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Redox-responsive polymers for drug delivery: from molecular design to applications

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Glutathione has been regarded as a significant signal for distinguishing between tumor and normal tissue. Recently, reactive oxygen species have attracted much attention for their close connection with many diseases. Taking advantage of the physiological signals, redox-responsive polymeric drug carriers constitute a significant research area in the various stimuli-responsive polymers for biomedical applications. During the rapid development of redox-responsive polymers, molecular design and related synthetic methodology plays a crucial role. In this review, we discuss the reduction- and oxidation-responsive polymeric drug carriers from the view of functional groups, as well as their applications in controlled release.

1. Introduction

Drug delivery systems are regarded as one promising approach to alter the pharmacokinetics and/or bio-distribution of drugs.[1] By means of the enhanced permeability and retention (EPR) effect discovered by Maeda in 1989, or active targeting molecules which are decorated on the surface of the system for specific recognition of the target area, to some extent, drug delivery systems have alleviated the main problems of many drugs, such as poor solubility and bio-distribution, inappropriate pharmacokinetics, and severe side effects.[2–6] As in the exhaustive research papers in the past decades, "2P" should be taken into account when designing drug delivery systems. The first "P" refers to "protect", that is, the drug carriers are required to protect the drugs from metabolism in blood circulation.[7,8] Besides particle size control, PEGylation was also considered as an ideal tool for reducing the chance of both immunological and kidney clearance.[9–11] The other "P" is "preserve", which means that the carriers should preserve the drugs for a suitable or even programmable time interval before entering malignant tissues or cancer cells.[12] To realize this function, new

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generations of drug delivery systems have been endowed with stimuli-responsiveness.[13,14] After navigation along the blood stream, drug carrier systems with pre-designed stimuli-responsiveness accumulated around or even entered the cancerous cells and disintegrated under the carcinoma physiological environment or external stimuli.[15]

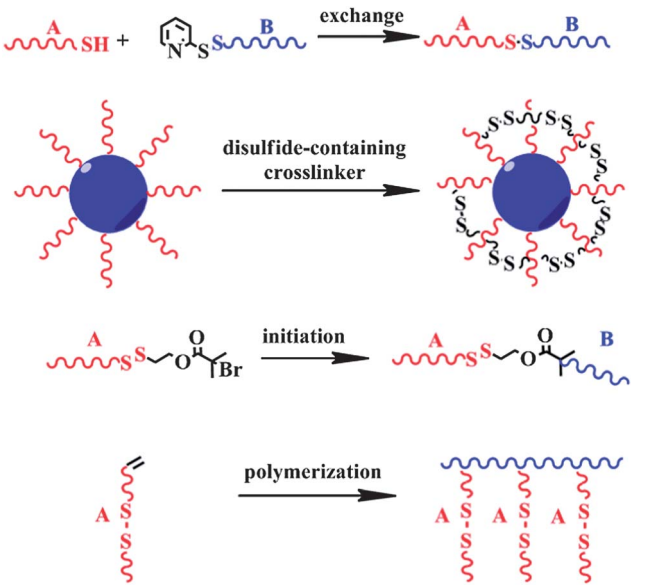
Most of the drugs would be pumped out of the tumor cell though the multi-drug resistance mechanism. As a result, they could not take effect even though they have entered the cells.[16] One goal of stimuli-responsive polymeric drug carriers was to enable the drugs to instantaneously release after entering the cell, so as to increase the drug concentration to the threshold to kill the cancer cells.[17] To better control the drug carriers, they have up to now been endowed with pH-, redox-, light-, magnet-, thermal-, gas- and ultrasonic-responsiveness.[18–33] In this review article, we focus on the redox-responsive polymeric drug delivery systems. After a brief introduction to the redox-responsive polymeric drug delivery systems, we will further discuss reduction-responsive and oxidation-responsive systems.

2. Redox-responsive polymeric drug delivery systems

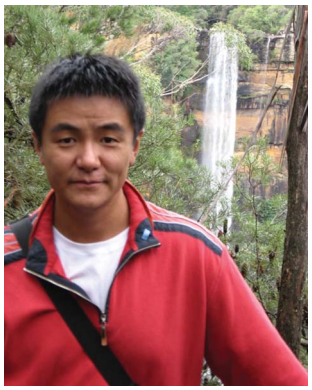
The basic principle of redox-responsive polymeric drug delivery systems is to utilize the distinct differences in redox potentials between tumors and normal tissues. It has been demonstrated in many papers that GSH/glutathione disulfide (GSSG) is the most abundant redox couple in animal cells. In the cytosol and nuclei, the concentration of GSH reaches 10 mM under the reduction of NADPH and glutathione reductase, while outside the cell the concentration drops to about 2–20 μM.[34] Moreover, *in vivo* research has demonstrated that the tumor tissues showed at least 4-fold higher GSH concentrations than that of normal tissue in mice.[35] On the other hand, reactive oxygen species (ROS) are believed to be implicated with some serious diseases like arteriosclerosis, heart injury and cancer.[36] All of these pathological signals can be exploited as guidance for redox-responsive drug delivery systems.

2.1 Reduction-responsive polymeric drug delivery systems

2.1.1 Systems with the disulfide linkage. Disulfide linkages have been applied broadly in reduction-responsive polymeric drug delivery systems.[37–44] As illustrated in Scheme 1, there are some general synthetic methods for incorporating the disulfide linkage, among which the thiol–disulfide exchange reaction is an efficient and mild method, while for crosslinking structures like shell cross-linked micelles, interlayer-cross-linked micelles and gels, disulfide-containing cross-linkers play an important role. Since Prochaska and Baloch's group put forward the concept of core-cross-linked micelles, numerous reports have



Scheme 1 Schematic illustration of the synthetic methods for incorporating the disulfide linkage.



Dr Lei Tao graduated from the University of Science and Technology of China, receiving his Bachelor and Master degrees in 1999 and 2002, respectively. After his PhD study in Warwick University (2003–2006), he moved to the University of California, Los Angels (UCLA, USA) in 2006, and then the University of New South Wales (UNSW, Australia) in 2008 as a postdoctoral research assistant. In 2010, he joined the Department of Chemistry, Tsinghua University. His research interests are focused on the synthesis of well-defined polymers through controllable polymerization methods and the application of those polymers in biological areas.

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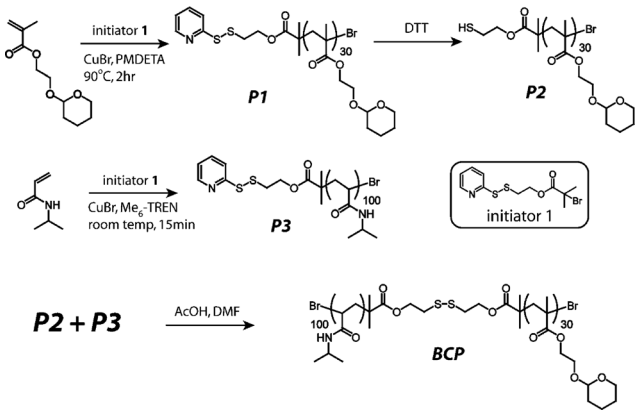
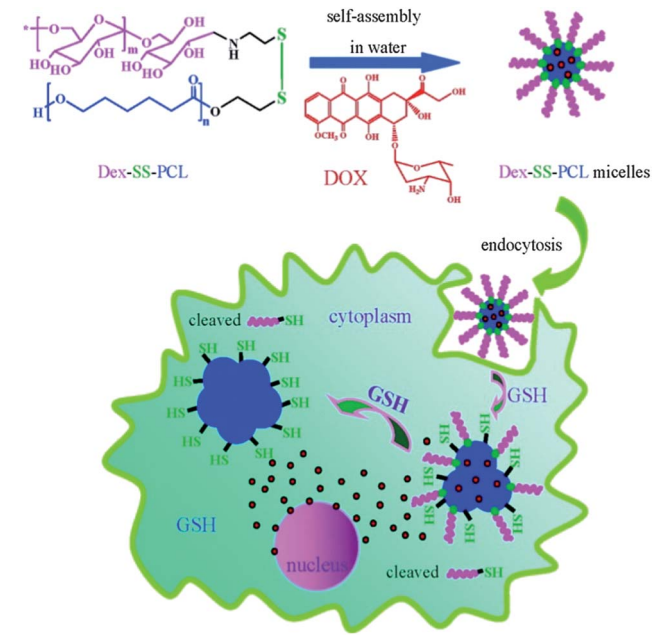
focused on different crosslinking methodologies, which has been summarized by O'Reilly *et al.* in their review.[45] Recently, with the rapid development of living/controlled polymerization, polymers with well-defined end-groups have been designed by atom transfer radical polymerization (ATRP), reversible addition-fragmentation chain transfer polymerization (RAFT) as well as ring-opening polymerization (ROP), in which disulfide may act as the end-group or be introduced to the end of the polymer chain by post-polymerization.[46–49] Besides, disulfide bonds can also be introduced into olefins, resulting in polymers with disulfide bonds on the side chains. In this section, we will provide a detailed discussion about these synthetic methods.

In biological areas, the thiol–disulfide exchange reaction has been found to be closely related to signal transduction, thiol protection and switching between the different conformational and functional states of enzymes.[50–53] In biomedical applications, it has been exploited extensively for constructing redox-responsive prodrugs, and gene and drug carriers.[34,54–58] For example, Meng and Zhong's group designed a facile way to prepare the disulfide-linked dextran-*b*-poly(ε-caprolactone) amphiphilic block copolymer using the thiol–disulfide exchange reaction under mild conditions (Scheme 2).[59] With an average size of 60 nm in phosphate buffer solution (PBS), the micelles released their cargo in a zero-order manner and almost all of the doxorubicin (DOX) anti-cancer drugs could be released in 10 h at 10 mM dithiothreitol (DTT). Confocal laser scanning microscopy (CLSM) images showed that DOX-loaded micelles showed effective inhibition to RAW 264.7 cells, while the left empty micelles showed non-toxicity. Using modular design, Thayumanavan and his group prepared a disulfide bond-containing ATRP initiator 1 (Scheme 3) and used it to initiate *N*-isopropylacrylamide and tetrahydropyran protected 2-hydroxyethyl methacrylate, respectively.[60] Disulfide bonds featured in the resulting di-block copolymer enabled the successful integration of three stimuli-responsive patterns, which not only showed synergistic effects, but also provided multiple-mode control of the resulting micelle system. One possible problem of the thiol–disulfide exchange reaction may lie in the oxygen sensitivity of thiol-containing compounds, which may increase the complexity of the pretreatment procedure.

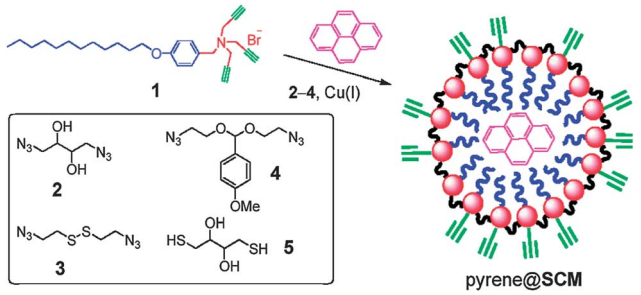


Scheme 3 Synthetic route of a multi-sensitive block copolymer.[60]

Apart from the direct disulfide linkage formation reaction, one of the most common strategies was crosslinking through disulfide-containing cross-linkers.[61] Up to now, there have been numerous structures built on the basis of cross-linking reactions.[62–65] Dithiodipropionic acid, bis(2,2′-hydroxyethyl)disulfide, cystamine and their derivatives were the most useful small molecules for disulfide functionality.[56] The resulting cross-linked micelle was observed to efficiently prevent drug leakage in circulation before reaching the target. After core-cross-linked micelles, Wooley's group raised the concept of "shell-cross-linked knedel-like" (SCK) particles, and latter Armes' group and McCormick's group applied this method to stimuli-responsive polymers.[66–68] However, cross-linking may slow down the response speed. Recently, Zhang and Zhao reported a surface-cross-linked micelle with extremely rapid release of the encapsulated pyrene (Scheme 4).[69] The reason for the fast release profile was associated with the electrostatic repulsion among



Scheme 2 Schematic presentation of redox-responsive Dex–SS–PCL micelles and the intracellular release of DOX.[59]



Scheme 4 Schematic representation of the surface cross-linked micelle.[69]

the headgroups. Once the covalent crosslinking shell was broken by the stimuli, the electrostatic repulsion would be predominant and the micelle exploded rapidly. This may provide inspiration for cross-linked micelles.

During recent decades, disulfide-containing ring-opening initiators, ATRP initiators and RAFT agents have been increasingly exploited as a convenient approach to disulfide-containing polymers with defined-structures.[60,70–72] For instance, Huang and Yan's group have recently synthesized a functional monomer with a disulfide bond, which was further polymerized into hyperbranched polyphosphate by self-condensing ring-opening polymerization.[71] With a hydrophobic disulfide domain and hydrophilic phosphate, these homopolymers could self-assemble into multi-core–shell micelles with potential applications in drug release. Kataoka and coworkers synthesized a series of block copolymers (PEG–SS–P(Asp), PEG–SS–P[Asp(DET)] and PEG–P[Asp(DET)]) by ring-opening polymerization, and the electrostatic attractions between the polycations and polyanions blocks drove them to self-assemble into polyion complex micelles (PICmicelles) (Scheme 5).[70]

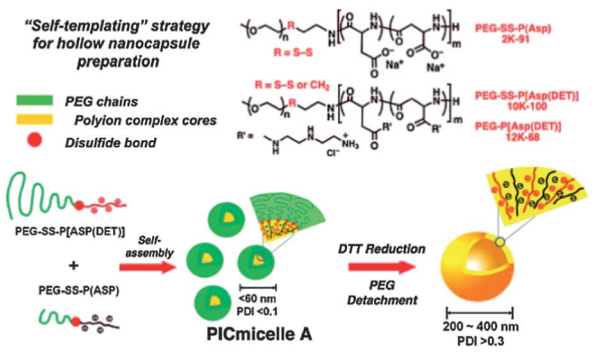
Interestingly, these micelles re-assemble into hollow nanocapsules under the reduction of the DTT, thus providing a "self-templating" approach towards hollow nanocapsules. Apart from introducing a disulfide bond into the initiator, nucleophilic attack of the thiocarbonyl group was a simple way to convert the end-group of RAFT polymers to thiols, which can not only react with the disulfide but extend the reaction to thiol chemistry.[72]

Olefin-based polymers with disulfide bonds hanging on the side chain could be obtained by the polymerization of disulfide-containing monomers. This strategy satisfied a tunable balance between the hydrophobic and hydrophilic blocks, and once the balance was broken by cleaving the disulfide bond, the assemblies would collapse to release the drugs. Moreover, according to the amount of DTT added, there could be a micelle-to-nanogel transition that provided a more complex release profile.[73] This micelle-to-nanogel transition afforded a facile technique to solve the drug leakage problem of uncross-linked polymeric carriers in clinical applications. Thayumanavan *et al.* synthesized self-cross-linked nanogels based on RAFT polymerization of oligoethyleneglycol methacrylate (OEGMA) and pyridyl disulfide ethyl methacrylate (PDSMA).[74] Nanogels with controlled size and guest release rate formed after adding a certain amount of DTT into the precursor solution. As presented in Scheme 6, fluorescence resonance energy transfer (FRET) was used to study the stability of the nanogels and their encapsulation ability: no green fluorescence emission indicated that the FRET occurred among the dye molecules in the network, while after adding 20 mM DTT, the breakage of the nanogels enabled the dyes to migrate to the hydrophobic domain of the dioleoyl phosphatidylcholine bilayer vesicles, which caused the decrement of the FRET ratio.

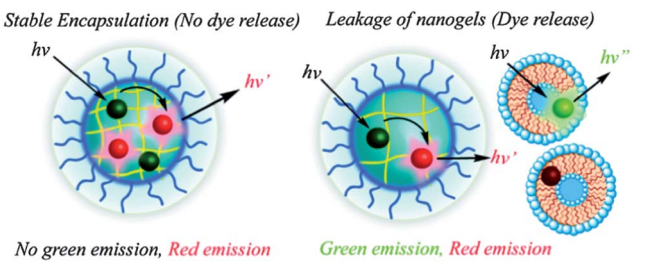
2.1.2 Systems with the diselenide linkage. Selenium and sulfur belong to the same group in the periodic table, and have many similar chemical properties. The lower bond energies of diselenide and the carbon–selenium bond (Se–Se 172 kJ mol^{-1}; C–Se 244 kJ mol^{-1}) made it possible to fabricate more sensitive drug carriers for site-specific drug release. The selenium-containing polymer was, however, still in its infancy due to the lack of efficient synthetic methods to overcome its poor solubility. Xu and Zhang's group have recently developed a series of selenium-containing polymers and have used various stimuli to trigger these polymers to release the model molecules.[75]

In 2009, Xu and Zhang's group reported a diselenide-containing polyurethane triblock copolymer, PEG–PUSeSe–PEG, using toluene diisocyanate as the chain extension agent (Scheme 7).[76] They investigated both the reduction- and oxidation-responsive behaviors of these assemblies, and the results indicated that the diselenide was much more sensitive: even under 0.01 mg mL^{-1} GSH the encapsulated Rhodamine B could still be released almost entirely in only 5 h, while they were stable without redox stimuli. To confirm its use in drug delivery and tumor inhibition, Pang, Huang and Yan *et al.* introduced the diselenium bond into a hyperbranched structure and found that the hyperbranched polydiselenide could not only be used as a biocompatible drug carrier but itself had the ability to inhibit tumor proliferation.[77]

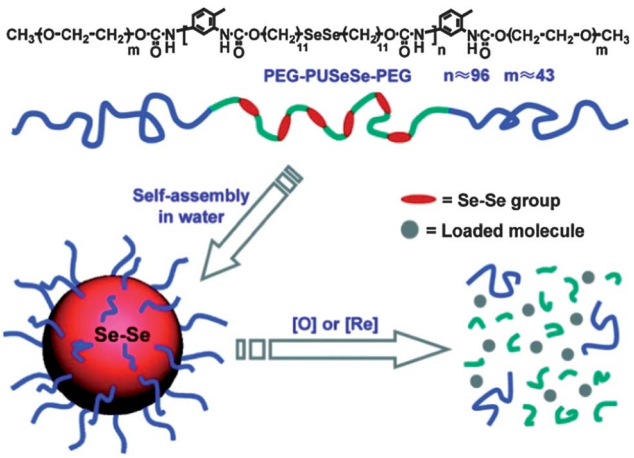
Until now, diselenide-containing polymers were still limited by the difficulty in the incorporation of the diselenide bond. To some extent, Xu and Zhang's work has depicted their fascinating future in controlled release and enzyme mimics. Recently, Zhu *et al.* reported the development of a new RAFT mediator based on diselenocarbonyl compounds.[78] After optimization, they obtained a comparatively universal selenium-containing RAFT agent which may be of significance for



Scheme 5 Self-assembly of PEG–SS–P(Asp) and PEG–SS–P[Asp(DET) and morphology transition under DTT reduction.[70]



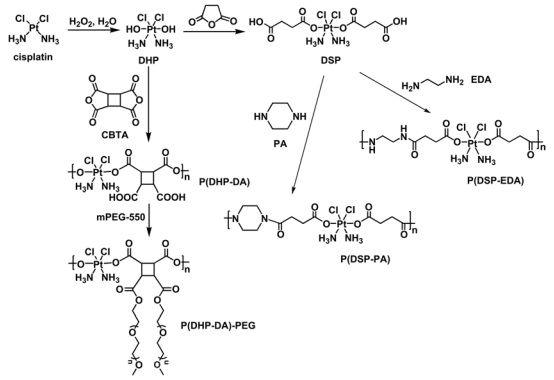
Scheme 6 Mechanism of the FRET experiment in comparing the stability of nanogels with or without a reducing agent.[74]



Scheme 7 Redox-responsive diselenide-containing PEG–PUSeSe–PEG block copolymers.[76]

preparing well-defined selenium-containing polymers. With more attempts in this field, diselenide-containing polymers will definitely grow into an important class of biomaterials.

2.1.3 Other explorations of reduction-responsive functional groups. Besides disulfide and diselenide bonds, there are a few reduction-responsive linkers that were less explored. These newly-investigated functional groups can be used not only in controlled release, but in catalysis, energy, water purification, microfluidics, actuators and sensors. Sui and Shen's group reported a series of interesting reduction-responsive platinum(IV)-coordinate polymers using condensation polymerization (Scheme 8).[79] Cisplatin is a broad-spectrum anti-cancer drug with severe side effects to normal cells, because of which it was conjugated onto polymers to alleviate its side effects as well as improve its anti-cancer efficiency. In their synthetic scheme, cisplatin was firstly oxidized to *cis*,*cis*,*trans*-diamminedichlorodihydroxy-platinum(IV) (DHP), which acted as a diol to react with dicarboxylic acid anhydrides, or react with succinic anhydride to obtain a diacid *cis*,*cis*,*trans*-diamminedichlorodisuccinato-platinum (DSP) species. As both DHP and DSP could be used in polycondensation, cisplatin could be



Scheme 8 Synthetic scheme of the platinum(IV)-coordinate polymers.[79]

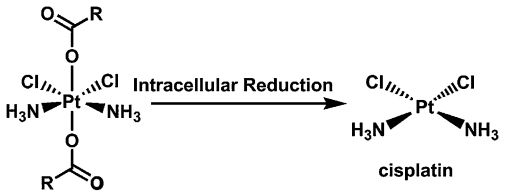
introduced into the polymer backbone with a high mass ratio. More importantly, after post-polymerization, these polymers would integrate into micelles that could be further used to encapsulate other drugs. These cisplatin derivatives could be reduced to release both cisplatin and the encapsulated drugs after endocytosis (Scheme 9). This is the first example that used redox-responsive drugs as the building blocks of drug carriers, which not only developed a new method to cisplatin conjugation but provided a new thought for the design of redox-responsive polymers. As most drugs have many reactive functional groups such as hydroxyl, carboxyl, amine, thiol groups, they may be applied in this procedure after suitable modification.

Trimethyl-locked benzoquinone (TMBQ) and the corresponding hydrocoumarin have been studied extensively, from the transformation mechanism and kinetics to their applications in prodrug design, solid-phase synthesis, probes and biological switches.[80] McCarley and his group used it as a trigger of responsive liposomes for the first time.[81] However, little attention has been paid to exploit it as switch for redox-responsive polymers until in 2012 Jo *et al.* applied the TMBQ redox-responsive chemistry for the design of polymeric drug carriers (Scheme 10).[82] Under the reduction of sodium dithionite, the TMBQ was shed from the polymer backbone, resulting in the disassembly of the nanoparticles. *In vitro* drug release experiments showed that this new nano-vehicle could release 52% of the drugs within 3 h in the presence of sodium dithionite, while only 13% of the drugs were released over 12 h without the reducing agent. Yet, the reducing concentration used in the experiment was relatively high compared with that in the cell, and there was no experimental data about the *in vitro* cytotoxity.

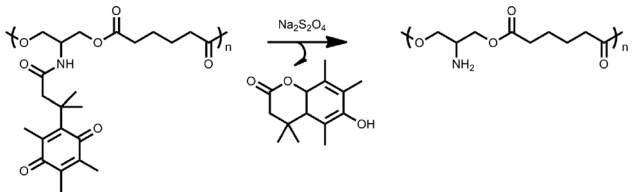
Another redox-responsive system was based on 4-*N*-amino-2,2,6,6-tetramethylpiperidin-1-oxyl-4-yl (TEMPO), which has vast applications in selective catalysis and battery materials.[83,84] Recently, it was used to tune the lower critical solution temperature of poly(*N*-isopropylacrylamide) (PNIPAM).[85] Further applications may be exploited in the field of redox-responsive drug delivery.

2.2 Oxidation-responsive polymeric drug delivery systems

Oxidation-responsive drug carriers rely on reactive oxygen species (ROS) such as hydrogen peroxide (H_2O_2) and hydroxyl radicals, whose origin is byproducts from aerobic metabolism. Like glutathione, ROS can be found in nearly every corner of the body, the concentration of which would increase significantly



Scheme 9 Reduction of a cisplatin derivative in tumor cells.[79]



Scheme 10 TMBQ shed from the polymer backbone upon reaction with sodium dithionate.[82]

during surgery or when suffering from many diseases, resulting in the damaging of cells.[36,86] As a result, the ROS can be used as signal molecules of arteriosclerosis, some nerve diseases and heart injury.[87] Taking advantage of ROS, oxidation-responsive polymeric drug delivery systems have enlarged the limits of redox-responsive drug carriers.[88]

2.2.1 Sulfide-containing oxidation-responsive systems. Poly(propylene sulfide) (PPS) was the first hydrophobic block used in the oxidation-responsive destabilization of vesicles.[89] The permeation of H_2O_2 into the PEG–PPS assemblies enabled the PPS core to be oxidized into hydrophilic sulfoxide and eventually into sulfone. As a result, the assemblies became more and more hydrophilic, and thus the curvature of the hydrophobic–hydrophilic interface became larger and larger, along with the morphology transformation from vesicles to micelles. Its advantage in drug delivery is that after oxidation, the size of these assemblies would eventually be sufficient for kidney clearance. To further investigate its application in drug delivery, Hubbell *et al.* used cyclosporin A as a model drug and further studied its ability to encapsulate and release hydrophobic drugs.[90] However, no oxidation-responsive drug release experiments were involved. Later, Hu and Tirelli conjugated this block copolymer with superoxide dismutase (SOD), endowing this hybrid system with both peroxide- and superoxide-responsiveness.[91] More importantly, it resembled the functionality of the SOD/catalase combination, while being more stable and efficient. This system acted as a scavenger, while the superoxide dismutase may be used as a new target molecule for controllable release. Mahmoud *et al.* have added pH-responsiveness on the basis of PPS to obtain redox- and pH-responsive polythioether ketal nanoparticles.[92] Dynamic light scattering (DLS) results showed that these nanoparticles would not degrade entirely unless in the buffer solution with both H_2O_2 and acid. Drug release experiments indicated that these nanoparticles would partially release their cargo upon oxidation stress; while treated with both H_2O_2 and acid, they would be fully degraded and nearly all the Nile Red would be released in 24 h. *In vitro* cell assays showed no toxicity of the carrier, which confirmed their potential in clinical applications.

As sulfur is relative stable, sulfide-containing oxidation-responsive polymers have not been reported extensively. In fact, the architecture of sulfide-containing polymers is almost, if not all, linear. More synthetic methods were needed for polymers with various architectures to function in different applications.

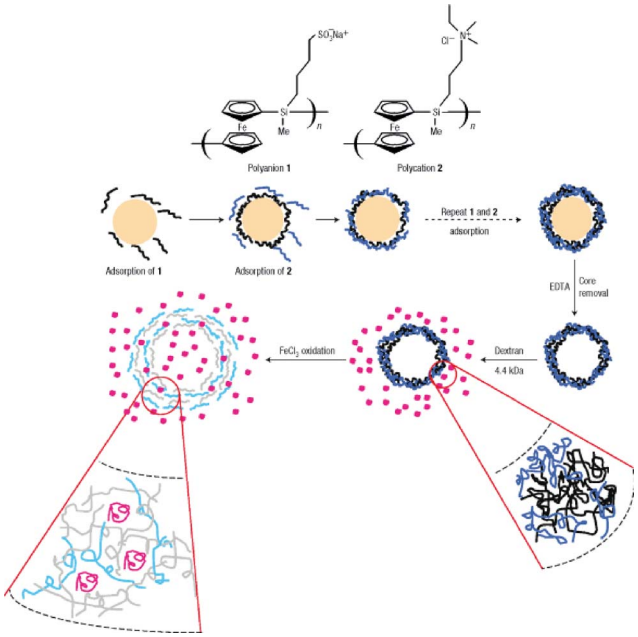
2.2.2 Selenium-containing oxidation-responsive systems. As was mentioned above, selenide is more reactive than sulfide, and polymers incorporated with selenium had more plentiful architectures. In addition, the weak bond energy of carbon–selenium brought multiple stimulus approaches, for example, various concentrations of oxidation agents. Replacing diselenium with single selenium, Xu and Zhang's group obtained a new tri-block copolymer, PEG–PUSe–PEG, with repeated selenide in the middle segment.[93] Upon oxidation by 0.1% H_2O_2, the pre-formed drug-loaded micelles released ~72% of the drugs in 10 h. Additionally, they have successfully prepared an amphiphilic block copolymer with selenium in the side chain.[94] The formed micelles disaggregate upon oxidation and re-aggregate into micelles on incubation with a mild reducing agent. Huang and Yan's group applied selenium for constructing an amphiphilic hyperbranched polymer with alternative selenium and phosphate groups in the main structure.[95]

Compared with the conventional covalent bond, supramolecular tools have the intrinsic advantages to overcome the complex synthetic routes required to incorporate the selenium. For example, Xu and Zhang's group developed approaches to selenium-containing oxidation-responsive systems with a selenium-containing surfactant and poly(ethylene glycol)-*b*-acrylic acid.[96] Hydrophobic interactions and electrostatic attractions between the surfactant and poly(acrylic acid) anion served as the driving force for the assemblies, which disassociated under the incubation of 0.1% H_2O_2 solution. The model molecule fluorescein sodium was loaded and released in a controllable manner for further exploring the potential applications. However, the toxicity of the surfactant used should be considered in clinical applications.

2.2.3 Ferrocene-containing oxidation-responsive polymers. Ferrocene-containing polymers have been the most studied species among the oxidation-responsive polymers, with applications ranging from biomedicine, biosensors, actuators, batteries, and liquid crystals to electronics and other related areas.[97–107] According to the location of ferrocene in the polymer, these polymers can be roughly divided into three types: polymers with ferrocene in the backbone, polymers with ferrocene on the side chain, and polymers with ferrocene as the terminal group.

Vancso's group reported an oxidation-responsive polymeric hybrid capsule fabricated by LBL assembly on colloidal microparticles followed by core removing, which is depicted with more detail in Scheme 11.[108] Oxidation-responsive poly(ferrocenylsilane)-containing polycations and polyanions was chosen as the main building blocks, while the outer layers of the capsules were composed of poly(styrene sulfonate) and poly(allylamine hydrochloride) (PAH) in order to suppress the excess swell in the oxidation state. Interestingly, both the size and permeation could be well-tuned *via* the redox state change, which can be very meaningful in biomedical applications and biomimetic research.

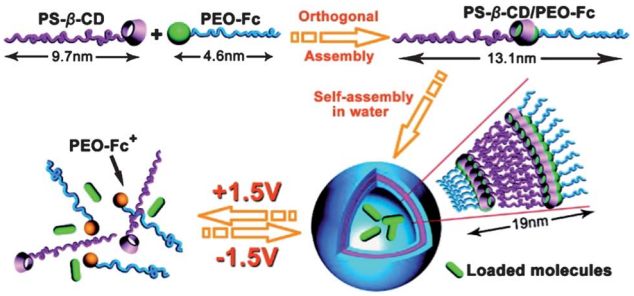
Gallei and Crespy's group successfully fabricated poly(vinylferrocene)-*block*-poly(methyl methacrylate) (PVFc-*b*-PMMA) nanocapsules with ferrocene on the side chain.[109] Microphase separation in the nanoparticles led to a patchy structure, with PVFc patches surrounded by the PMMA phase. Furthermore, these patches could be oxidized into hydrophilic



Scheme 11 LBL process of the polymeric hybrid capsule and its redox-responsive "breath".[108]

ferrocenium, forming many leaky tunnels for the encapsulated liquid. Gao *et al.* developed another facile way to synthesize ferrocene-containing polymers.[110] Instead of direct polymerization, they prepared the single-component microcapsules by the *in situ* reaction of PAH with ferrocenecarboxaldehyde in $CaCO_3$ nanoparticles. In contrast to the typical electrostatic attractions, the microcapsules were stabilized by the hydrophobic interactions of the ferrocene group and the protection of hydrophilic PAH after the core removal.

Polymers decorated with ferrocene as the terminal group are usually used to construct more complex systems, utilizing ferrocene-related host–guest chemistry. Depending on the redox state of ferrocene, the inclusion complexation between ferrocene and cyclodextrin has been verified to associate and disassociate reversibly. For example, Chen and Jiang have exploited the ferrocene-terminated diblock copolymer poly(*N*,*N*′-dimethylacrylamide)-*b*-poly(*N*-isopropylacrylamide) and cyclodextrin-decorated CdS quantum dots to obtain a redox-responsive hybrid hydrogel at elevated temperatures.[111] Our group have prepared a pseudo-block copolymer *via* orthogonal assembly between cyclodextrin-modified poly(styrene) and ferrocene end-functionalized poly(ethylene oxide) in aqueous solution (Scheme 12).[112] These supramolecular block copolymers could further self-assemble into polymeric vesicles with voltage-responsiveness. The association–disassociation balance could be changed by electro-stimuli: upon a +1.5 V voltage stimulus, the vesicles disassembled into small pieces in less than 5 h, while under a −1.5 V voltage, the fragments could reassemble into vesicles. Further controlled release experiments elucidated that the release rate can be well-controlled by slightly tuning the voltage strength, exhibiting great potential in electrochemical therapeutic applications.[113] To further explore

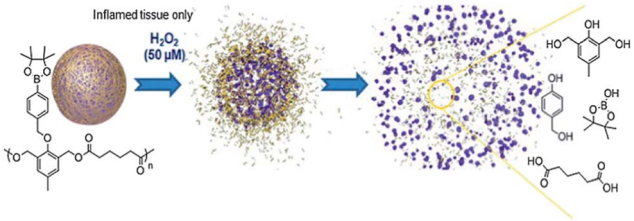


Scheme 12 Orthogonal assembly of PS-β-CD and PEO–Fc and their voltage responsiveness.[112]

the application of this host–guest chemistry based electrical-responsive pattern, we decorated oligo(ethylene glycol) with ferrocene and β-cyclodextrin to obtain Fc–OEG–Fc and β-CD–OEG-β-CD, respectively.[114] These two monomers would form a supramolecular polymer with a 1 : 1 ratio as a result of host–guest inclusion, and the supramolecular polymers further hierarchically self-assemble into fibres with voltage-responsive degradation and self-healing properties.

Ferrocene-containing polymers have found applications in switches, probes and electric devices. In biomedical applications, they may serve as long-term drug delivery pumps that release drugs upon exerting electricity, and thus may be helpful to ensure maximal therapeutic effects.

2.2.4 Other emerging oxidation-responsive systems. Boronic ester groups are an emerging oxidation-responsive functional group that may be exploited in clinical applications.[115] Almutairi and her group have made use of self-immolative polymers with a boronic ester as the trigger for controlled burst release (Scheme 13).[116] Removal of the boronic ester cap at the inflammation site or cancerous tissue produces phenols which undergo subsequent quinone methide rearrangement. As a result, the nanoparticles crumbled into small molecules along with the drug release. What made it superior to the conventional drug release profile is that these nanoparticles degraded entirely into small molecules upon stimuli, enabling the guest molecules to release without any carrier adsorption. However, the cytotoxity of these small molecules should be taken into consideration for clinical applications. Fréchet *et al.* conjugated boronic esters onto the lateral of dextran using smart synthetic chemistry, and the resulting microparticles were very sensitive to oxidants, for their release half-life was



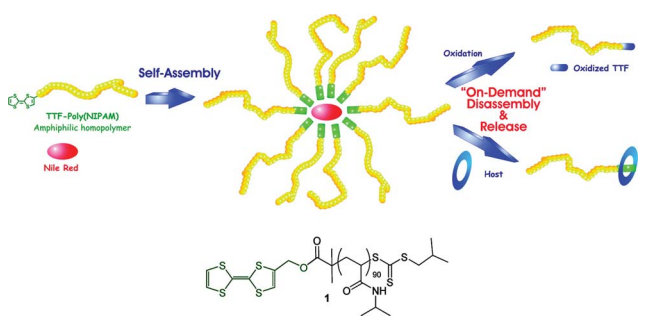
Scheme 13 The degradation of self-immolative nanoparticles caused by H_2O_2 in inflamed tissue.[115]

36 min at 1 mM H_2O_2 while that without H_2O_2 was greater than one week.[117] Additionally, *in vitro* cell cytotoxicity assays showed that these microspheres were non-toxic, which may provide a facile method to ease the potential toxicity of these self-immolative polymeric drug carriers.

Aside from boronic esters, some other redox-responsive groups such as tetrathiafulvalene, mesoporous silicon, polythioketal and oligoproline have also been used in bio-related polymer synthesis.[36,118–120] For example, Cooke and Woisel have found that tetrathiafulvalene (TTF) end-modified PNIPAM homopolymers would self-assemble into micelles in aqueous solution (Scheme 14).[118] The main reason for the stability of this micelle is presumably the integration of hydrophobic interactions of TTF groups, S···S interactions and π–π stacking. These micelles could be broken by oxidation and host–guest inclusion of the TTF group and tetracationic macrocycle cyclobis(paraquat-*p*-phenylene) ($CBPQT^{4+}$). Further, the amphiphilicity of this polymer could be manipulated by adding $CBPQT^{4+}$ or the randomly methylated β-cyclodextrin.[121] Because of TTF's diverse redox and inclusion chemistry, this polymer may be used in drug carrier, biological probe, redox-responsive switch, and molecular machine.

3. Conclusion and perspective

Taking advantage of the specific micro-environment of cancer tissues, redox-responsive carriers satisfy the trend of non-invasive therapy. The incorporation of various redox-responsive functional groups onto the polymer rendered the polymer with "intelligence", and thus the assembled drug carriers would be able to transport to the required region. In fact, the physicochemical discrepancy between cancerous and normal tissues is rather small for conventional chemical stimuli, so the development of redox-responsive polymeric drug carriers moves towards a more sensitive trigger. To realize the goal, more attention should be focused on the relative concepts in organic chemistry. Moreover, the hetereogeniety of tumor cells will inevitably increase the difficulty of drug carriers to take effect *in vivo*. Shen and Gu's group have pointed out recently that polymeric nanoparticles responsive to both GSH and ROS may provide an approach to the hetereogeneity of tumor microenvironment.[122] In fact, there were indeed some redox-responsive functional groups, for example, sulfide, disulfide, selenium, diselenium and ferrocene, that have been studied for both reduction- and oxidation-responsive drug delivery. However, few comprehensive *in vivo* experiments have been performed, and more attention should be paid to this field. Additionally, designing drug carriers with specific structures (core–shell, compartmental nanoparticles and hybrid nanoparticles) while lowering the cost is still a dilemma. Furthermore, integrating multiple functionalities into one drug carrier is still a challenge. For instance, to visualize the drug release, combining imaging and treatment would be attractive, which would aid the drug distribution studies as well as the controlled release.



Scheme 14 Formation of the micelles and their oxidation- and host-responsive disassembly.[118]

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