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REVIEW

Selenium/tellurium containing polymer materials in nanobiotechnology

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Summary Selenium/tellurium containing polymers have been attracting growing interest due to their unique properties and potential applications as bio-nanomaterials. The introduction of selenium or tellurium chemistry into block copolymers endows self-assembled nanomaterials with novel stimuli responsiveness and enhanced sensitivity. This review article provides an overview on recent advances of selenium/tellurium containing polymers. We summarize the redox response and reversible self-assembly behaviors, γ-ray responsive systems for combined chemo- and radio-therapies, and coordination-responsive systems for controlled delivery are highlighted. The review then reveals how selenium-containing polymers can modulate reactive oxygen species and work as gene delivery vehicles or self-delivery therapeutics.

Introduction

Selenium was discovered in 1817 by the Swedish scientist Jöns Jacob Berzelius, one of the founders of modern chemistry, who named it after *selene*, the Greek word of moon [1]. Located right below selenium in the chalcogen group of the period table is its congener tellurium, which was actually discovered 35 years earlier, in 1782 by Franz-Joseph Müller von Reichenstein. Tellurium was so named by Martin Heinrich Klaproth in 1798, after *tellus*, the Latin word for earth [2]. In the past few centuries, people have come to understand that, despite their strange odor, selenium and tellurium compounds do possess unique and interesting properties. For example, in 1970s selenium was proved to be incorporated into proteins to produce selenoproteins which perform as important antioxidant enzymes [3]. Great progresses have since been made to synthesize selenium-containing compounds with anti-oxidant properties ever since [4—7]. Similarly, after the pioneering use of tellurium compounds in organic synthesis, rising interest has been directed toward the field of tellurium chemistry [8—11].

Nanomaterials have been a thriving area of research over the past few decades. Block copolymers can self-assemble into a rich variety of complex nano-architectures with unique functions [12—14]. The incorporation of a diversity synthetic chemistry allows the fabrication of polymer materials with various stimuli responsiveness. One of the

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most promising applications is to work as controlled delivery vehicles [15—19]. Different stimuli have been integrated into delivery systems [19—25]. The recent trend, however, is to discover new materials that can alter their properties in response to changing environments with enhanced sensitivity so as to function in physiological conditions, since the biological signals or disease-related biomarkers are usually of ultra-low concentrations [26]. A feasible method to achieve this purpose is to introduce new functional moieties into polymer systems, which may broaden their applications and pushing forward the development of the current systems in the meantime.

Developing selenium- or tellurium-containing polymers with unique properties and potential application as bionanomaterials has been an interesting field of research which has been gathering attention and interest [27]. The unique chemistry of selenium or tellurium endows polymer materials with enhanced sensitivity and novel stimuli response properties. This review will provide an overview of the research related specifically to the selenium/tellurium-containing polymers as a new class of self-assembled nanomaterials, but polyselenophenes and polytellurophenes for optical and electronic applications are beyond the scope of this review. To begin with, we systematically summarize the recent progresses in the exploitation of the redox responses of the selenium-containing polymer nanoassemblies. Next, dynamic reversible self-assemble systems utilizing selenium chemistry are discussed, including switchable catalytic bioactivity at different states of oxidation. We then review the innovative γ-ray responsive delivery systems for their potential to combine chemo- and radio-therapies, and further demonstrate how tellurium could increase the sensitivity of γ-ray response. Specifically, strategies for fabricating competitive-ligand regulated coordination responsive systems and gene delivery vectors are summarized. Furthermore, we highlight the selenium-containing polymer materials with novel functions such as the catalytic elimination of reactive oxygen species (ROS), or the self-delivery of therapeutics, featuring the biological activity of selenium groups. Finally, the future outlook for perspectives and challenges are discussed at the end of the paper.

Redox responsive materials

Redox reactions, or those involving the transfer of electrons, are ubiquitous in our daily life, such as combustion, photosynthesis, batteries, etc. Redox reactions take part in processes that are indispensable to all life forms, such as photosynthesis or aerobic respiration. On a higher level, various pathways of signal transduction rely on the generation and transportation of electrons. Imbalanced redox conditions are known to cause various disorders in cells or organs [28].

One of the most charming characters of selenium-containing polymers is their redox response [27]. Selenium-containing compounds are blessed with unique redox properties. It still remains a challenge to fabricate a dual-redox responsive system by simple design. In this perspective, diselenide species are of interest as they are active to either oxidation as well as reduction. Previous studies on selenium-containing polymers are limited by its poor solubility in solvent and bad stability against oxidation. In 2010, our group succeeded in synthesizing a diselenide-containing block copolymer. Typically, selenium was introduced by the reaction of sodium selenide or sodium diselenide with an alkyl bromide. The sodium selenide or sodium diselenide was prepared from the material of selenium powder and sodium borohydride and used immediately after preparation. The main chain selenium-containing polymer is normally prepared by the stepwise polymerization of a selenium containing diol with slightly excess amount of toluene-2,4-diisocyanate (TDI). Polyethylene glycol (PEG) is attached to the NCO groups on both ends to increase the solubility in water, thus making the polymer amphiphilic. The diselenide or monoselenide groups on the hydrophobic polyurethane backbone can be protected by the microenvironment provided by the hydrophilic—hydrophobic—hydrophilic structures of block copolymers in aqueous environment.

The diselenide-containing block copolymer demonstrated unique dual redox responsive behaviors (Fig. 1) [29]. Due to the hydrophilic PEG shell, the polymer self-assembled into stable spherical micelles with average diameter of about 76 nm. They could load cargoes like doxorubicin (Dox), rhodamine B (RB) efficiently similar as typical polymer micelles. In the presence of redox stimuli, they could afford quick release in a controlled manner. It should be noted that the redox response could be triggered under very mild conditions. The loaded cargo was totally released within 5 h after the addition of 0.01% H_2O_2, while upon treatment with 0.01 mg/mL glutathione (GSH), the cargo was also released within 5 h. The dual response of the selenium-containing polymer micelles is attributed to the redox activity of Se—Se bonds: it could be cleaved either by oxidation to seleninic acid or reduction to selenol in different redox environments. As cellular or organism disorders are often related to intricate redox changes in physiological environments, the diselenide containing polymers may serve as promising candidates for future development of programmable responsive biomaterials (Scheme 1).

After recognizing the redox responsiveness of the diselenide-containing polymer, a coassembly study shed light on how to achieve more complex diselenide-containing systems via supramolecular approach. Our group reported a general approach to fabricate stimuli responsive system by the coassembly of diselenide-containing block copolymers and polymer lipids (Fig. 2) [30]. Coassembly can integrate the merits of both building blocks, that is, biocompatibility of polymer lipids and dual-redox responsiveness of diselenide-containing block copolymers. By adding a little amount of dual redox responsive polymer into the polymer lipid system (mass ratio between polymer lipid and diselenide block copolymer is 10:1), the coassemblies retained good redox responsiveness. Thus, in the presence of 0.1% H_2O_2 or 0.05 mM GSH, most of the coassemblies were disrupted. Good responsiveness could be achieved even though only a little amount of diselenide-containing block copolymer was involved. Owing to the good biocompatibility of polymer lipids, it is suitable for further application under physiological conditions. Together with the good biocompatibility owing to the polymer lipids, further applications of this coassembly system in physiological conditions could be envisaged.