamine, thereby forming the SCM structure. The hydrophilic PPEGMA outer shell maintained the stability of SCMs, while the intermediate PHEMA layer, functionalized with double bond, introduced crosslinking sites. The pH-sensitive poly (methacrylic acid) (PMAA) core enabled the encapsulation of the anticancer drug doxorubicin (DOX) and rendered the SCMs responsive to the acidic tumor microenvironment. The pKa of the carboxylic acid groups in PMAA was around 5–6, and they existed in the form of carboxylic acids (-COOH) at acidic pH and deprotonated to carboxylate ions at higher pH. Under neutral conditions, electrostatic interactions between the carboxylic groups on SCMs and the amino groups of DOX favored loading of more DOX, whereas these interactions were weakened under tumor pH conditions, triggering the rapid release of DOX.[86] Simultaneously, disulfide-cross-linking not only enhanced the stability of SCMs, restraining premature DOX release in normal tissues, but also permitted rapid DOX release in tumor cells where GSH concentrations are beyond 2 mm. Their data revealed that DOX-loaded SCMs showed a low percentage of cumulative DOX release under normal physiological conditions but exhibited

a significantly higher cumulative release percentage and faster release kinetics when placed in a tumor milieu characterized by weakly acidic pH and 10 mm GSH. This indicated that SCMs can not only enhance the efficacy of cancer therapy but also mitigate toxic side effects on normal tissues by virtue of their stimuli-responsive and tumor-targeted drug release profile.[87]

Redox- and Enzyme-Responsive Micelles

The study presented docetaxel (DTX)-loaded micelles (pDM) as a tumor microenvironment-responsive delivery platform. These micelles were ingeniously constructed from a pH-sensitive amphiphilic copolymer, poly((1,4-butanediol)-diacrylate-β-N,N-diisopropylethylenediamine)-polyethyleneimine (BD-PEI), and a matrix metalloproteinase (MMP)-responsive polymer, poly((1,4-butanediol)-diacrylate-β-N,N-diisopropylethylenediamine)-peptide-polyethylene glycol (PEG) (BD-peptide-PEG). In 4T1 tumor-bearing mice, upon reaching the tumor site, the PEG coating of the micelle was selectively shed by the overexpressed MMP-9, which in turn amplified the accumulation of DTX within 4T1 cells. Thereafter, DTX could be swiftly released in an acid-triggered manner, capitalizing on the lower pH typically observed in tumor microenvironments. Both in vitro and in vivo assessments demonstrated that pDM exhibited potent abilities to inhibit tumor growth and suppress metastasis.[88] This strategic design of pDM, integrating pH sensitivity with MMP responsiveness, represented a sophisticated approach to enhance targeted drug delivery to tumors and improve the therapeutic outcome of DTX, highlighting their potential as a robust cancer therapeutic modality.

pH- and Light-Responsive Micelles

Wu et al designed and synthesized an amphiphilic ABA-type triblock copolymer POEGEA-*b*-P(BaSt-*co*-PFS)-*b*-POEGEA, which contained a hydrogen bond (H-bond) moiety (barbituric acid, Ba) in its middle hydrophobic B block. The presence of pendant Ba molecules in the hydrophobic core enhanced the loading capability of methotrexate

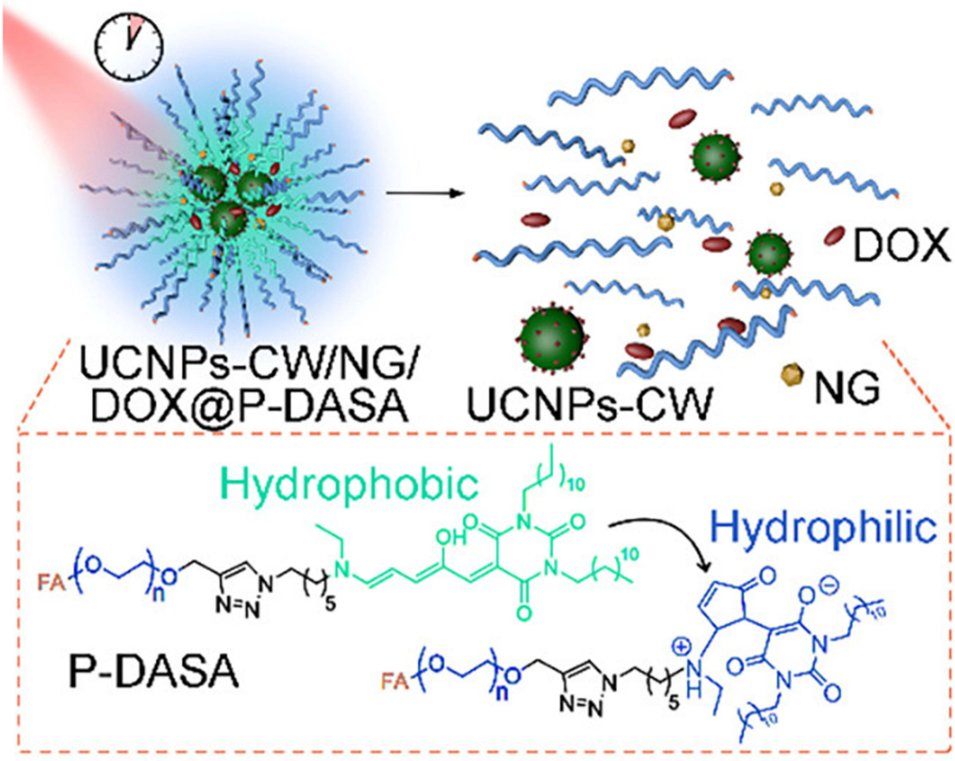

Figure 6 Self-assembly of UCNPs-CW/NG/DOX@P-DASA Reprinted with permission from Zhang Y, Zhang X, Chen W, et al. Self-assembled micelle responsive to quick NIR light irradiation for fast drug release and highly efficient cancer therapy. *J Control Release*. 2021;336:469-479. Copyright (2021). Elsevier.[89]

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(MTX) and transportation stability, due to the formation of specific Ba/MTX H-bond interactions. IR780, functioning as a photothermal agent, was concurrently encapsulated through hydrophobic interactions for a combined chemo-/photothermal therapies (CT/PTT) modality. Upon irradiation, the increased temperature weakened the Ba/MTX H-bond interactions, enabling the release of MTX. Their data confirmed that MTX release could be regulated by diverse H-bond stimuli, particularly temperature. The hyperthermia produced from IR780 led to the breaking and dissociation of H-bond, which in turn promoted the controlled MTX release for CT therapy.[90]

Temperature- and GSH-Responsive Micelles

The amphiphilic block copolymer P(AAm-co-AN)-b-PEI-ss-PEG-FA, possessing an upper UCST of 42°C, was capable of self-assembling into polymeric micelles under physiological conditions, which can further encapsulate the chemotherapeutic drug doxorubicin (DOX) and the photosensitizer ALS polymer to yield dual-responsive polymer micelles, DOX&ALS@MFM. Upon near-infrared (NIR) light irradiation, the local temperature swiftly rose, causing the UCST polymer to transiting from hydrophobic to hydrophilic, while the high intracellular concentration of GSH disrupted the disulfide bonds within the micelles, ultimately leading to the release of both ALS and DOX. Additionally, the photosensitizer ALS, under NIR light stimulation, generated singlet oxygen to eradicate tumor cells. Consequently, a multimodal tumor therapeutic strategy combining chemotherapy, photothermal therapy (PTT), and photodynamic therapy (PDT) was achieved.[91]

Light- and GSH-Responsive Micelles

For example, Zhang et al developed a near-infrared light responsive polymer P-DASA, which were comprised of hydrophilic polyethylene glycol segment and photo-responsive hydrophobic donor–acceptor Stenhouse adduct (DASA) (Figure 6). This polymer self-assembled with UCNPs-CW which were modified with IRDye® 800CW as antenna, the anticancer drug doxorubicin (DOX), and nitroglycerin (NG) to form micelles—UCNPs-CW/NG/DOX@P-DASA—that respond promptly to near-infrared (NIR) light exposure. Post-endocytosis and under brief NIR light illumination, the upconversion luminescence emission of UCNPs-CW at 541 nm triggered the photocleavage of DASA, shifting its conformation from hydrophobic to hydrophilic. This transformation precipitated the swift and complete disintegration of the micelles, culminating in the release of 83.7% of DOX within 30 minutes. Simultaneously, upon micelle disruption, NG acted as a nitric oxide (NO) donor,[89] and reacted with the overexpressed GSH in tumor cells. This reaction generated NO intracellularly, which inhibited the P-glycoprotein-mediated efflux of drugs in tumor cells.[92,93] The design of these micelles drastically reduced the NIR irradiation time, condensing it from hours to merely five minutes. This innovation will significantly expedite the therapeutic process while avoiding thermal damage.

Oxidation- and Temperature-Responsive Micelles

In this example, poly(hydroxyethyl acrylate-co-phenyl vinyl sulfide) (P(HEA-co-PVS)) was employed as an oxidizable amphiphilic LCST copolymer to fabricate an oxidation- and temperature-responsive polymer micelle system. The amphiphilic copolymer is composed of the hydrophilic HEA segments and the hydrophobic PVS units. Upon exposure to oxidative conditions, the PVS units was oxidized into more hydrophilic phenyl vinyl sulfoxide and/or sulfone, leading to the increased LCST of the copolymer. Then the micelles disassembled, triggering an oxidation and temperature-responsive release. Once internalized into cancer cells, the micelles were oxidized due to the high levels of ROS inherent in these cells. By encapsulating doxorubicin (DOX), a chemotherapeutic agent, within these micelles, the intracellular oxidation process was expedited, as DOX promoted the generation of oxygen radicals within cells, thereby more effectively suppressing the growth of KB cells in vitro. Consequently, these oxidation- and temperature-responsive micelles discharged their payloads in response to oxidative intracellular conditions—comprising both native ROS and DOX-induced radicals—augmenting the therapeutic impact against cancer.[94]

pH- and NIR-Responsive Micelles

Biodegradable and biocompatible amphiphilic block copolymers have shown tremendous potential in drug delivery, especially in the controlled drug release in cancer therapy. Yadav et al engineered a near-infrared (NIR) responsive shell-

crosslinked (SCL) micelles via the Diels-Alder (DA) click reaction between the amphiphilic copolymer, poly(d,l-lactide) 20-b-poly((furfuryl methacrylate)10-co-(N-acryloylmorpholine)78) (PLA20-b-P(FMA10-co-NAM78)) and a diselenide-containing crosslinker, bis(maleimidoethyl) 3.3′-diselanediyldipropionoate (BMEDSeDP). Anticancer drug doxorubicin (DOX) and the near-infrared sensitizer indocyanine green (ICG) were efficaciously encapsulated within these SCL micelles. The DOX/ICG-loaded SCL micelles exhibited pH and NIR-responsive drug release, characterized by a burst release under NIR laser irradiation. In vitro cytotoxicity assays revealed that SCL micelles were non-cytotoxic to normal HFF-1 cells, whereas DOX/ICG-loaded SCL micelles demonstrated pronounced antitumor activity against HeLa cells, highlighting their selective therapeutic efficacy.[26]

ATP- and pH-Responsive Micelles

Adenosine triphosphate (ATP) is a vital high-energy molecule in biological processes. It provides energy for cellular metabolism through the cleavage of phosphoanhydride bonds. As the direct energy supplier in life activities, ATP is widely present both inside and outside of cells. However, the intracellular concentration of ATP is approximately 1–10 mm, significantly higher than the extracellular concentration (about 0.4 mM).[95] This difference is particularly evident in tumor tissues with high growth and metabolic rates. Therefore, the significant disparity in ATP content between the intracellular and extracellular environments can be leveraged to develop ATP-responsive nanocarriers.

PBA and its derivatives can form stable ester linkages with diol compounds (eg ATP) in aqueous solutions, which is facilitated by an increase in both pH and the concentration of diol compounds. Utilizing this dual responsivity of PBA to pH and ATP, Yoshinaga et al developed plasmid DNA (pDNA)-loaded polymer micelles (PMs) for pH-responsive endosomal escape and ATP-mediated pDNA decondensation. The PMs were made from PEG-based block copolymers which were modified with 4-carboxy-3-fluorophenylboronic acid (FPBA) and GlcAm groups. These PMs demonstrated robustness in the extracellular environment, efficient escape from endosomes after cellular uptake, and pDNA decomplexation triggered by increased intracellular ATP concentrations. The results showed that ATP-responsive optimized PMs could effectively decomplex loaded pDNA intracellularly, thereby promoting gene transfection.[96]

Conclusions and Perspectives

In the field of tumor treatment, particularly in drug delivery, recent research has identified several major challenges. First, tumor cells can develop resistance to drugs, leading to reduced treatment efficacy. Second, ensuring that drugs specifically target tumor sites without affecting normal tissues is a significant challenge. Additionally, the physical and chemical barriers within the tumor microenvironment, such as high pressure, dense extracellular matrix, low pH, and hypoxia, significantly hinder drug penetration and distribution.[97] Individual differences in genetic background, lifestyle, and disease state among patients can influence drug absorption, distribution, metabolism, and excretion,[98] thus affecting the therapeutic efficacy.

In terms of drug delivery, controlling premature drug release before reaching the target site is a critical issue. This necessitates the development of intelligent drug release systems that are responsive to specific triggers such as pH changes, temperature fluctuations, or enzymatic activity. Besides, ensuring the stability of drugs within the intricate in vivo environment is crucial to protect them from chemical or biological degradation. Another critical aspect is enhancing drug targeting to minimize damage to healthy tissues, which is essential for optimizing therapeutic outcomes. And current researches are focused on developing highly specific targeting ligands or antibodies.[99] Furthermore, some drug delivery systems may trigger excessive immune responses, leading to rapid drug clearance or allergic reactions,[100] presenting another hurdle that must be addressed in the design and refinement of these systems.

Amphiphilic copolymer micelles are self-assembled nanostructures formed by amphiphilic block copolymers in aqueous solutions. These micelles consist of a hydrophobic core that encapsulates hydrophobic drugs or other therapeutic agents, surrounded by a hydrophilic shell that stabilizes the structure in water. They are designed to improve drug solubility, enhance targeted delivery, and reduce toxicity, making them valuable tools in drug delivery systems, particularly for cancer therapy.

Among them, stimulus-responsive micelles offer several advantages in targeted drug delivery for tumor therapy. They enhance targeting and specificity by selectively releasing their payload in response to stimuli such as pH changes, redox conditions, enzymatic activity, or temperature fluctuations, which are characteristic of tumor environment. This selective release significantly lowers systemic toxicity and side effects associated with conventional chemotherapy, while increasing therapeutic efficacy through enhanced accumulation at the tumor site. The development of drug delivery systems in vivo varies with the type of stimuli, with each possessing its own advantages and limitations when used in the body. For example, light-responsive systems are effective at superficial depths but have limited signal penetration and focusing capabilities in transdermal applications, which restricts their use in deeper tissues. Nevertheless, light-activated platforms hold clinical potential in vivo, especially for surface areas, where light-responsive systems can offer more precise control over intracellular biochemical reactions.[101] Additionally, the multifunctionality of these micelles allows for the design of carriers capable of carrying multiple therapeutic agents or incorporating imaging agents for theranostic applications, providing a platform for personalized treatment strategies tailored to individual patient needs.

Despite these advantages, there are several challenges that need to be addressed. Firstly, developing micelles that respond precisely to specific stimuli can be complex due to the intricate nature of tumor biology and the need for precise tuning of the responsiveness. Besides, optimizing the biodistribution of these micelles to achieve maximum therapeutic effect while minimizing off-target effects remains an ongoing challenge. Furthermore, translating these micelles from bench to bedside requires extensive preclinical and clinical studies to ensure safety and efficacy. To date, three polymeric micellar nanomedicines have been approved for the market: Genexol®PM, Nanoxel®M, and Paclical®. Genexol®PM, the earliest polymeric nanomedicine approved for human use, was introduced in 2007 in South Kore a, the Philippines, India, and Vietnam. However, the clinical translation of stimulus-responsive micelles faces several challenges. First, there is the issue of drug release controllability and consistency. Additionally, safety remains a major concern, as the biocompatibility and biodegradability of micelles must be ensured to prevent toxicity or immune reactions. The manufacturing process is complex and costly, which limits their large-scale production and widespread use. Furthermore, the in vivo behavior of micelles, including their distribution and elimination, is not fully understood, making pharmacokinetics more complicated and requiring more clinical data to verify their performance in different patient populations. Currently, there is a lack of accurate in vitro and in vivo models to evaluate the actual treatment scenarios in patients, leading to inconsistencies between clinical and preclinical outcomes. Therefore, future preclinical studies should focus on developing and utilizing innovative technologies to aid in assessment, such as precisely simulated organoids, organs-on-a-chip, and patient-derived xenografts. These advanced models can provide more relevant and predictive data, bridging the gap between preclinical research and clinical application.[102] It can be a lengthy and resource-intensive process. Lastly, the development and production of these advanced micellar systems can be expensive, potentially limiting their accessibility.

To address these challenges, several potential solutions are currently being explored. For example, more complex mechanisms for drug release that are triggered under specific conditions can be developed to enhance responsiveness, specificity, and efficacy. Additionally, the use of biodegradable and biocompatible materials can improve the safety profile of the drug delivery system by reducing immune reactions. Furthermore, by adjusting the surface properties and size of the micelles, it is possible to optimize their biodistribution, which helps maximize accumulation in tumor tissues while minimizing uptake in non-target organs. As for clinical translation challenges, optimizing micelle design, streamlining manufacturing processes, and precisely tracking drug distribution can improve release consistency and safety. Personalized treatment strategies and adaptive clinical trial designs can help address the complexities of pharmacokinetics and reduce clinical risks. With continued innovation and refinement, stimuli-responsive micelles hold great promise for advancing tumor therapy by providing safer, more effective, and personalized treatments.

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Disclosure

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