Review

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Synthesis and Application of Selenium Nanoparticles for the Modulation of Inflammatory Diseases

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Abstract

Inflammation is a fundamental response process to injury, which is coordinated by various inflammatory mediators, including reactive oxygen species, inflammatory immune cells and cytokines. Excessive inflammatory responses can drive the development of numerous diseases, making modulation of inflammatory responses a crucial strategy in the treatment of inflammatory diseases. Selenium (Se), an essential trace element for human health, plays a crucial role in alleviating severe inflammatory diseases by scavenging free radicals, achieving antioxidant effects and modulating the innate and adaptive immune systems in the inflammatory microenvironment. Among the different forms of Se element, Selenium nanoparticles (SeNPs) stand out for their low toxicity and high utilization rate, offering them unique advantages in the fields of medicine and materials science. In addition, functional modification of SeNPs enhances their biological activities in modulating the process of inflammatory diseases. In this review, the construction of various types of SeNPs are firstly discussed. Then, we review the diagnosing effects of modified SeNPs and highlight their biomedical applications in the treatment of inflammation. Finally, we summarize the limitations in the current research of SeNPs as well as the major challenges in clinical transformation, and anticipate the application prospects of new functionalized SeNPs in the treatment of inflammatory diseases.

Keywords: selenium nanoparticles; inflammation; theranostic; anti-oxidative stress; immune modulation

Introduction

Orchestration of inflammatory responses

Inflammation, as a fundamental response process of the body's tissues to injury, primarily involves the recruitment and activation of blood-derived inflammatory cells in the local blood flow, thereby stimulating repair mechanisms and mediated by various inflammatory mediators [1]. As shown in Figure 1, in the early stages of tissue injury, pathogen infection induces damaged cells elevate reactive oxygen species (ROS) and recruit various immune cells, such as macrophages, neutrophils and T cells. These immune cells release inflammatory cytokines, activate inflammatory signaling pathways, and further enhance the production of ROS, thereby amplifying the inflammatory response [2–3]. Eventually, as the inflammatory process progresses, immune cells involved in inflammation are gradually cleared through apoptotic pathways. Phagocytic cells respond to apoptotic cells and inflammatory mediators, and

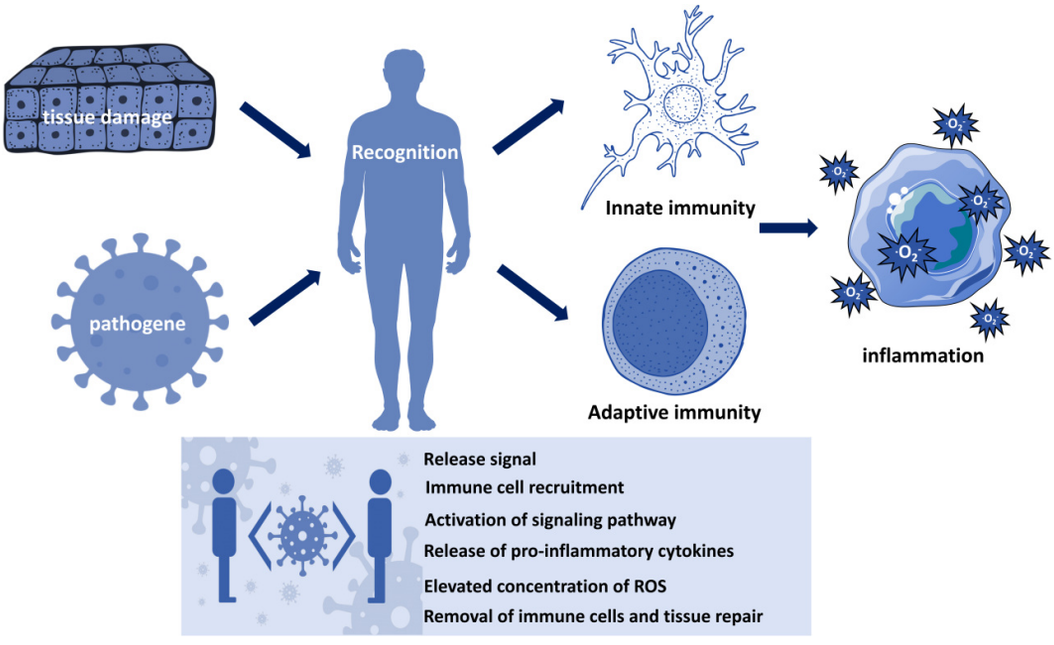


Fig. 1 The basic process of inflammation development pathogen.

transport the inflammatory mediators through the bloodstream to organs such as the liver for metabolism, allowing the inflammatory mediators to be gradually cleared. At the same time, damaged blood vessels and tissues begin to repair, and inflammation is alleviated and subsides (Fig. 1) [4–6]. Notably, ROS plays a very crucial role in the development of inflammation [7, 8]. Excessive ROS can cause damage to proteins, lipids, DNA, and other biological macromolecules, which initiates the release of inflammatory mediators and intensifies the inflammatory response, a process known as oxidative stress [9], The interplay between oxidative stress and inflammation forms an over-activated inflammatory response, and a vicious cycle [10, 11].

Additionally, inflammatory related cytokines are another major factor driving the inflammatory process. Major pro-inflammatory cytokines include tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), IL-6, and IL-1, whereas transforming growth factor beta 1 (TGF-β1) is regarded as an anti-inflammatory cytokine [12, 13]. Table 1 lists the relationship between various cytokines and inflammation, it also includes some secondary inflammatory cytokines [14–27]. Among them, TNF-α is a documented pro-inflammatory cytokine affecting the inflammatory process, primarily secreted by macrophages and plays crucial roles in modulating polarization of inflammatory cells [28]. IL-6 is an important cytokine produced by various types of cells such as activated T cells, B cells, and macrophages. It promotes the proliferation and differentiation of B cells [29]. In addition, IL-1β serves as a primary inducer of the synthesis and expression of several secondary inflammatory cytokines, including IL-6 [30]. Notably, IL-1 is a potent pro-inflammatory mediator in both acute and chronic inflammation, capable of inducing vasodilation and increasing vascular permeability. It also promotes the synthesis of secondary inflammatory cytokines, including IL-6 and TNF-α, thereby exacerbating the inflammatory microenvironment [31]. In addition, inducible nitric oxide synthase (iNOS) is an enzyme expressed by immune cells in response to inflammation or infection, which catalyzes the conversion of L-arginine to nitric oxide (NO), thus prompting the inflammatory process [32–35]. TGF-β1, on the other hand, has complex roles, exhibiting both anti- and pro-inflammatory effects in inflammation depending on different context [36]. The binding of TGF-β1 to its receptors can activate downstream Smad-dependent and non-Smad-dependent signaling pathways, reducing the production of inflammatory cytokines and reducing the migration and activation of inflammatory cells. However, under certain circumstances, TGF-β1 can promote inflammation and fibrosis, particularly in microenvironments of chronic inflammatory and tumor [37]. In addition, other cytokines such as TNF-β, IFN-γ, IL-2, IL-8, IL-10, IL-17, and IL-22 are also involved in the

Table 1 Cytokines associated with inflammation.

Cytokines	Relationship to inflammation	Ref.
TNF-α	A pro-inflammatory cytokine that regulates inflammatory cell populations, in addition to many other factors that affect the inflammatory process.	[12, 13, 28]
TNF-β	It is a multifunctional cytokine that primarily participates in regulating cell-to-cell interactions, affecting cell growth, differentiation, and death, as well as being involved in the regulation of immune responses and inflammatory reactions.	[14,15]
TGF-β1	Through its immunomodulatory and fibrotropic effects, it participates in the formation of a microenvironment conducive to the continuation and progression of inflammation.	[12, 13, 35, 36, 37]
IFN-γ	Belonging to the Type I interferon family, it promotes the activation of macrophages, enhancing their ability to phagocytize and kill pathogens. At the same time, it also enhances the proliferation and differentiation of T cells.	[16, 17]
IL-1	Stimulate the release of other inflammatory cytokines such as IL-6, IL-8, TNF-a, etc., further exacerbating the inflammatory response.	[12, 13, 29, 32]
IL-1β	Influence the progression of inflammation by regulating the synthesis and release of inflammasomes, as well as controlling the activation of the IL-lβ processing protease Caspase-1.	[12, 13, 30]
IL-2	By modulating the activity of T cells, it indirectly promotes the occurrence and development of inflammatory responses.	[18, 19]
IL-6	Stimulate the proliferation and differentiation of immune cells and also induces the production of acute-phase reactive proteins.	[12, 13, 29]
IL-8	During inflammation, the expression level of IL-8 increases, which can promote the chemotaxis, activation, and degranulation of neutrophils.	[20, 21]
IL-10	By inhibiting the production and release of pro-inflammatory cytokines, reducing the activation and proliferation of inflammatory cells, and regulating the function of immune cells.	[22, 23]
IL-17	By stimulating the production of inflammatory mediators and chemokines in a variety of cell types, the inflammatory response is enhanced.	[24, 25]
IL-22	It has dual effects of anti-inflammatory and proinfammatory. On the one hand.it can promote the proliferation and differentiation of epithelial cells to resist the invasion of pathogens: on the other hand, it can also induce the production of certain inflammatory factors, attracting immune cells to the site of inflammation and exacerbating the inflammatory response.	[26, 27]
iNOS	An enzyme expressed by immune cells when they are stimulated by inflammation or infection catalyzes the conversion of L-arginine to nitric oxide (NO).	[33, 34, 35]

inflammatory response.

Except for inflammatory factors, numerous oxidative stress-related signaling pathways are involved in the process of inflammation. Among them, nuclear factor-kappa B (NF-κB), a redox-sensitive transcription factor, is essential to the inflammation responses [12].

The NF-κB pathway can be activated by a wide range of pro-inflammatory stimuli, including oxidative stress, free radicals, stress responses, bacterial infections, and viral infections [38]. During the inflammatory process, activated NF-κB is translocated to the nucleus and acts as a downstream component of toll-like receptor (TLR)-mediated tissue repair processes and a key component of the inflammatory signal cascade [39]. NF-κB regulates gene expression of various inflammatory cytokines, such as TNF-α, IL-1β, and IL-6, thereby amplifying the inflammatory signal and attracting immune cells to the site of inflammation [40]. Additionally, the activation of the NF-κB pathway directly promotes the activation and migration of immune cells [41]. For instance, it can induce the expression of adhesion molecules on endothelial cells, thus assisting immune cells to traverse the vascular wall and migrate to inflamed tissues [42]. Overactivation of this pathway can exacerbate the inflammatory response [43, 44]. Therefore, it is possible to effectively control inflammation, reduce tissue damage, and promote tissue repair by reducing the generation of ROS, inhibiting pro-inflammatory cytokines activation, and regulating inflammatory-related signaling pathways. These strategies offer promising approaches for treatment of inflammatory diseases.

Characteristics of selenium

Selenium (Se), a trace element first discovered by Swedish chemist Jöns Jacob Berzelius in 1817 was initially considered to be a toxin, and high doses of selenium intake can cause “seleniosis” [45]. However, in 1957, Schwarz and Foltz accidentally discovered that Se can prevent liver necrosis in rats, marking the beginning of its recognition as an element beneficial to health [46]. Recent studies have affirmed that Se is an essential trace mineral critical crucial for maintaining health [47]. As shown in Fig. 2, in the medical field, it acts as an antioxidant that effectively scavenges free radicals, mitigates oxidative stress, protects cells from oxidative damage, supports cellular survival and growth, and plays a vital role in preventing and treating of cancer

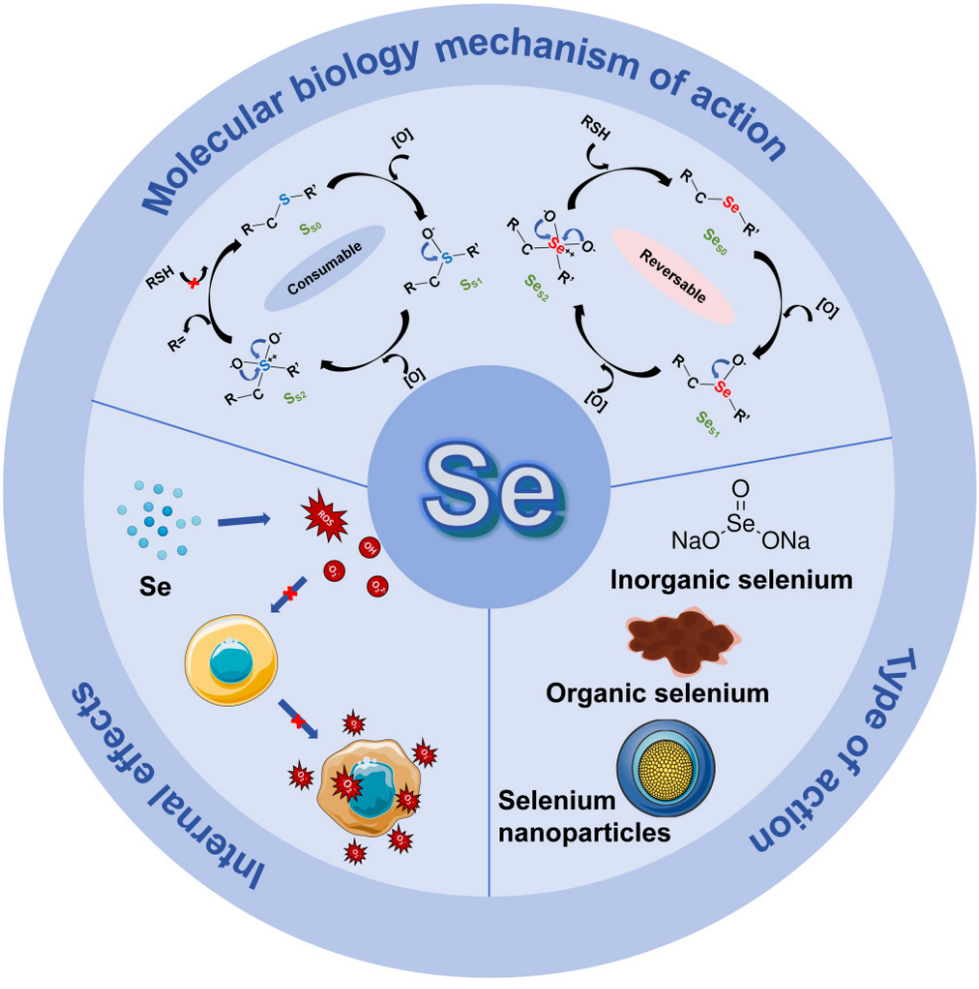


Fig. 2 Basics and biological functions of selenium.

and cardiovascular diseases [48, 49]. The role of Se in redox homeostasis is primarily achieved through various selenoproteins [50]. Through the food chain, Se is ingested and primarily absorbed in the intestine in the form of selenomethionine (SeMet) and selenocysteine (Sec), and then transported to various parts of the body via the bloodstream. Within cells, Se amino acids can be incorporated into proteins, replacing the corresponding sulfur-containing amino acids to form selenoproteins. The Sec residues within these proteins catalyze redox-based reactions, thereby acting as antioxidants and protecting cells from oxidative damage (Fig. 2) [51]. Commonly, Se exists in inorganic and organic forms with various valence state. Inorganic Se mainly includes two forms: selenate (Se^{4+}) and selenite (Se^{6+}) while organic Se is commonly regarded as amino acids with a +2 oxidation state. Though organic Se is more easily absorbed by the human body, its stability is generally lower, and its cost-effectiveness is inferior to that of inorganic Se. Despite its numerous health benefits, Se has a narrow therapeutic window, and excessive intake of either inorganic or organic Se can lead to toxicity [52]. In comparison to other valence states of selenium, zero-valent selenium nanoparticles(SeNPs) exhibit lower toxicity [53], high specific surface area and favorable biocompatibility, which endow them with unique advantages in fields such as medicine, environmental protection, and materials science (Fig. 2) [54]. In recent years, with the development of nanotechnology, the design and synthesis of selenium nanomedicines have attracted attention in biomedical research. Specifically, SeNPs have demonstrated promising anti-inflammatory activity within the context of inflammatory responses. Current research focuses on the functional modification of SeNPs to modulate the redox balance within cells, affecting function of immune cells and modulating of inflammatory related signaling pathways, thereby exhibiting excellent anti-inflammatory therapeutic effects. This review summarizes the synthesis and modification strategies for Se nanomedicines and

their related biological effects in the treatment of inflammation.

Functional Design and Synthesis of SeNPs

The synthesis methods for SeNPs are varied, including physical synthesis, chemical reduction, and biological synthesis (Fig. 3) [55]. Physical synthesis of SeNPs involves various physical processes to convert Se into nanoscale particles. Chemical synthesis is currently the most widely used methods for SeNPs preparation, which allows precise control of particle size and morphology. However, it often involves toxic reducing agents during synthesis and generates hazardous by-products. Biological synthesis, in contrast, requires neither special conditions nor equipment, employing biological extracts as reducing agents and stabilizers. This method utilizes bacteria, fungi, algae, and protein molecules or plant extracts to prepare them in a solvent, offering higher cost-effectiveness.

Physical synthesis method for construction of SeNPs

The physical synthesis of SeNPs is mainly achieved through evaporation condensation, laser ablation, microwave radiation, gamma-ray radiation, and ultrasonic processing [56]. Among them, laser ablation is the widely used method. Under high-temperature conditions, Se absorbs laser energy, transitions to an excited-state Se, and subsequently cools to form SeNPs [57]. For instance, with a diameter of (115±38) nm, SeNPs are synthesized through pulsed laser ablation in liquids, demonstrating significant inhibitory effects on *Escherichia coli* and *Staphylococcus aureus* [58]. Additionally, selenium nanoparticles synthesized by ablating selenium and silicon targets in distilled water exposed to the radiation of a fiber laser marker's nanosecond laser (1 050–1 070nm), have shown antibacterial activity against both Gram-positive and Gram-negative bacteria (Fig. 4) [59]. Since physical methods are relatively straightforward to operate, high energy consumption and specialized equipment are commonly required, limiting their scalability and practical application.

Chemical reduction method for synthesis of SeNPs

Chemical reduction method for synthesizing SeNPs is primarily based on redox reaction. The Se sources, such as sodium selenite, selenic acid, and Se dioxide are commonly regarded as oxidizing agents, while chemical reagents like vitamin C (Vc) and others act as reducing agents. These oxidizing and reducing agents interact and undergo a redox reaction to produce SeNPs [60]. By using chemical reduction method, SeNPs are functionalized with *Sargassum*

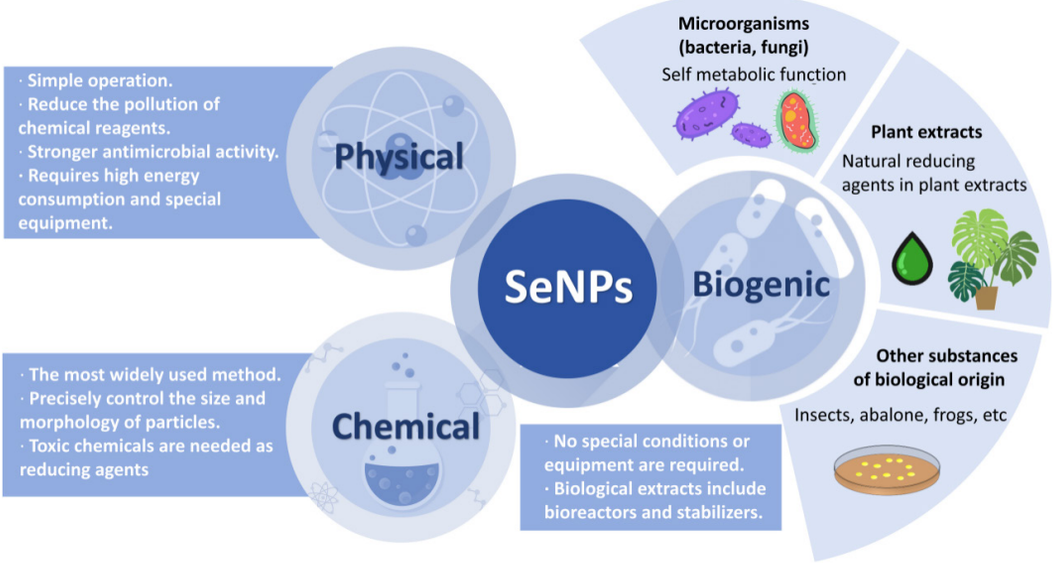


Fig. 3 Different methods to synthesize SeNPs. Physical synthesis is easy to operate, has less chemical pollution and exhibits strong antimicrobial activity, but it requires high-energy equipment; chemical synthesis is the most widely used method and can precisely control the size and morphology of particles, but the synthesis involves toxic reducing agents; biosynthesis is environmentally friendly and does not require special conditions as well as equipment.

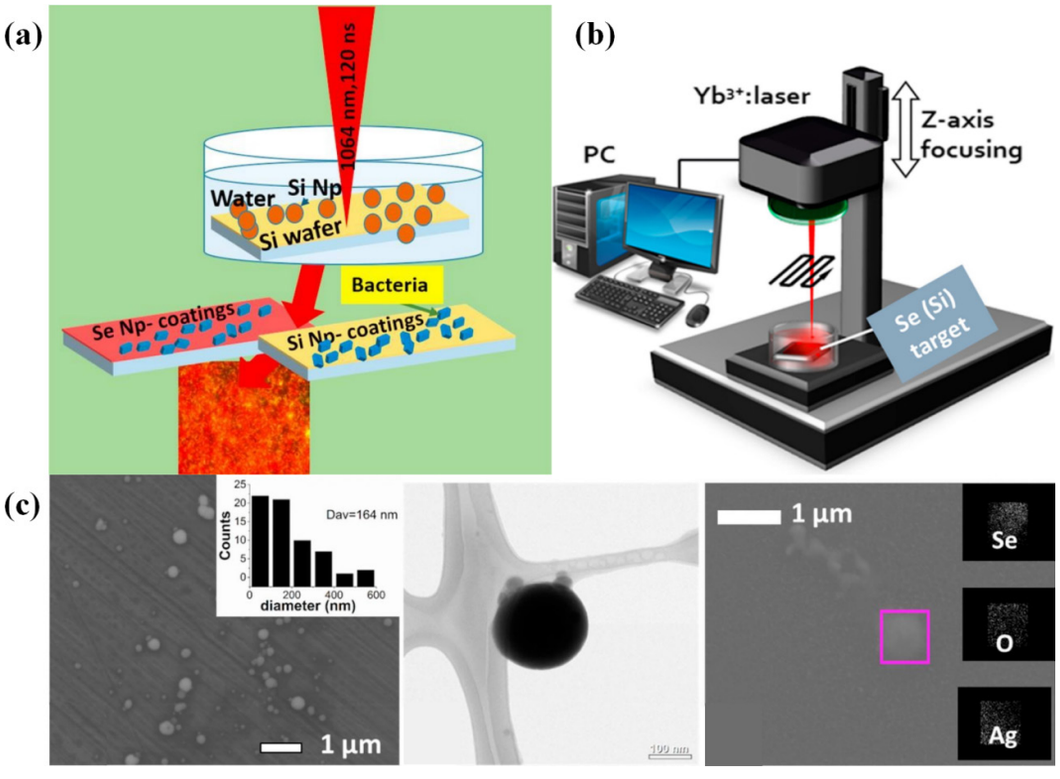


Fig. 4 Antibacterial coatings of Se and Si nanoparticles. (a) Schematic of the method of laser ablation in distilled water to obtain nanoparticles such as selenium. (b) Schematic of the experimental setup: HTF MARK fiber nanosecond laser marker. (c) Scanning electron microscopy (SEM) (left) and transmission electron microscopy (TEM) images of Se nanoparticles in their deposits and coatings, respectively; nanoparticle size distribution (left side inset), and elemental composition of the selected area, obtained *via* EDX-analysis (right). Reproduced with permission from Ref. [59] © 2018 Elsevier B.V.

fusiforme polysaccharides (SFPS) and offering a method to utilize SFPS as a carrier for SeNPs [61]. In addition, the novel SeNPs are synthesized by $SeCl_4$ as a precursor, and reducing agents like hydrazine, potassium borohydride, and thioglycolic acid in aqueous solutions. Moreover, ultrasonic chemical methods are employed in this study to synthesize nano-selenium and the effects of preparation parameters on the morphology and particle size of selenium are studied [62]. Functionalized SeNPs, due to their unique physicochemical properties, can target specific diseases and develop more efficient and less toxic therapeutic methods. For instance, a straightforward synthesis strategy is developed by Chen et al. for functionalized antiallergic selenium nanoparticles (LET-SeNPs) [63]. Subsequently, based on the high safety of the trace element Se and Prussian blue (PB), as well as the unique activity of Se in strong electron donation and its redox properties, they construct a nano-superstructure containing a Fe^{2+}-Se-Fe^{3+} electron transfer chain (Se@PB) by doping Se into PB. This structure enhances the physical and biochemical radiosensitization effects by accelerating electron transfer and disrupting redox homeostasis (Fig. 5) [64]. Additionally, they construct bridge-connected DSeMSNs by incorporating diselenide bonds into the structural framework of MON through an improved sol-gel method [65].

However, the simple chemical synthesis method cannot meet the complex performance requirements of SeNPs. To enhance the stability and performance of SeNPs, it is often necessary to add stabilizers or modifiers, such as sugars, proteins, lipids, and polymers. These additives can improve the stability, biocompatibility, and bioactivity of SeNPs, and they also serve various biological functions [66]. For instance, metal-polyphenol participation in synthesis can exert certain biological functions. Nano selenium is successfully synthesized through the redox reaction of sodium selenite and ascorbic acid, using chitosan as a dispersing agent. The resulting nanoparticles are then coated with a multifunctional tannin-zinc complex (TZn) formed by the chelation of tannic acid (TA) and zinc ions, resulting in CSe@TZn NPs with superoxide dismutase and glutathione peroxidase activities (Fig. 6) [67]. Similarly, combined bovine serum albumin-stabilized selenium nanoparticles

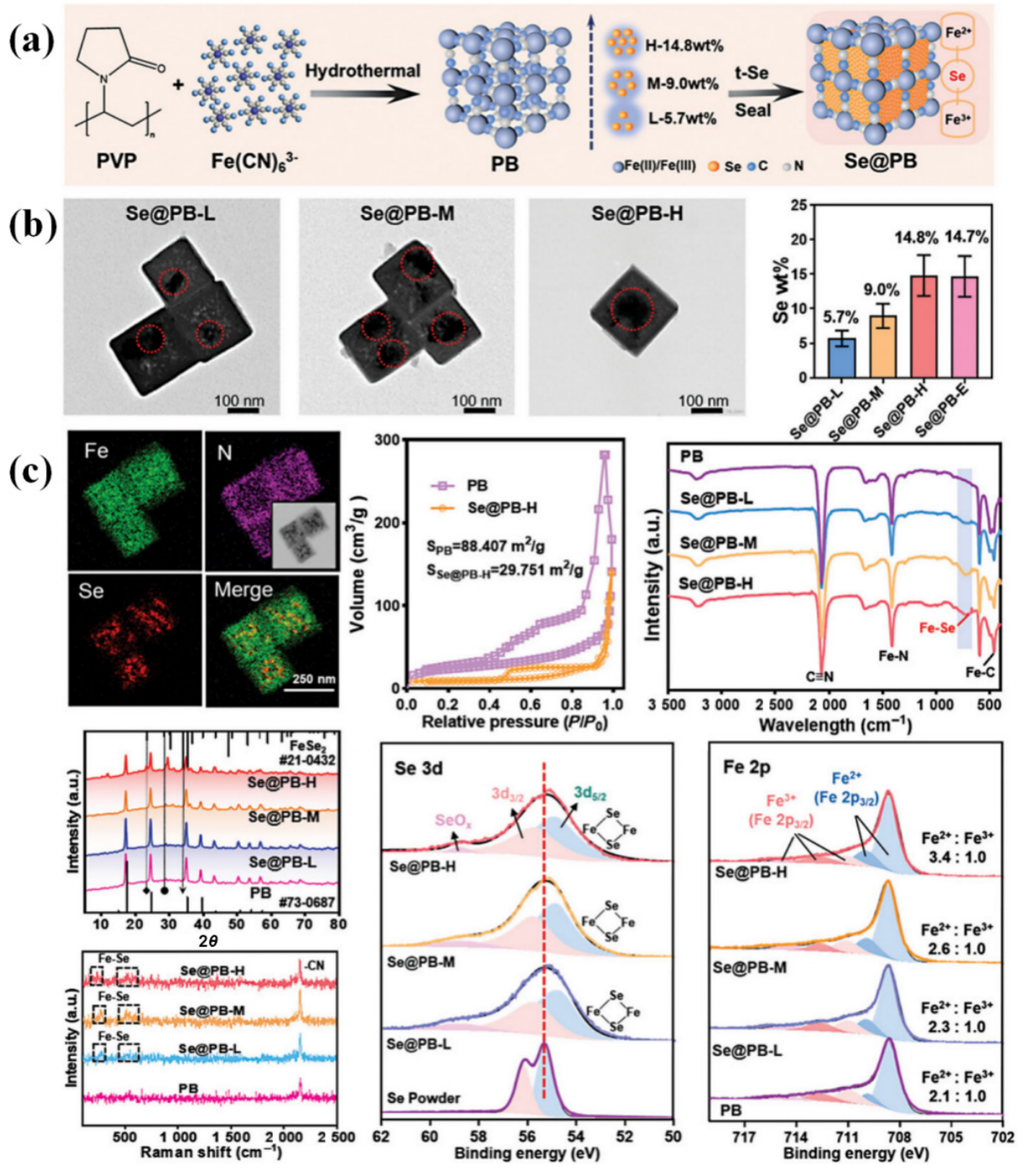


Fig. 5 Selenium-doped nanoheterojunctions for highly efficient cancer radio sensitization. **(a)** Schematic illustration of the synthetic process of Se@PB nanoplatform. **(b)** TEM images of Se@PB nanoplatform with different Se ratios L, M, and H represent low, middle, and high Se content respectively. The percentage of Se weight in different nanosystems. **(c)** Characterizations of Fe^{2+}-Se-Fe^{3+} chain. Element mapping of Se@PB-H (upper left), isothermal adsorption-desorption (upper middle) curves of PB and Se@PB-H. FTIR (upper right), XRD and Raman spectra of Se@PB nanoplatform with different Se content (lower left). XPS spectra of Se 3d (lower middle) and Fe 2p (lower right). Reproduced with permission from Ref. [59] © 2024 The Authors.

(BSe) with a metal-polyphenol complex, a multifunctional metal-polyphenol-coated Se nanoparticles BSe@MT is synthesized [68]. In addition, sodium alginate powder is used as a stabilizer and capping agent to synthesize clustered SeNPs through reduction with vitamin C, thereby enhancing the stability and efficiency of the synthesized particles [69]. Chitosan-stabilized selenium nanoparticles (CTS-SeNPs) are constructed by reducing sodium selenite with Vc, and the optimal synthesis conditions for CTS-SeNPs are determined using orthogonal experiments, which exhibit

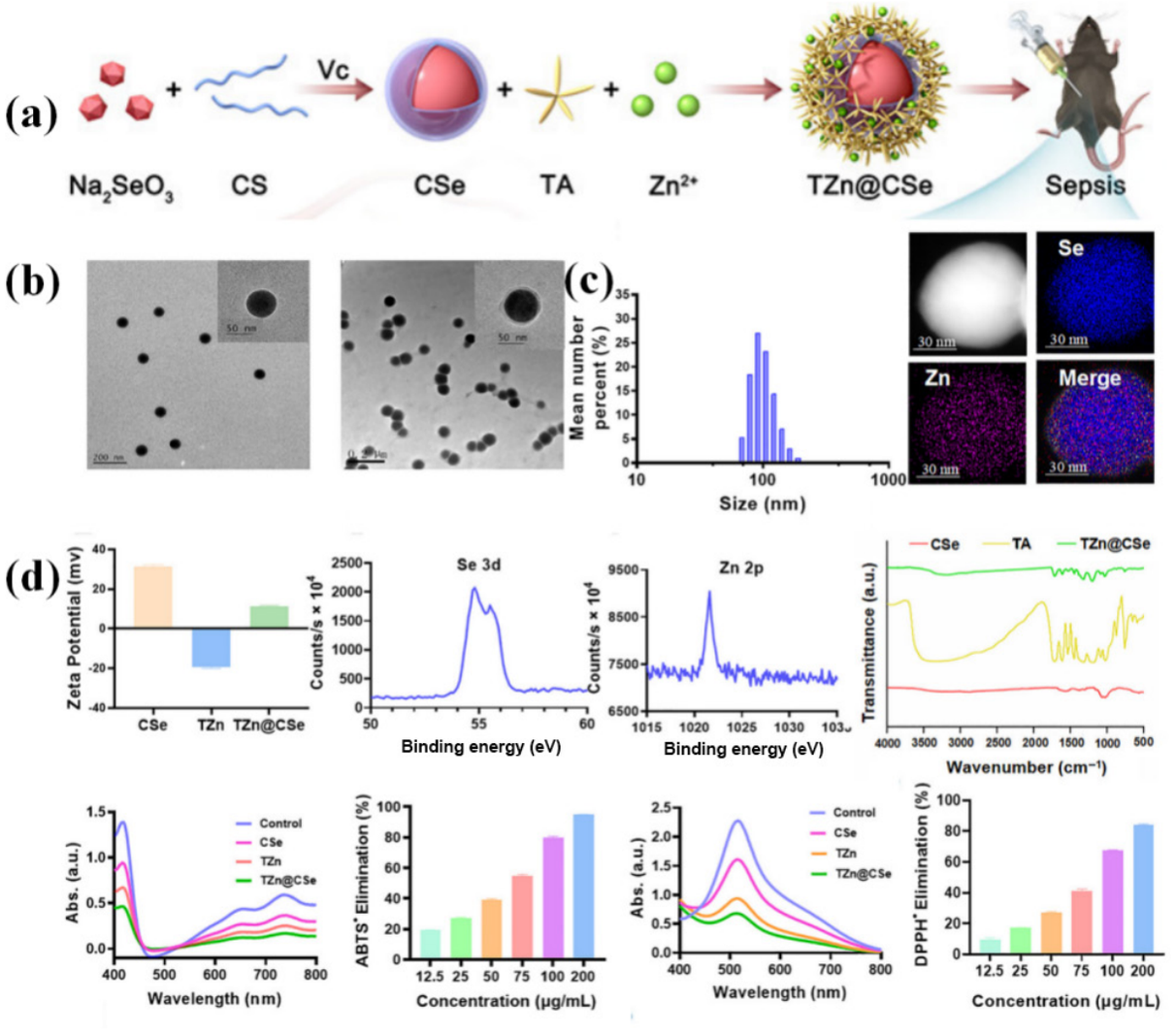


Fig. 6 Synthesis and characterization of multifunctional selenium-based metal polyphenol nanoparticles. **(a)** Illustration of the synthesis of TZn@CSe. **(b)** TEM images of CSe NPs (left) and TZn@CSe (right). **(c)** Hydrodynamic diameters (left) and elemental mapping (right) of TZn@CSe. (d) Characterization of TZn@CSe nanoparticles: zeta potential, X-ray photoelectron spectra of Se 3d, and Zn 2p, FTIR (upper) and UV–Vis absorption spectra with elimination ratio in different concentrations of TZn@CSe (lower), respectively. Reproduced with permission from Ref. [67] © 2024 American Chemical Society.

enhanced anti-diabetic activity [70], and laminarin polysaccharide (LP) decorated selenium nanoparticles (LP-SeNPs), with an average diameter of about 60 nm, are synthesized by mixing a laminarin polysaccharide stock solution with 0.5 mL of sodium selenite solution (0.1 M) and adding 1 mL of ascorbic acid aqueous solution, which subsequently demonstrate stronger pro-apoptotic capabilities against cancer cells [71].

Given the targeting demand of drug delivery, cell- or tissue-targeted SeNPs nanosystems are constructed. The specific molecules or groups are modified on the surface of SeNPs through chemical reactions, enabling them to bind to the receptors of target cells or tissues. This targeted approach facilitates specific recognition and binding to target cells or tissues, thereby reducing distribution and side effects in non-target areas [72]. Besides, a novel type of mesoporous SeNPs has been established, using borneol as a targeting agent, resveratrol and β-cyclodextrin as drug carriers. A progressive release delivery system called MSe-Res/Fc-β-CD/Bor has been synthesized. It is made by modifying Bor, enveloping β-cyclodextrin, and loading Res into MSe. This system interacts with esterases in the blood or within cells to first release borneol, thereby helping the nano-system to cross the blood-brain barrier (BBB) and achieve targeted improvement for Alzheimer's disease (Fig. 7) [73]. An anticancer SeNPs composed of two anticancer agents, sesamol, SeNPs, as well as polyethylene glycol (PEG) are

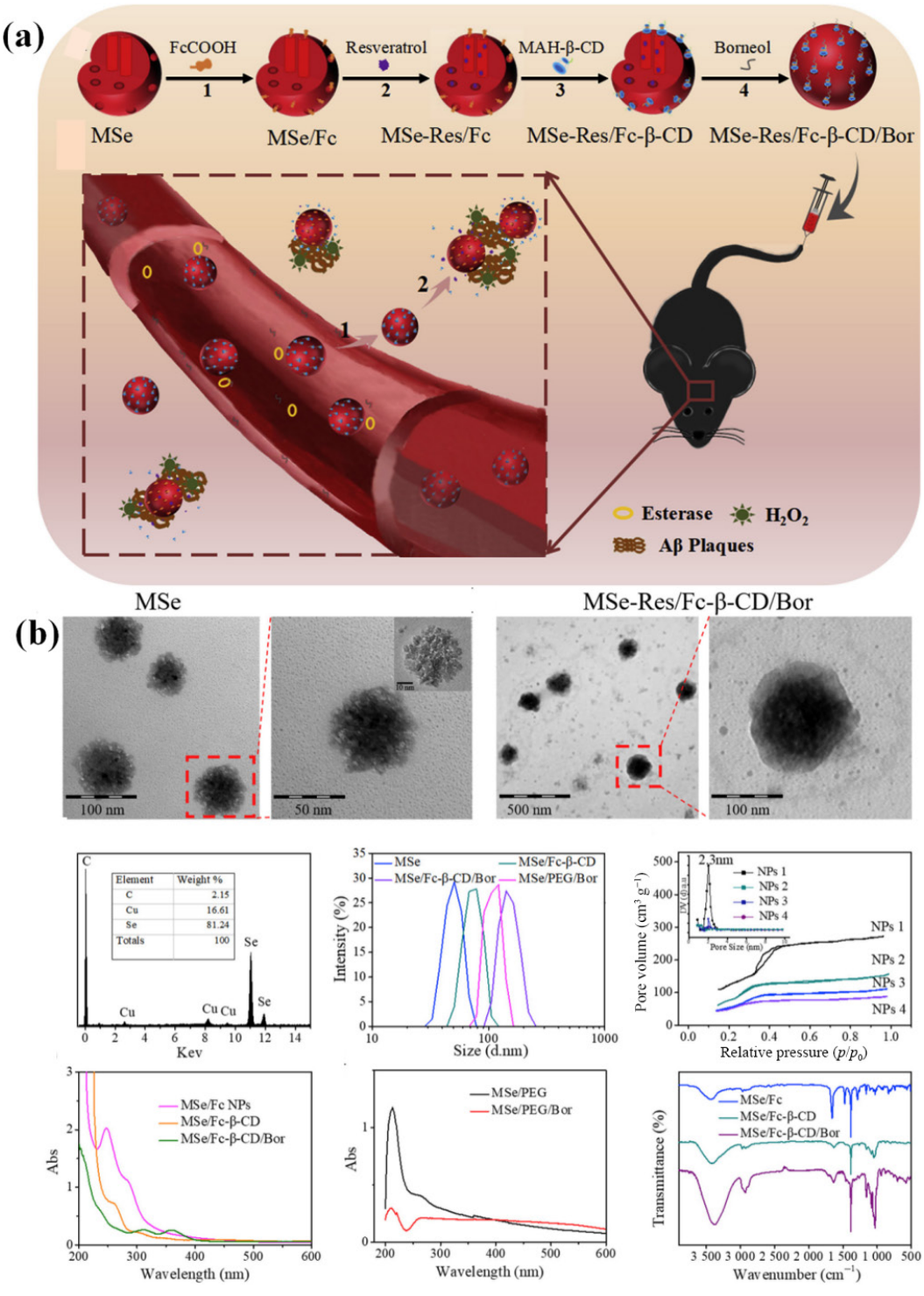


Fig. 7 Synthesis and characterization of a mesoporous nano-selenium delivery system for the multi-channel synergistic treatment of Alzheimer's disease. **(a)** The preparation and schematic interpretation of MSe-Res/Fc-β-CD/Bor. **(b)** Characterization of MSe, MSe/Fc-β-CD, MSe/PEG/Bor and MSe/Fc-β-CD/Bor. TEM and HTEM images of MSe: TEM images of MSe-Res/Fc-β-CD/Bor (upper). EDX analysis (middle left) of MSe. The hydrodynamic sizes of MSe, MSe/Fc-β-CD, MSe/PEG/Bor and MSe/Fc-β-CD/Bor in PBS (middle middle). Nitrogen adsorption-desorption isotherm (middle right). UV spectra of MSe/Fc, MSe/Fc-β-CD, MSe/Fc-β-CD/Bor (lower left), UV spectra of MSe/PEG and MSe/PEG/Bor (lower middle). FTIR spectra of MSe/Fc, MSe/Fc-β-CD and MSe/Fc-β-CD/Bor (lower right). Reproduced with permission from Ref. [73] © 2019 Elsevier B.V.

synthesized for treatment of cancer and properties of these SeNPs are demonstrated by various techniques [74]. Zou et al. conjugated SeNPs with hyaluronic acid (HA) to create a tumor-targeting delivery vehicle which can successfully load paclitaxel (PTX), with enhanced active targeting *in vivo* leading to improved antitumor activity of the particles [75]. Moreover, 5-fluorouracil surface-functionalized selenium

nanoparticles (5FU-SeNPs) are synthesized. With the formation of Se-O and Se-N bonds and physical adsorption, spherical SeNPs are coated with 5FU, yielding a stable conjugate structure with surface decoration by 5FU [76]. Furthermore, the above methods are improved to obtain Pluronic F-127 stabilized paclitaxel-loaded SeNPs [77] or construct tumor-targeting peptide RGDfC-conjugated SeNPs, to create a biocompatible gene carrier (RGDfC-SeNPs) [78].

It is evident that functionalization and targeting modifications play a crucial role in the chemical synthesis of SeNPs. The introduction of molecules with high biocompatibility can enhance their stability within biological systems, while the modification with biofunctional molecules can provide therapeutic effects for diseases. Targeting modifications enable SeNPs to more accurately localize to the diseased sites, reducing damage to normal cells. Although chemical synthesis methods can precisely control the size and shape of SeNPs, the use of toxic chemical reagents during the synthesis process may cause environmental risks. Additionally, harmful by-products may be generated during the synthesis process, which necessitates additional treatment and purification steps. Therefore, seeking green synthesis methods for nanomaterials has become a prominent topic in recent research on SeNPs.

Biosynthesis method for synthesis of SeNPs

Biosynthesis is an effective method to convert selenium sources into selenium nanoparticles by using microorganisms, plants or other bio-sourced substances.

This synthesis method typically employs bacteria and fungi, which utilize their metabolic functions to reduce selenate in the environment into elemental SeNPs. These nanoparticles produced through biosynthesis exhibit small size, uniform and stable structures, heat resistance, safety, and environmental friendliness, making this approach a mainstream method for SeNP construction. Various studies have demonstrated the efficacy of different microorganisms in synthesizing SeNPs. For instance, spherical SeNPs are indirectly prepared by catalyzing the reduction of selenite using cell-free extracts from *Enterococcus* bacteria, which secrete metal-reducing metabolites. The synthesized nanoparticles were characterized by using Fourier-transform infrared spectroscopy (FTIR), X-ray diffraction (XRD), and transmission electron microscopy (TEM) [79]. In another example, red, amorphous, spherical SeNPs are synthesized from sodium selenite by probiotic strain *Lactobacillus casei* ATCC 393 in a $NaHSeO_3$ Se source, with characterization conducted *via* scanning electron microscopy (SEM) and ultraviolet–visible (UV–Vis) spectroscopy [80]. Additionally, *L. casei* ATCC 393 is used to convert sodium selenite into SeNPs under anaerobic conditions. Lysozyme and ultrasonication are employed to purify the intracellular SeNPs produced, facilitating bacterial cell lysis, followed by an organic water extraction system. The extracted SeNPs are characterized using TEM, SEM, energy-dispersive X-ray spectroscopy (EDX), X-ray photoelectron spectroscopy (XPS), and Fourier-transform infrared spectroscopy (FTIR). Additionally, their *in vitro* antioxidant activity is demonstrated (Fig. 8) [81]. Furthermore, *Lactobacillus acidophilus* HN23 is utilized for the reduction of sodium selenite, resulting in composed of 65.8% Se elemental in nanoparticles, alongside polysaccharides and polypeptide compounds [82]. Moreover, SeNPs are synthesized using extracts from the fungus *Fusarium solani* [83], and a novel polysaccharide-SeNPs complex is created by decorating SeNPs with polysaccharides obtained from the *Trametes versicolor* (FLDP), which are characterized using TEM, dynamic light scattering, and XPS [84].

In addition to microorganisms, plants also serve as natural reducing agents in SeNPs synthesis. The chemical components found in these plant extracts can effectively reduce Se salts to form SeNPs. For instance, spherical SeNPs are synthesized using Anabaena PCC 7120 in sodium selenite, and characterized by UV–Vis spectroscopy, SEM-EDX, TEM, and FTIR analysis [85]. A method was also proposed for preparing SeNPs using corn zein [86], or Aloe vera extract gel [87] as the Se source reducer, with characterization performed via. SEM, FT-IR, and XPS and achieving a high yield of SeNPs. Additionally, Grateloupia livida polysaccharide functionalized selenium nanoparticles (GLP-SeNPs) are successfully prepared in a simple redox system consisting of sodium selenite and ascorbic acid [88]. Orange-red amorphous zero-valent spherical GLPs-SeNPs are synthesized using a redox system of selenite and ascorbic acid, with the GLPs serving as stabilizing and dispersing agents [89]. Moreover, in

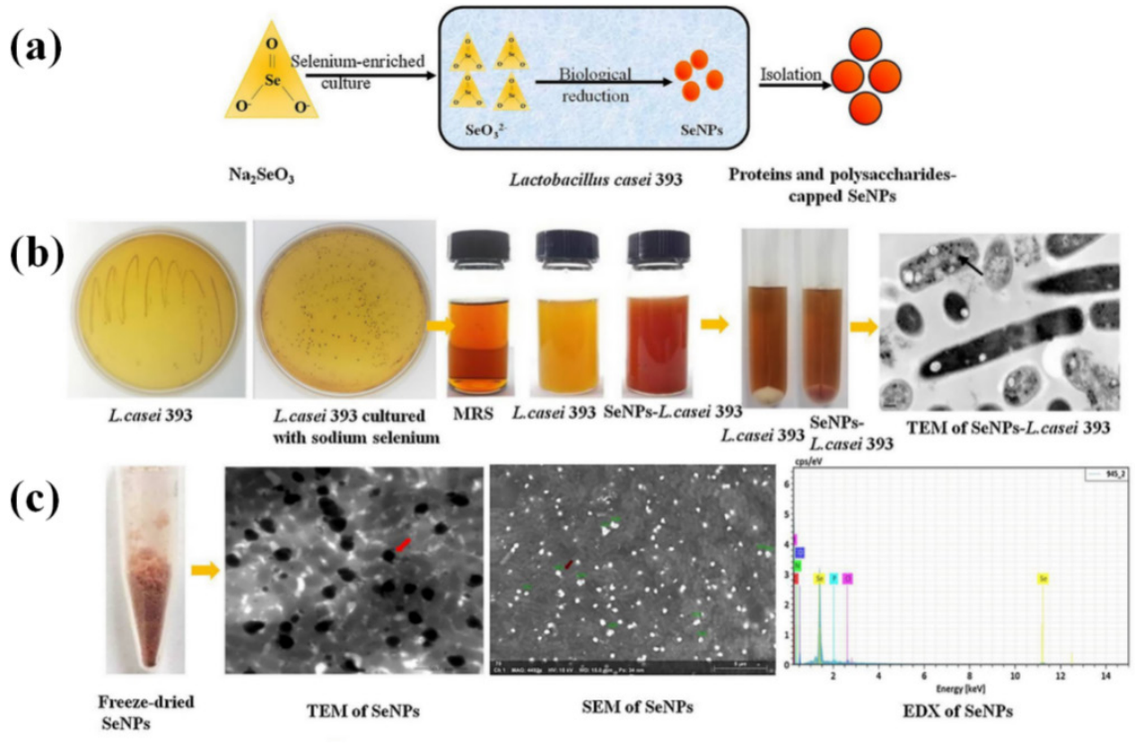


Fig. 8 Preparation, and characterization of polysaccharides and proteins-capped selenium nanoparticles synthesized by *Lactobacillus casei* ATCC 393. **(a)** The hypothesis schematic of the biogenic synthesis process of biomolecules-capped SeNPs by probiotic *L. casei* 393. **(b)** Observations of *L. casei* 393 cultured under 200g/mL sodium selenite stress by TEM. **(c)** TEM (left), SEM analysis (middle), and EDX spectrometry (right) of SeNPs. Reproduced with permission from Ref. [81] © 2018 Elsevier B.V.

the sodium selenite-ascorbic acid redox system, PSP-selenium nanoparticles (PSP-SeNPs) are successfully synthesized using 0.1 mg/mL of *Polygonatum sibiricum* polysaccharide (PSP) as a stabilizer. These PSP-SeNPs possess a monodisperse spherical structure of zero-valent Se, and the interaction between hydroxyl groups on the PSP chains and the surface of SeNPs contributes to the stable structure (Fig. 9) [90]. Zahran et al. used a green biosynthesis strategy for obtaining SeNPs. Additionally, dietary microalgae prepared SeNPs [91] or biofunctionalized chitosan-modified SeNPs encapsulating paclitaxel (PTX-chit-SeNPs) are constructed for cancer treatment [92]. Interestingly, the hawthorn extract aqueous solution is utilized as both reducing agent and stabilizer to prepare mono-dispersed, stable selenium nanoparticles (HE-SeNPs) [93]. Additionally, Se-ZnO bimetallic nanoparticles are synthesized from the aqueous extract of the brown seaweed Padina boergesenii, which are characterized by UV, FTIR, SEM-EDX, and high-resolution transmission electron microscopy (HRTEM) analysis [94]. Additionally, after pulverizing marine algae biomass and ultrasonicating in a water bath, an aqueous extract of the marine algae Champia parvula can be obtained, which can be used to fabricate selenium-zinc (Se@Zn) nanoparticles [95].

In addition to conventional methods, several naturally derived substances play dominant roles in the synthesis process of SeNPs. One innovative approach involves the utilization of *Tetrahymena thermophila*, in which amorphous spherical and irregular SeNPs are biosynthesized within the organisms. Notably, three specific proteins potentially play a crucial role in this synthesis process, suggesting a complex interaction that warrants further investigation [54]. With high dispersibility and stability, another new type of SeNPs is synthesized by using the polysaccharide-protein complex (PSP) isolated from the viscera of abalones, which severs as a capping agent in preparing SeNPs. The dispersibility of PSP-SeNPs remains stable for up to 12 months at 4 °C [96, 97]. Additionally, a bacterial strain, *Proteus mirabilis* YC801, isolated from the gut of adult *Monochamus alternatus*, demonstrates extremely high tolerance to selenite. This strain shows exceptional efficiency in converting selenite into red SeNPs, reducing nearly 100% of 1.0 and 5.0 mmol/L selenite within 42 and

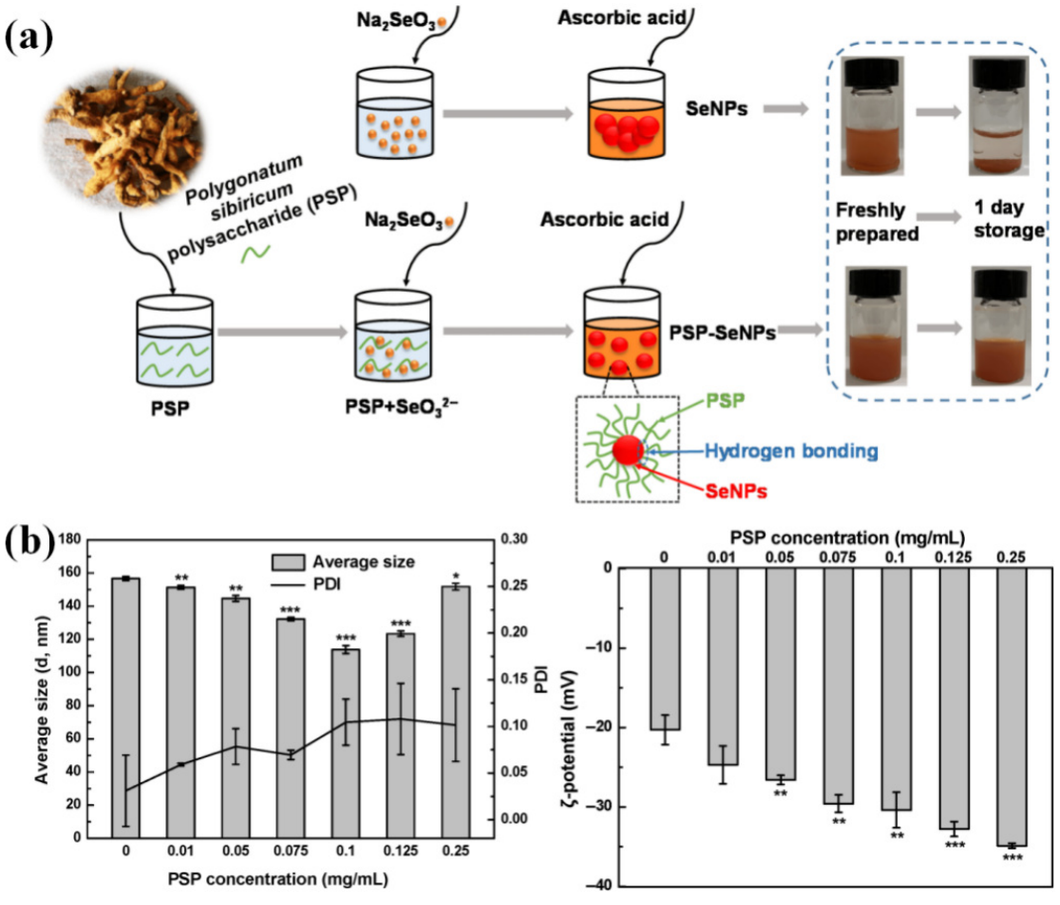


Fig. 9 Construction of polygonatum sibiricum polysaccharide functionalized selenium nanoparticles. **(a)** Synthetic scheme for the preparation of SeNPs and PSP-SeNPs and images of the dispersions before and after storage for 1 day. **(b)** Size distribution (left) and ζ-potential (right) of SeNPs and PSP-SeNPs prepared with different concentrations of PSP; values marked with * $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$ indicated significant differences when compared to SeNPs. Reproduced with permission from Ref. [90] © 2022 The Authors.

48 hours, respectively [98].

Through their metabolic functions or intrinsic chemical components, microorganisms or plant extracts could realize the synthesis of SeNPs. Microorganisms can metabolically reduce selenate in the environment to form SeNPs, while the chemical constituents in plant extracts effectively reduce selenium salts to generate SeNPs. These two biosynthesis methods can better meet the biosafety and environmental requirements. However, the inconsistent growth rates of microorganisms and the variability in obtaining plant extracts can impact production efficiency of SeNPs. Additionally, the complexity of metabolic processes in bio-sourced systems poses challenges for precisely controlling characteristics of SeNPs, limiting the broader development of biosynthetic approaches. So far, chemical synthesis of SeNPs has achieved a relatively mature production system, with some research outcomes successfully translated into practical applications. For example, Chen et al. have been granted 43 national invention patents related to the chemical synthesis of SeNPs have achieved the technical transformation of 13 innovations. They have also developed a GMP-compliant production process capable of ton-scale output, and have conducted multi-center clinical studies [99]. In addition, the high production costs and stringent requirements for equipment and technology of physical synthesis methods, limit their feasibility for large-scale manufacturing.

Compared to physical and chemical methods, biosynthesis of SeNPs is relatively nascent, and there are fewer successful studies of scaling up for industrial applications. Nonetheless, with the growth demand for green synthesis methods, research on biosynthesis of SeNPs is also continuously deepening. For instance, Guo et al. developed a highly efficient method for biosynthesizing selenium nanoparticles (SeNPs) using *Bacillus licheniformis* S13 and *Bacillus subtilis* S12 strains. This study included the establishment of a large-scale

fermentation process and a comprehensive system for extracting and purifying biological SeNPs. Application experiments have been conducted in fields such as selenium-enriched crop and animal production, with the related patent successfully transferred [100]. The biosynthesis of SeNPs is a green preparation technology with broad application prospects. With the continuous deepening of relevant research and the continuous maturity of technology, biosynthesized SeNPs are expected to achieve further industrial transformation.

Imaging Modalities of SeNPs

SeNPs act as drug carrier and simultaneously serve as diagnosis agent for monitoring metabolism of nanoparticles and their therapeutic effects. The current imaging techniques employed for SeNPs include fluorescence imaging (FI), magnetic resonance imaging (MRI), computed tomography (CT), photoacoustic imaging (PAI), and photothermal imaging (PTI) [101].

Fluorescence imaging (FI)

Fluorescence imaging (FI) primarily relies on fluorescent substances for labeling, which emit fluorescent signals under the excitation of specific wavelengths of light, thereby enabling the localization, tracking, and imaging of target substances. Although SeNPs do not possess fluorescent properties, they can be modified with fluorescent moleculars, such as fluorescein, green fluorescent protein (GFP), or quantum dots, enabling SeNPs to realize photosensitive imaging. For instance, a nanosystem known as Ru-Se@GNP-RBCM is constructed, wherein ruthenium complex-modified selenium nanoparticles (Ru-Se NPs) are encapsuled with red blood cell membranes (RBCM) and bacteria-responsive gelatin nanoparticles (GNP). Ruthenium complexes with strong fluorescence were combined with Se NPs to provide real-time imaging, allowing for precise monitoring of the infection treatment process alongside the antibacterial action [102]. Additionally, GSH-Se nanozymes are prepared using glutathione and sodium selenite through the hydrothermal method. These fluorescent nanozymes exhibit glutathione peroxidase activity, emit fluorescence upon binding with the novel gentamicin chlortetracycline (CTC), and show a linear relationship with concentration. Moreover, low cytotoxicity of GSH-Se makes it suitable for rapid fluorescent detection of CTC in food as well as for intracellular imaging analysis of CTC [103]. Furthermore, photostable SeNPs modified with a thiol group named Bi_2Se_3@PEG/DOX/Ce6 are synthesized. By incorporating the photosensitizer Ru(II)-polypyridine complex, this nanoparticles can realize the identifying various types of tumors [104]. Finally, a targetable selenium-containing amphiphilic polymer nanomedicine carrier, RGD-PEG-PUSeSe-PEG-RGD, is designed with fluorescence imaging capabilities. This nanocarrier not only serves as a substrate for TrxR reduction but also facilitates controlled release of the chemotherapeutic drug gemcitabine (GEM) upon TrxR stimulation. The compound 5,10 (15)-bis (4-aminophenyl)-15,20-diphenylporphyrin (Por) is used as an imaging guidance agent to enhance GEM chemosensitization and prevent anti-relapse/metastasis treatment (Fig. 10) [105].

Magnetic resonance imaging

Magnetic resonance imaging (MRI) is a medical imaging technique that utilizes a magnetic field and radio waves to create detailed images of the internal body structures and functions. A notable Gd^{3+}-doped $MoSe_2$ nanosheets are prepared. $MoSe_2(Gd^{3+})$-PEG, which possesses a transition metal dichalcogenide (TMDC) structure is utilized as a T1-weighted MRI contrast agent for *in vivo* tumor diagnosis [106]. Additionally, magnetic iron diselenide ($FeSe_2$) nanoparticles are developed and further modified with polyethylene glycol (PEG) to form $FeSe_2$-PEG nanoparticles, exhibiting a high R2 relaxivity rate and strong near-infrared (NIR) absorption, making them suitable for MRI diagnosis [107]. Furthermore, nano-selenium and manganese carbonate are utilized to modify magnetite, creating a nanoscale diagnostic and therapeutic agent (MCDION-Se). In this theranostic system, the manganese carbonate dissolves in the weakly acidic microenvironment of tumor tissues, releasing Mn^{2+} ions. The combination of released Mn^{2+} ions and magnetic magnetite endows this system with tumor-specific responsive dual-modal magnetic resonance imaging capabilities (Fig. 11) [108].

Computed tomography

Computed tomography (CT) employs X-rays and computer technology to scan the cross-sectional sections of tissues and generate high-resolution images. Jiang et al. prepared Cu-Fe-Se nanosheets (CFS NSs) in an aqueous solution under ambient

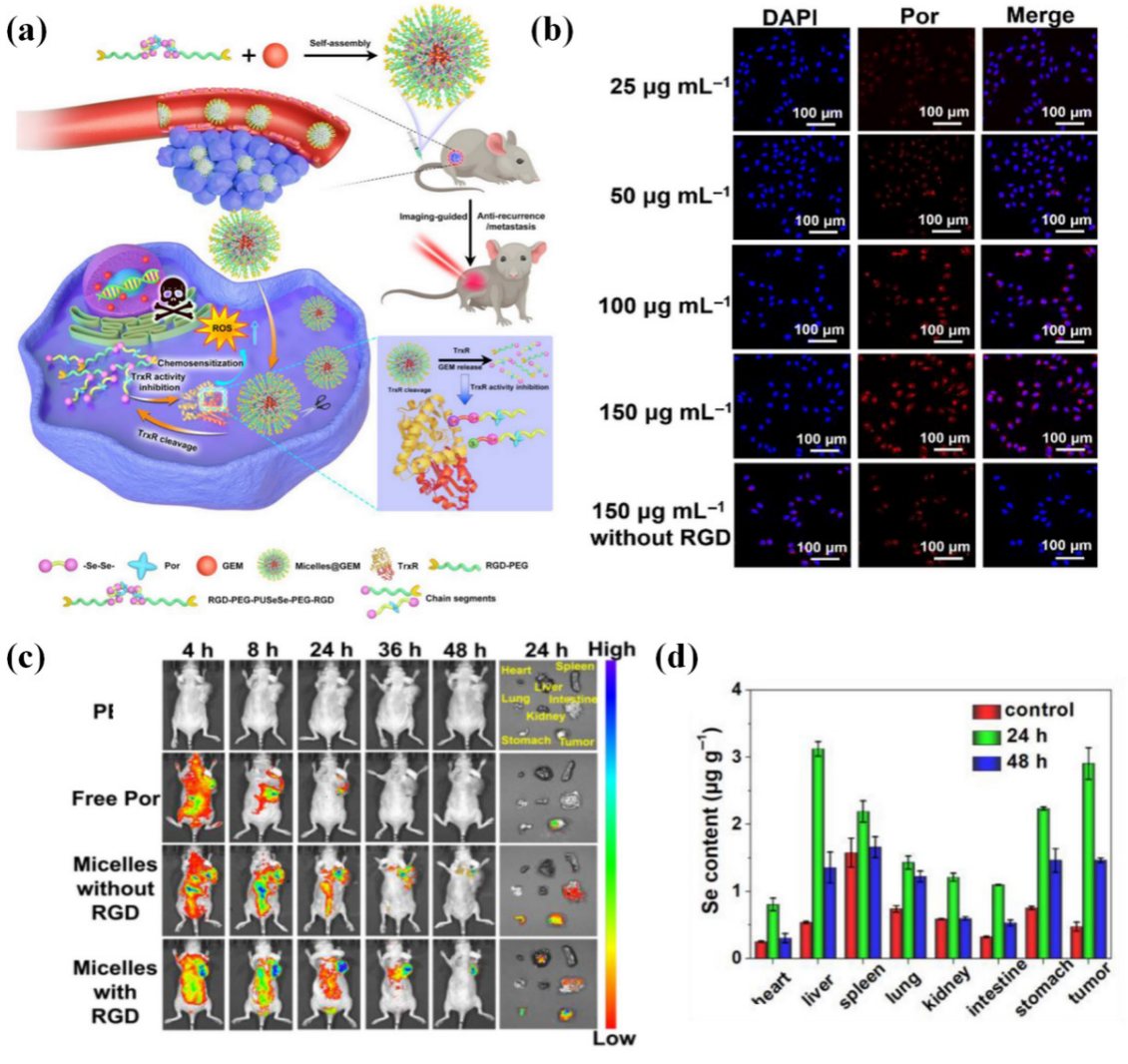


Fig. 10 Cellular and *in vivo* fluorescence imaging of thioredoxin reductase-interfering SeNPs delivery system. **(a)** Schematic illustration of TrxR-responsive DDS for ROS-mediated chemo-sensitization and anti-recurrence/metastasis therapy based on TrxR activity inhibition. **(b)** Confocal microscopy images of A549 cell uptake after incubation with RGD-PEG-PUSeSe-PEG-RGD at different concentrations for 24 h (Scale bar = 100 nm). **(c)** Fluorescence images of the mice and dissected organs recorded at an excitation of 580 nm and an emission of 720 nm. **(d)** Biodistribution of RGD-modified micelles in the major organs of mice. Reproduced with permission from Ref. [105] © 2020 Elsevier B.V.

conditions using a sequential co-precipitation method. They functionalized these nanosheets with the anticancer drug doxorubicin (CFS@DOX) through electrostatic interactions and labeled them with the radioactive isotope 99 mTc via surface coordination effects, resulting in excellent colloidal stability (Fig. 12) [109]. Additionally, a novel nanocomposite UCNP-Bi(2)Se(3) is synthesized and exhibits highly efficient upconversion luminescence (UCL) as well as reasonable computed tomography (CT) imaging capabilities, demonstrating their potential for both UCL imaging and photothermal therapy (PTT) [110].

Photothermal imaging

Photothermal imaging (PTI) utilizes infrared detectors and optical imaging lenses to receive the distribution patterns of the infrared radiation energy emitted from target. These patterns are reflected onto the photosensitive elements of the infrared detector, thereby generating an infrared thermal image. A Se customization strategy based on conjugated oligomer TPSe nanoparticles (TPSe NPs) has been synthesized. They achieve bright NIR second window (NIR-II) emission up to 1 400 nm, demonstrating relatively high photothermal conversion efficiency of 60%, and show photothermal ablation effects on cancer cells and tumors *in vivo*, showing good imaging effects *in vivo* cancer phototherapy diagnosis (Fig. 13) [111]. Moreover, bismuth selenide (Bi_2Se_3) nanoparticles

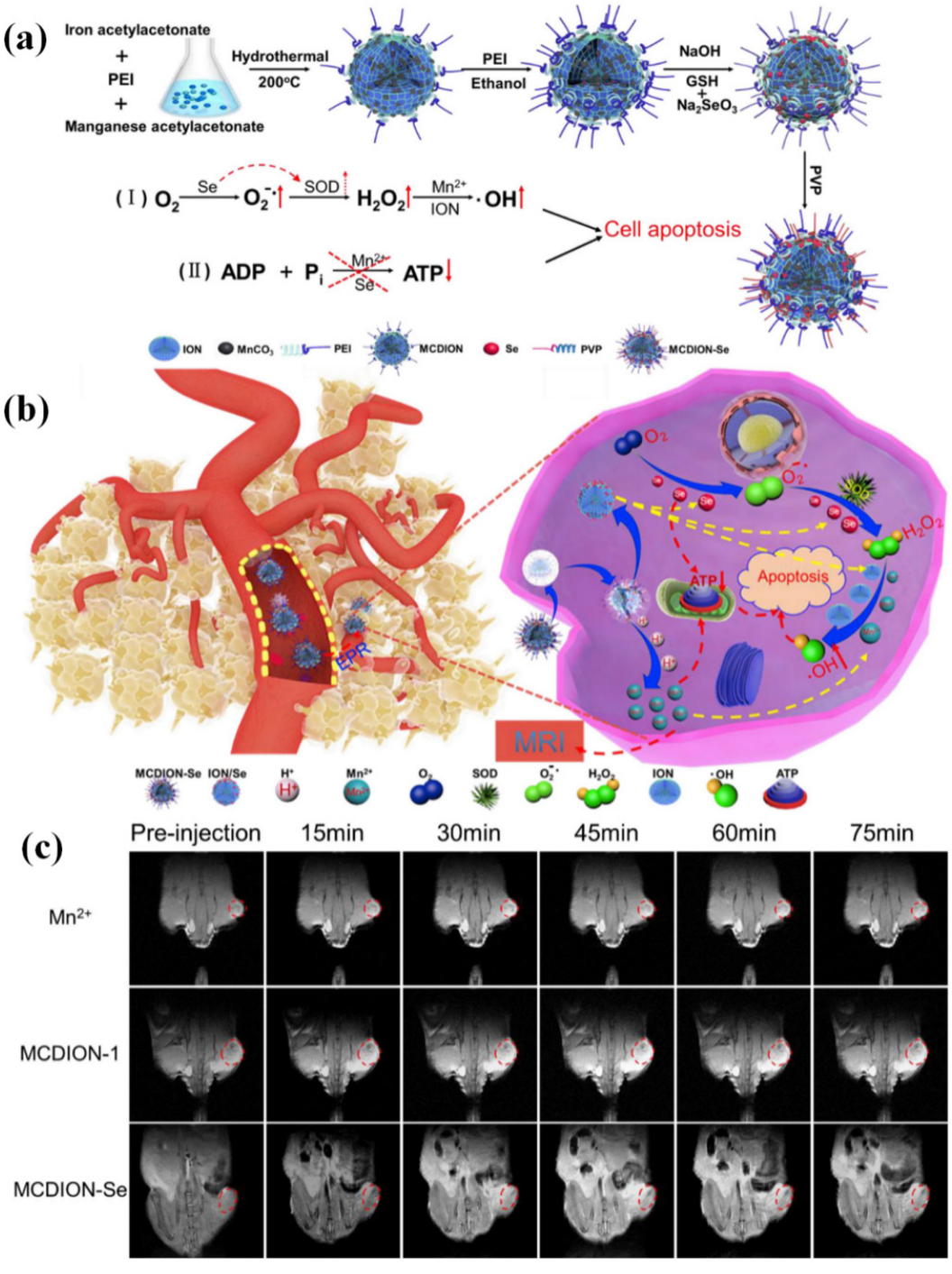


Fig. 11 A pH-responsive platform combining chemodynamic therapy with limotherapy for simultaneous bioimaging and synergistic cancer therapy. **(a)** Illustration of the synthetic process of MCDION-Se. **(b)** The cascade reaction of MCDION-Se in the intracellular environment. **(c)** T1-weighted MR images of tumor-bearing mice acquired at pre-injection and post-injection of Mn^{2+}, $MCDION^{-1}$, and MCDION-Se. Reproduced with permission from Ref. [108] © 2019 Elsevier B.V.

(NPs) coated with polydopamine (PDA)/human serum albumin (HSA)/doxorubicin (DOX) have been designed and synthesized. These nanoparticles not only possess infrared thermal imaging capabilities but also exhibit strong NIR absorbance, showing their high efficacy and stability for efficient photothermal therapy (PTT) applications [112].

Photoacoustic imaging

Photoacoustic imaging (PAI) is based on the principle of photoacoustic effect, which means pulsed laser irradiates tissues, leading to the generation of ultrasonic signals from light-absorbing domains within the tissues. By detecting these signals and employing reconstruction algorithms, it is possible to

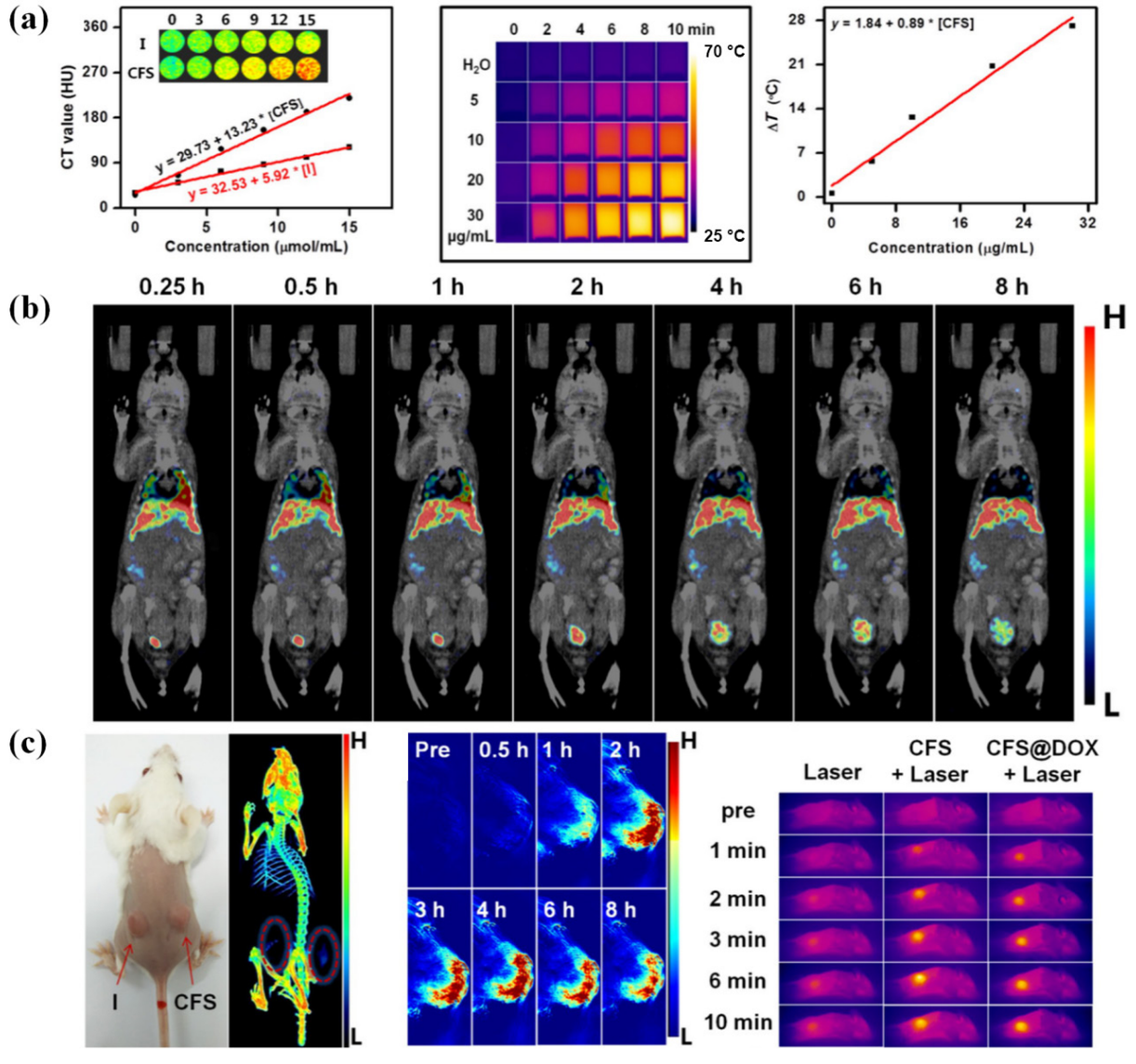


Fig. 12 Cu-Fe-Se ternary nanosheet-based drug delivery carrier for multimodal imaging and combined chemo/photothermal therapy of cancer. **(a)** The intensity of CT images and X-ray attenuation in Hounsfield units (HU) of CFS NSs (left), photothermal images (middle) and the corresponding heating curves (right). **(b)** SPECT/CT images of a mouse bearing a tumor at different times after intravenous injection of CFS NSs. **(c)** Photograph and 3D *in vivo* CT image of a mouse bearing two tumors (left), *in vivo* PA images of the tumor acquired at different times after the mouse was intravenously injected with CFS NSs (middle), and infrared thermal images collected at different times post injection of 4T1 tumor-bearing mice (right). Reproduced with permission from Ref. [109] © 2018 American Chemical Society.

reconstruct and visualize the distribution of light absorption within the tissue. For instance, multifunctional theranostic agent $Ni_{0.85}Se$NPs (PAA–$Ni_{0.85}Se$ NPs) are reported, which are made from ultrasmall poly(acrylic acid)-functionalized Ni through a simple environmental water precipitation strategy. The use of poly(acrylic acid) (PAA) endows the nanoparticles with PAI imaging property [113]. In addition, with high stability and low *in vivo* toxicity, $MoSe_2(Gd^{3+})$-PEG nanosheets exhibit strong absorption in the near-infrared region, making them suitable as contrast agents for PAI [106]. Lastly, gold selenium core-shell nanostructures (AS-I/S NCs) modified with ischemic myocardial targeted peptide (IMTP) and mitochondrial targeted antioxidant peptide SS31 have been designed, exhibiting excellent NIR-II photoacoustic imaging for MI/RI processing, With gold nanorods possessing the photoacoustic effect as the core, a shell containing nano-selenium was continuously coated on it, enabling it to be excited by near-infrared second region light in the low background signal area of biological tissues, and it has a good photoacoustic imaging effect on the left ventricular wall of the rat

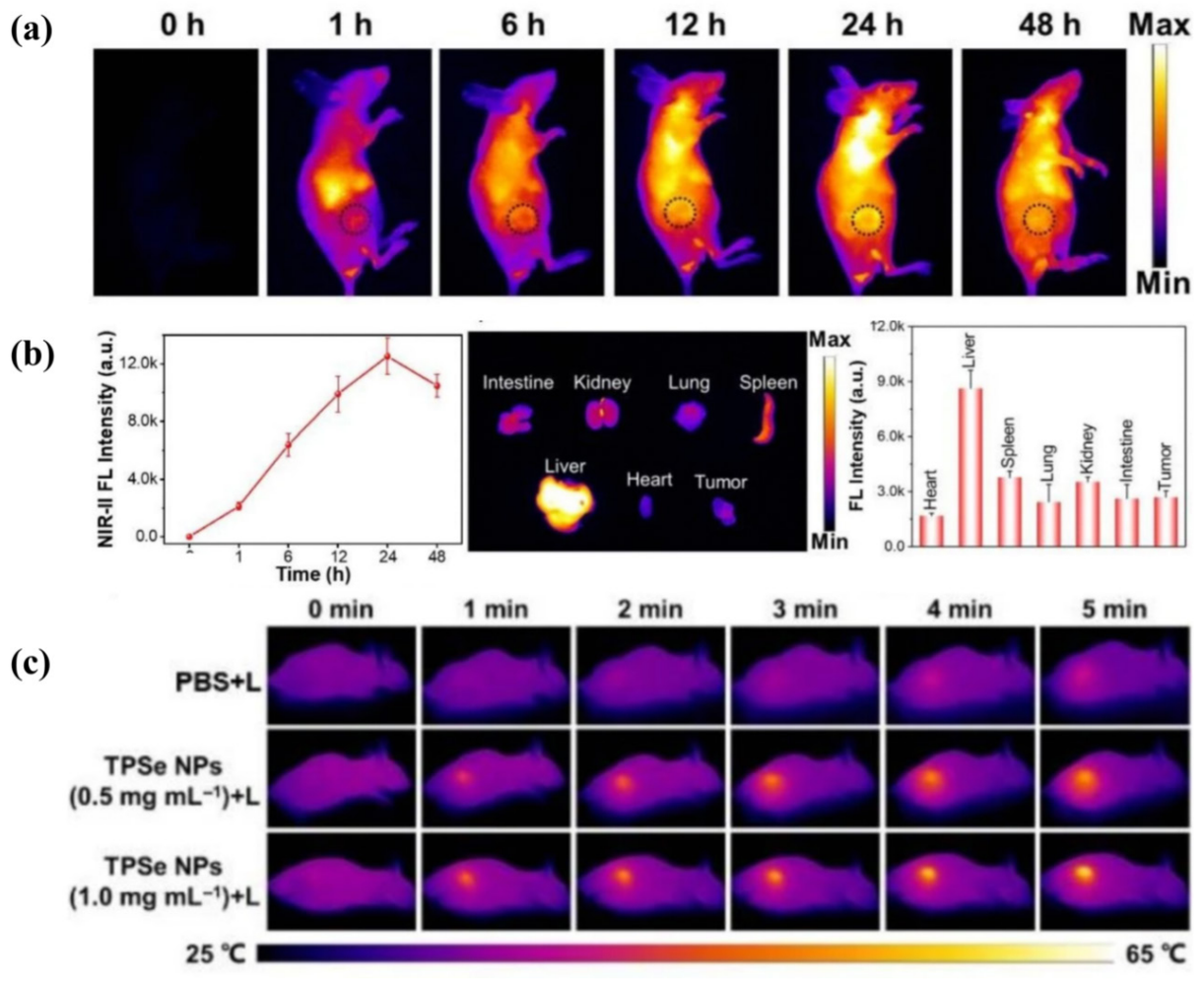


Fig. 13 Selenium-integrated conjugated oligomer nanoparticles with high photothermal conversion efficiency for NIR-II imaging-guided cancer phototheranostics *in vivo*. **(a)** *In vivo* fluorescence imaging of HCT116 tumor-bearing mice at 0, 1, 6, 12, 24 and 48 h after intravenous administration of TPSe NPs. **(b)** Fluorescence intensity from (a) plotted as a function of time post-injection (left). Fluorescence image (middle) and statistical fluorescence intensity of major organs after 24 h post-injection of TPSe NPs (right). **(c)** Thermal image of the mice in PBS + Laser (L) group and TPSe NPs + L group upon irradiation. Reproduced with permission from Ref. [111] © 2023 The Authors.

body (Fig. 14) [114].

Therapeutic Functions of SeNPs in Inflammation Diseases

Among various formats of selenium, SeNPs have emerged as a promising therapeutic agent in treatment of various diseases due to its ability to enhance the bioavailability of selenium while minimizing potential side effects. Possessing the anti-inflammatory and antioxidant properties, SeNPs can alleviate inflammatory responses and oxidative stress through multiple mechanisms, thus contributing to the treatment of inflammatory diseases [55]. The following sections discuss the therapeutic effects of SeNPs in inflammation, focusing on their ability to inhibit oxidative stress, regulate inflammatory mediators, and influence inflammation-related signaling pathways.

Suppressing oxidative stress

ROS are highly reactive oxygen-containing compounds generated during cellular metabolism. While low concentrations of ROS are essential during cellular metabolism, immune defense, and cell differentiation, excessive ROS productions cause damage to the body, leading to oxidative stress and promoting inflammatory responses [115]. SeNPs have been shown to significantly reduce the level of ROS and suppress oxidative stress, thereby ameliorating inflammation. For instance, a novel mesoporous selenium-hyaluronic acid nanozyme therapeutic system (MSe-HA NPs) is constructed to target the

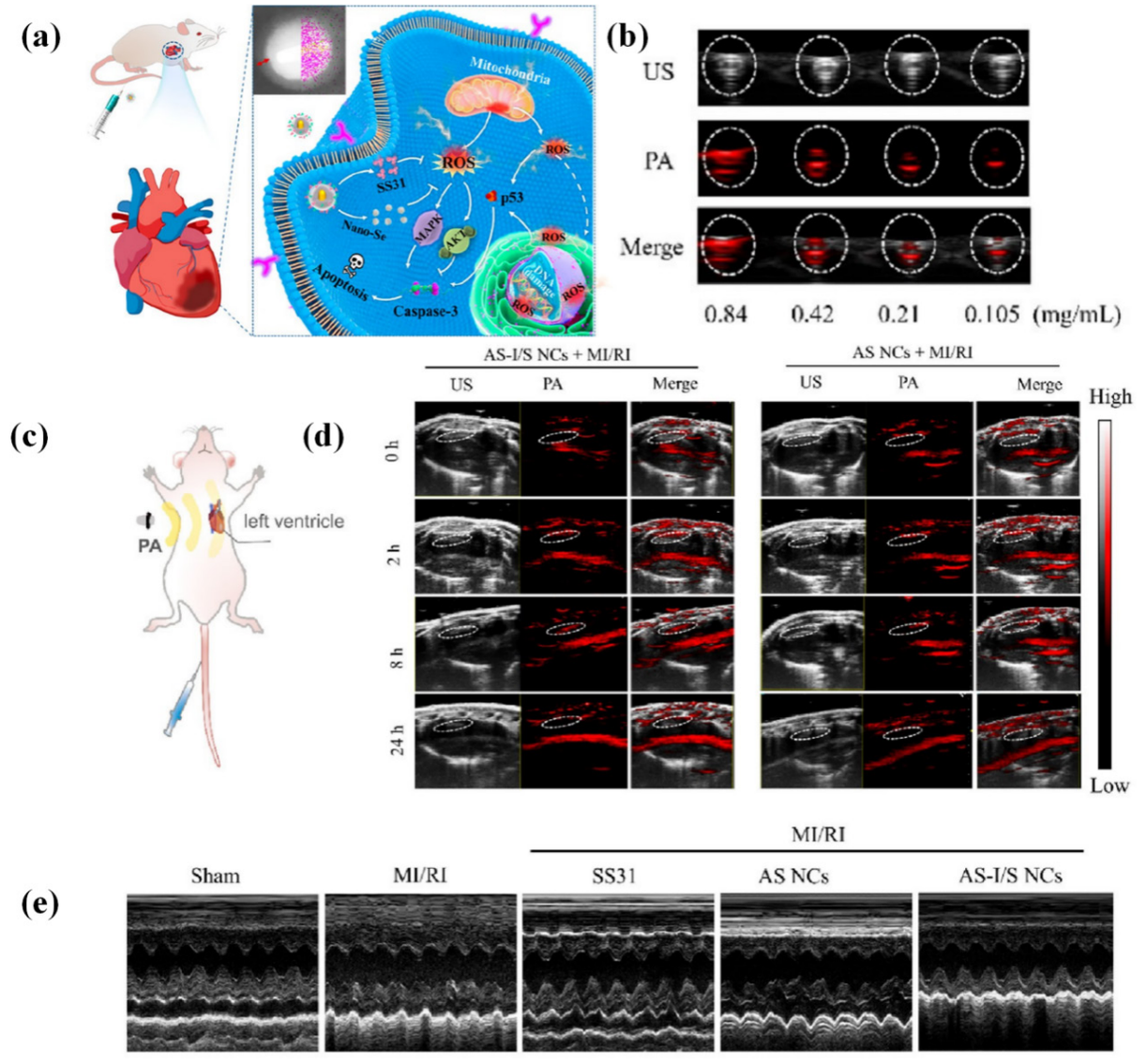


Fig. 14 Light-activated gold–selenium core–shell nanocomposites with NIR-II photoacoustic imaging performances for heart-targeted repair. **(a)** Schematic diagram of selenium core–shell nanocomposites for heart-targeted repair. **(b)** Ultrasonic and photoacoustic signal images of AS-I/S NCs *in vitro*. **(c)** Photoacoustic imaging of left ventricular wall *in vivo*. **(d)** Ischemic myocardium-targeted photoacoustic imaging of AS-I/S NCs *in vivo*. **(e)** Echocardiography of rats. SS31, AS NCs, and AS-I/S NCs were administered *in vivo* for 3 days. Reproduced with permission from Ref. [114] © 2022 American Chemical Society.

elimination of ROS in inflammatory macrophages, thereby treating systematic inflammation of sepsis. In addition, the high specific surface area of the mesoporous selenium nanoenzymes exhibits an excellent ROS scavenging activity of up to 81%, which is nearly double that of solid SeNPs [116]. Another study, quercetin combined with SeNPs exhibited excellent therapeutic effect in thioacetamide (TAA)-induced hepatocellular carcinoma rat model, resulting in an increase in glutathione peroxidase (GPx) activity, enhanced clearance of ROS, and improved oxidative stress [117]. Furthermore, palladium nanoparticles (Pd NPs) are combined with SeNPs to develop a multi-nanosystem, which can scavenge hydroxyl radicals (·OH) and provide photothermal effects, reduces the inflammatory response in macrophages, and finally achieve therapeutic purposes for rheumatoid arthritis (RA) [118]. In the neuroprotective model of spinal cord injury, epigallocatechin-3-gallate-selenite nanoparticles (EGCG-Se NP) are constructed to scavenge excessive ROS and inhibiting oxidative stress [119]. Additional studies have demonstrated the anti-arthritic effects of SeNPs dispersed in 1% coumarin (CA), which are found to reduce ROS level by modulating the levels of antioxidant genes including CAT, GPx1, and COX-2, thereby protecting cells from oxidative stress [120].

Moreover, dextrin-stabilized SeNPs(diameter: 64 nm±0.158 nm) can effectively enhance the levels of antioxidant enzymes, such as superoxide dismutase (SOD), GPx, and CAT in the liver, spleen, and kidneys of arthritic rat model, effectively suppressing oxidative stress and exerting anti-inflammatory therapeutic effect [121]. Additionally, ginger-derived SeNPs exhibit free radical scavenging properties in a nicotine-induced nephrotoxicity model. The COX-2 gene can promote the synthesis of prostaglandin E2 (PGE2), which in turn increases ROS. These particles control nephrotoxicity by modulating the transcription levels of the COX-2 gene, through antioxidant-mediated anti-inflammatory activity [122]. Another study reported that SeNPs can prevent the development of oxidative stress by upregulating two antioxidant-related enzyme genes, nuclear factor erythroid 2-related factor 2 (Nrf2) and HO-1, in an epileptic mouse model, thereby providing neuroprotection, inhibiting inflammatory responses and apoptotic cascades [123]. Moreover, a hydrogel based oxidized hyaluronic acid (OHA) crosslinked with hyaluronic acid adipic dihydrazide (HA-ADH) is utilized to deliver SeNPs for the treatment of an osteoarthritis rat model. This OHA/HA-ADH@SeNPs significantly reduce the production of ROS and remarkably promote the expression of GPx1. Concurrently, the expression of GPX1 in SW1353 cells was suppressed by siRNA, deciphering the link between GPX1 and oxidative stress, indicating that GPX1 can inhibit oxidative stress (Fig. 15) [124]. In addition, SeNPs can also inhibit intestinal inflammation by reducing the concentration of ROS in the jejunum and promoting the development of broiler chickens [125]. Notably, the hyaluronic acid-selenium nanoparticles targeting CD44 can scavenge ROS and other free radicals, showing potential for treatment of spinal cord injuries [126].

Regulating inflammatory mediators

Except for inhibiting oxidative stress, SeNPs also play a key role in suppressing inflammation by modulating the levels of cytokines and locally related molecules in the inflammatory response. For example, porphyra polysaccharide-functionalized SeNPs effectively alleviated ulcerative colitis by scavenging ROS, reducing the levels of pro-inflammatory factors NO, iNOS, TNF-α, IL-1β, and simultaneously increasing the level of the anti-inflammatory factor IL-10 [127]. In a sodium arsenite kidney damage animal model, SeNPs can suppress expression of pro-inflammatory factor IL-1β and promote expression level of anti-inflammatory factor IL-10 [128]. The combination of SeNPs with prodigiosins (PDGs) has shown anti-inflammatory effects in a depression-like behavior rat model induced by chronic unpredictable mild stress [128]. This system significantly reduces pro-inflammatory factors such as IL-1β, TNF-α, and IL-6, while increase the expression of anti-inflammatory factor IL-10 [129]. In BDE-209 caused jejunal inflammation chicken model, SeNPs can alleviate the inflammation by reducing the expression levels of IL-1β, IL-2, IL-6, and IL-17, and increasing the expression levels of IL-10 and IFN-γ [130]. It is discovered that nano selenium can inhibit the expression of inflammatory cytokines, such as IL-1β, IL-6, IL-17, TNF-α, and IFN-γ in the colon, and regulate the growth of gut microbiota, thereby alleviating intestinal inflammation. The study further investigated the correlation between the relative abundance of different species at the genetic level and markers of colitis, and by improving the relative abundance of bacterial genera, it significantly suppressed the expression levels of pro-inflammatory factors in mice with colitis, thus improving intestinal inflammation caused by long-term DSS treatment (Fig. 16) [131]. In addition, in the influenza model induced by H1N1, the levels of selenium in the body are reduced after H1N1 virus infection, and there is an abnormal increase in inflammatory factors in the lung tissue, leading to the occurrence and exacerbation of the inflammatory response. The analysis of cytokine detection results suggests that the virus-mediated inflammatory response may be related to the IL family, including IL-1β, IL-6, IL-8, IL-22 and so on. SeNPs can inhibit the inflammatory response in H1N1 mice by reducing the expression level of inflammatory cytokines TNF-β, IL-8, and IL-22 (Fig. 17) [132].

In addition to regulating inflammatory cytokines, SeNPs also comprehensively alleviate local inflammation by modulating inflammatory related molecules. For instance, SeNPs and metformin are encapsulated within macrophage-derived nanovesicles to form a complex for the treatment of spinal cord injuries. While modulating the expression of inflammatory factors such as TNF-α, IL-1β, IL-6, and iNOS, they can also reduce the activity of

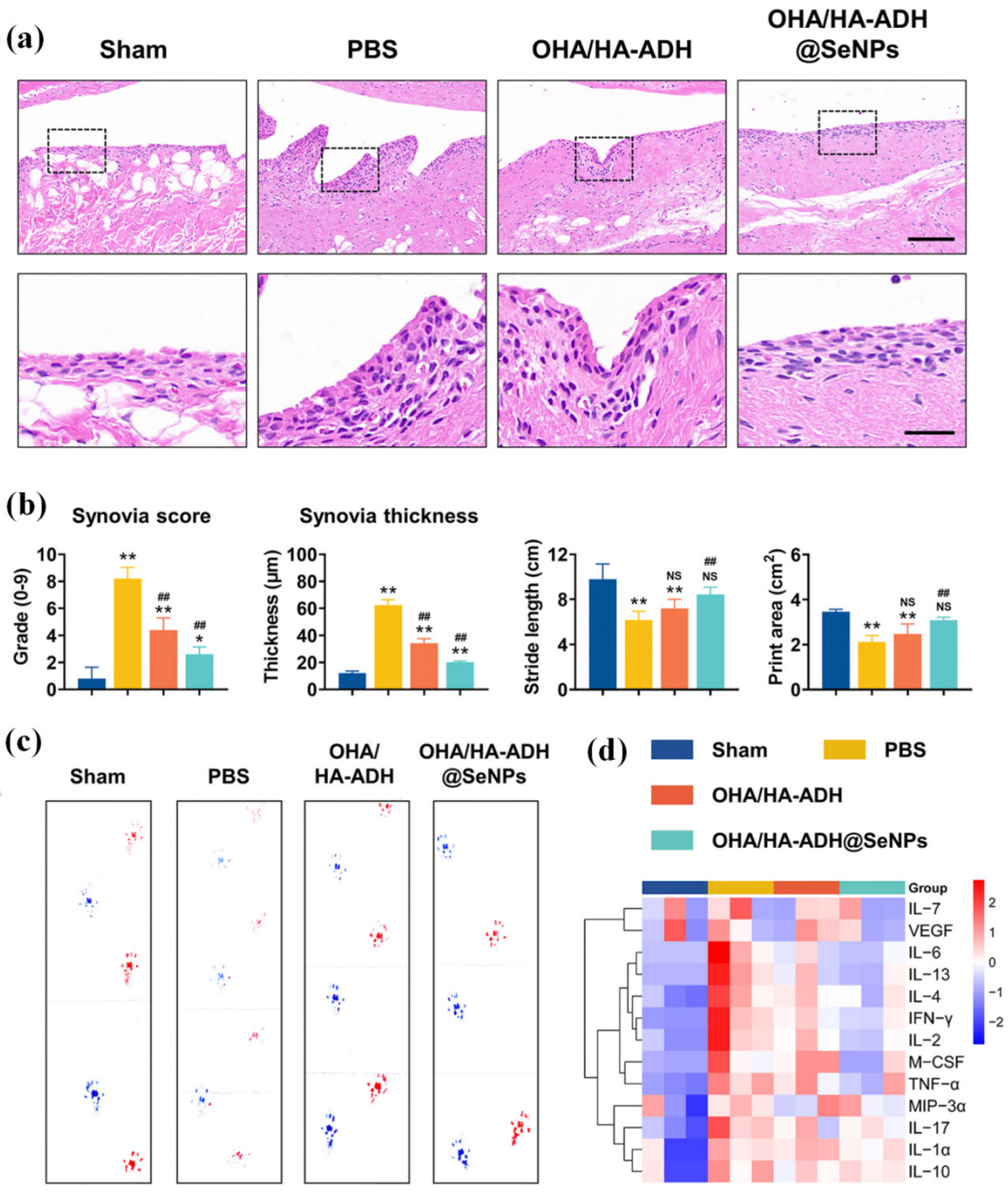


Fig. 15 An injectable hydrogel with selenium nanoparticle delivery for the treatment of osteoarthritis in rats by reducing ROS production and promoting GPx1 expression. **(a)** H&E staining of the synovium. **(b)** Quantitative analysis of inflammation in the synovium with H&E (left and middle left). Quantification of footprints: stride length (middle right) and footprints area (right). **(c)** The footprints of rat 8 weeks after surgery. Red: modeling side, blue: healthy side. **(d)** Heatmap of the relative expression of inflammatory cytokines. Columns represent sample groups and rows represent cytokine species. Reproduced with permission from Ref. [124] © 2023 The Authors.

malondialdehyde (MDA) and decrease cell apoptosis in cells or tissues, thereby exerting an anti-inflammatory effect (Fig. 18) [133]. It is reported that SeNPs synthesized by reducing selenite significantly decrease the expression levels of cytokines iNOS, NO, TNF-α, and oxidative products MDA and kidney injury molecule-1 (KIM-1) in renal tissues, modulate renal inflammation, and promote the repair of damaged renal cells through antioxidant actions [134]. Through a biological method, lycopene-coated selenium nanoparticles (LYC-SeNPs) are synthesized to alleviate kidney inflammation in a glycerol induced acute kidney injury rat model. LYC-SeNPs have demonstrated the ability to reduce the levels of IL-1β, IL-6, and TNF-α, as well as the expression of nitric oxide synthase 2 (NOS2), an enzyme that catalyzes

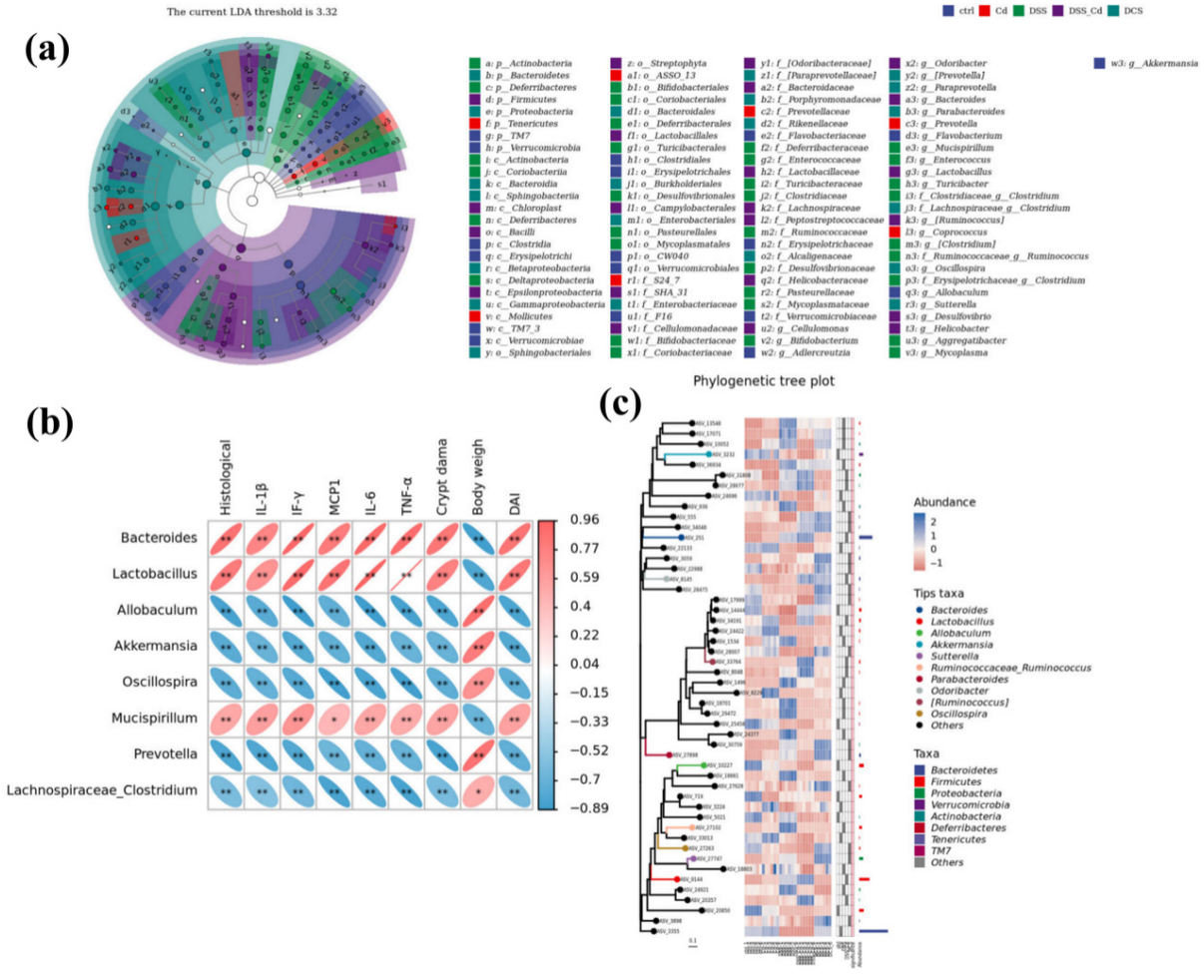


Fig. 16 SeNPs alleviate intestinal inflammation by inhibiting the expression of inflammatory cytokines in the colon. **(a)** LEfSe analysis. **(b)** Correlation analysis between the relative abundance of species and enteritis-related indicators. **(c)** Genus-level evolutionary tree of the species in colon. Reproduced with permission from Ref. [131] © 2024 The Authors.

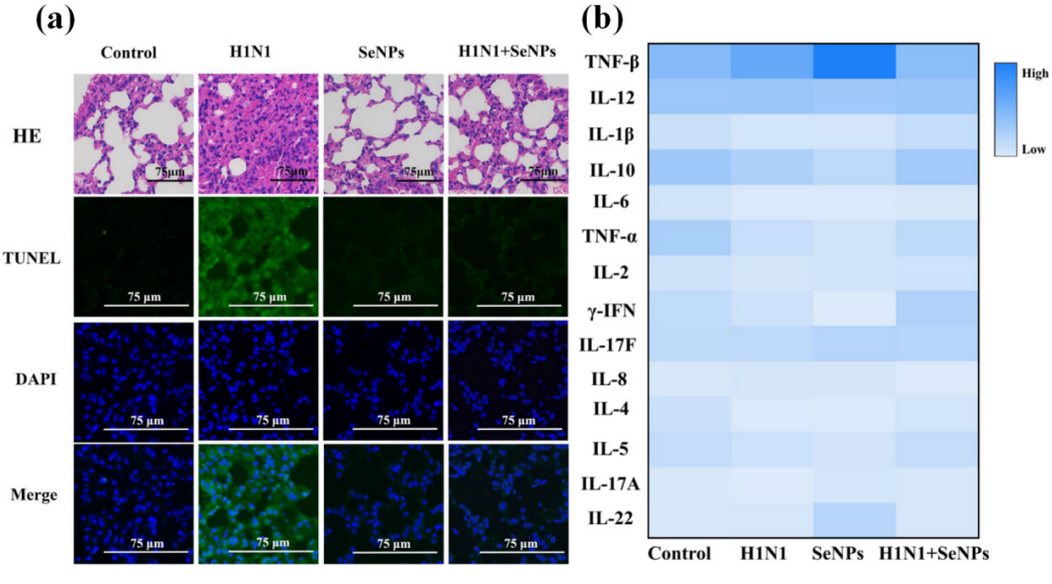


Fig. 17 Selenium nanoparticles control H1N1 virus by inhibiting the inflammatory response and cell apoptosis. **(a)** H&E staining of lung morphology, inflammatory exudation, and apoptotic responses in mice infected with H1N1 influenza virus and treated with SeNPs in selenium-deficient mice. Scale bar = 75 μm. **(b)** Regulation of inflammatory factors *in vivo* by SeNPs and alteration of corresponding cytokines in selenium-deficient mice infected with H1N1 influenza virus after treatment with SeNPs. Reproduced with permission from Ref. [132] © 2023 The Authors.

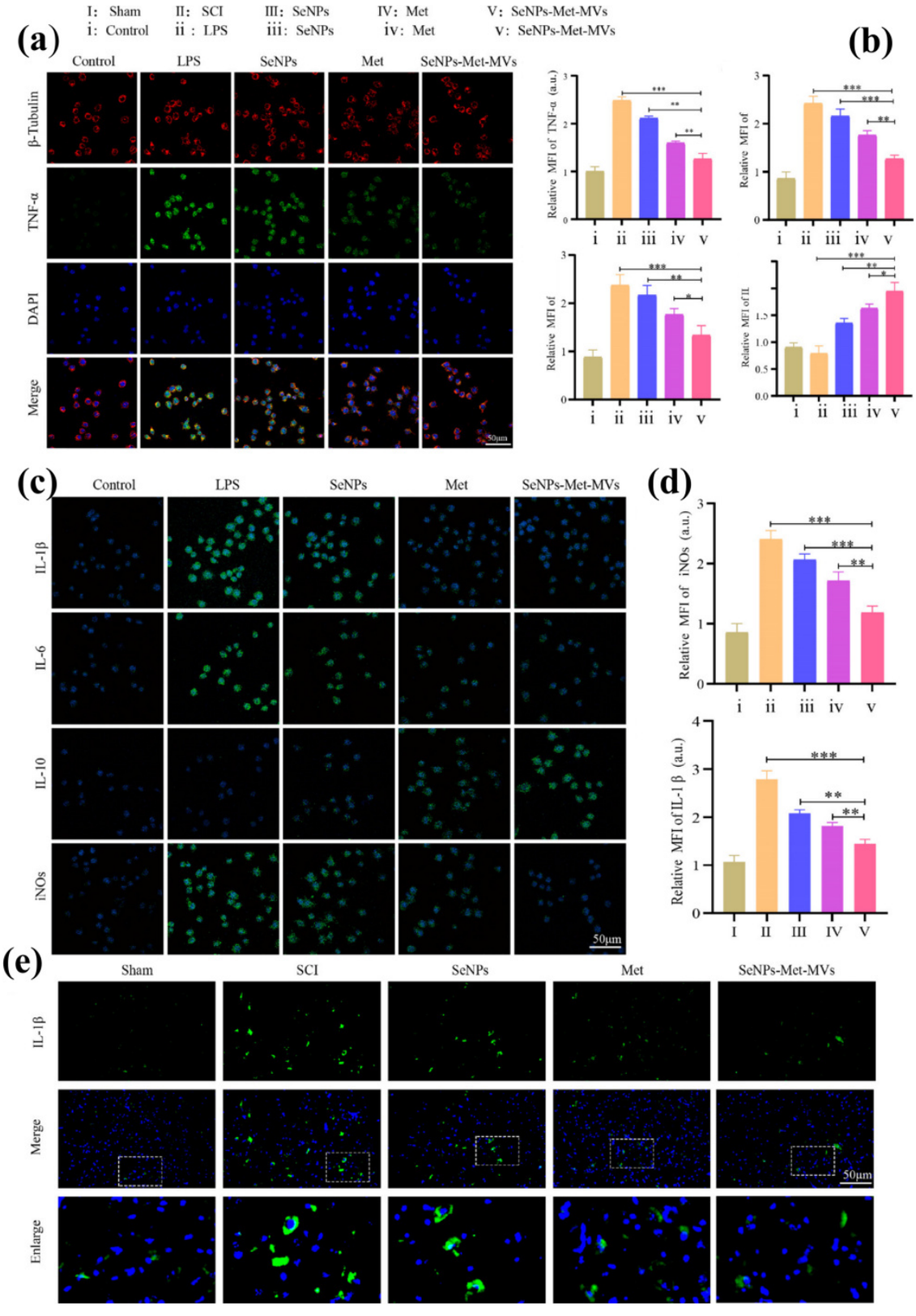


Fig. 18 Anti-inflammation study of SeNPs-Met-MVs. **(a)** Immunofluorescence experiments in BV2 cells (red: β−Tubulin, green: TNF-α, blue, DAPI presented the nuclei). **(b)** Fluorescence statistics of TNF-α in BV2 cells (middle right). Fluorescence statistics of IL-1β (left), IL-6(middle left), and IL-10 (right) in BV2 cells. **(c)** Immunofluorescence images of different factors (IL-6, IL-1β, IL-10, iNOS) in BV2 cells. **(d–e)** Statistics of immunofluorescence intensity of iNOS in BV2 cells. Immunofluorescence images and statistics of IL-1β in spinal cord tissue (Scale bar = 50 μm). Reproduced with permission from Ref. [133] © 2023 American Chemical Society.

the conversion of L-arginine to nitric oxide (NO) in the body [135]. Moreover, nano selenium is found to elevate the levels of GABA and glutathione in a cypermethrin neurotoxicity rat model, while inhibiting the increasement of MDA, TNF-α, IL-1β levels, showing its potential for anti-inflammatory and antioxidant effects [136]. In diabetic mice model, porous Se@SiO_2 nanospheres can reduce the levels of MDA, TNF-α, IFN-γ, and IL-1β, and increase the levels of GPx4 and GSH/GSSG, thus inhibiting excessive lipid oxidation and alleviating inflammation to ameliorate diabetic retinopathy [137].

Furthermore, regulating the activity of inflammatory related immune cells is also very important. For example, hydrogel microbeads are synthesized by coating a protective shell of calcium alginate (SA) hydrogel on hyaluronic acid-modified SeNPs. They can reduce the secretion of pro-inflammatory cytokines such as TNF-α, IL-6, IL-1β, and TGF-β1, decrease the infiltration of neutrophils and monocytes, and increase regulatory T cells, effectively alleviating symptoms of colitis [138]. Moreover, self-sustaining selenium-encapsulated nanoparticles (SSSe-NPs) are synthesized for the treatment of myocardial infarction. The SSESe-NPs exert anti-inflammatory activity by reducing macrophage infiltration, modulating the polarization of M2/M1 in the infarcted tissue, decreasing the expression of inflammatory cytokines such as IL-1β, IL-6, and TNF-α, and enhancing the expression of anti-inflammatory cytokine IL-10 (Fig. 19) [139]. Furthermore, porous Se@SiO_2 nanoparticles are reported to reduce inflammation in acute kidney injury caused by ischemia-reperfusion. This is achieved through decreasing the pro-inflammatory cytokines TNF-α, IL-1β, MCP-1, and reducing the number of M1 macrophages [140].

Impacting inflammatory signaling pathways

Furthermore, SeNPs exert their anti-inflammatory process better by modulating various signaling pathways. SeNPs inhibit the activation of macrophages by suppressing the activation of the LPS-stimulated NF-κB signaling pathway, thereby alleviating the inflammatory response. For instance, chitosan-stabilized SeNPs (CS-SeNPs) are constructed and their anti-atherosclerotic activity is explored. CS-SeNPs were found to effectively elevate the protein levels of IκBα while reducing the phosphorylation levels of IκBα (P-IκBα) and p65 (P-p65), indicating that both the canonical and alternative pathways of the NF-κB signaling were inhibited, thereby alleviating vascular inflammation [141]. In another study, *Sapium sebiferum* polysaccharides decorated SeNPs are constructed for treatment of acute colitis. These particles effectively suppressed DSS-induced colitis and the levels of p-p65/p-IKBα in macrophages activated by inflammation, indicating the activation level of NF-κB. This suggests that ULP-SeNPs can regulate the inflammatory response by inhibiting NF-κB activation [142].

Additionally, SeNPs reduce oxidative stress primarily through the MAPK pathway. For instance, lactose- or maltodextrin-encapsulated SeNPs (LET-SeNPs) are constructed for the treatment of antiallergy. By suppressing ROS-induced activation of COX-2 and MAPKs, LET-SeNPs inhibit the release of histamine and inflammatory cytokines, showing a high therapeutic effect on allergic dermatitis [143]. Moreover, SeNPs remarkably increase the expression of the cellular protection and antioxidant pathway, such as Keap1/Nrf2/HO-1. In addition, after being loaded with Enteromorpha intestinalis extract, SeNPs exhibit anti-inflammatory activity by upregulating the Keap1/Nrf2/HO-pathway [63].

In addition, SeNPs can simultaneously affect TLR related signaling pathways, thereby synergistically regulating inflammation. SeNPs can alleviate oxidative stress through the Nrf2/Keap1/MKP1/JNK pathway and downregulate pro-inflammatory factors *via* the TLR4/MAPK pathway. For example, berberine polysaccharide loaded-selenium nanoparticles (BRP-SeNPs) enhance the activity of antioxidant enzymes such as SOD and GSH-Px, leading to reduced content of MDA, and decreased expression levels of pro-inflammatory factors such as NO, IL-1β, and TNF-α. Western blot analysis further indicated that BRP-SeNPs mitigate oxidative stress through the Nrf2/Keap1/MKP1/JNK pathway and downregulate pro-inflammatory factors via the TLR4/MAPK pathway, suggesting their potential for treating carbon tetrachloride-induced oxidative stress and inflammation [144].

Except for the above-mentioned signal pathways, there are several other signal pathways involved in the process of SeNPs regulating inflammation. SeNPs

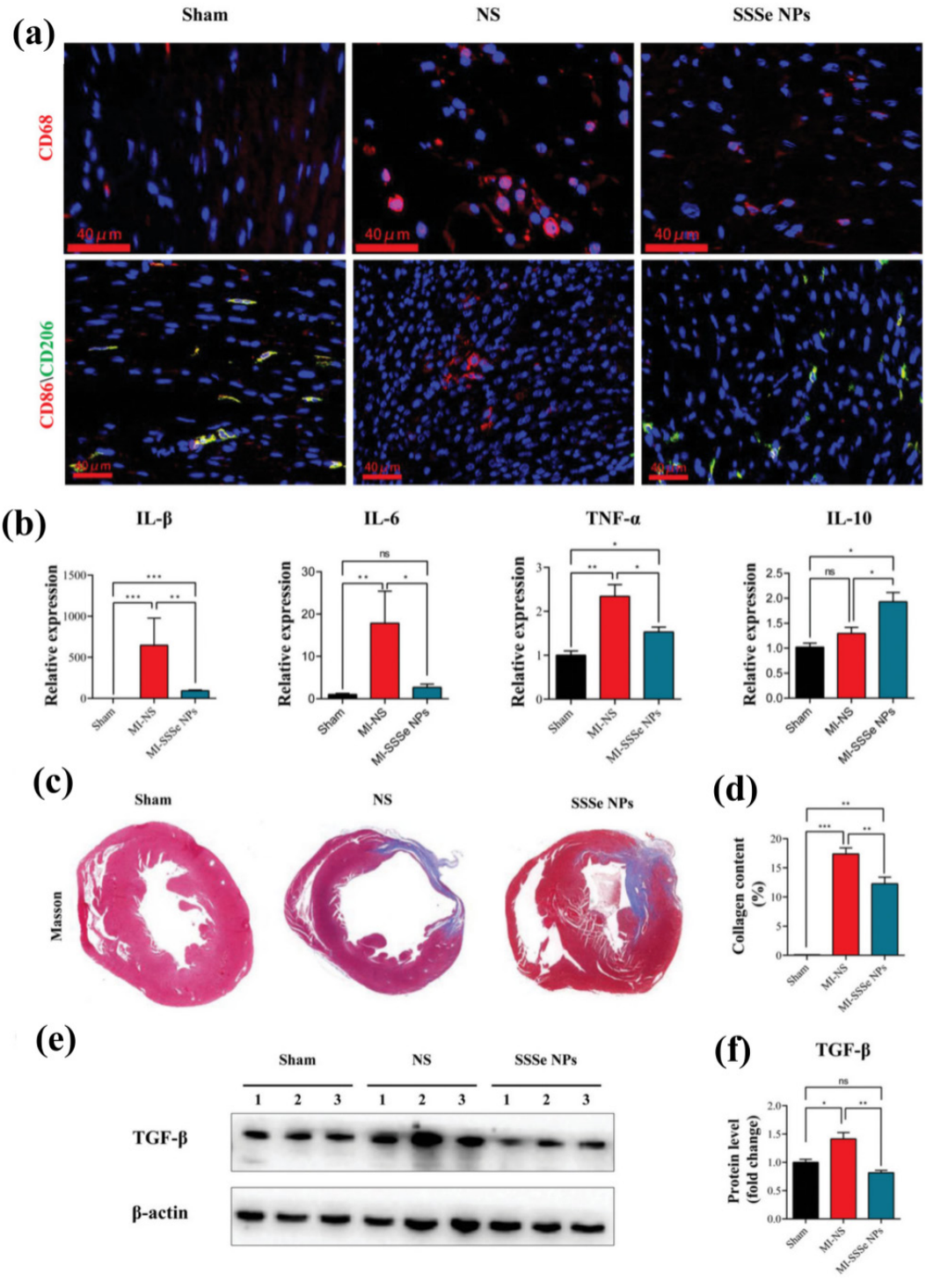


Fig. 19 SSSe NPs administration alleviates myocardial inflammation and fibrosis in MI mice. **(a)** Immunofluorescence staining of CD68 with the mannose receptor and in heart tissues. The nuclei were stained with DAPI. **(b)** RT-qPCR analysis of the mRNA levels of the pro-inflammatory cytokines IL-1β, IL-6, and TNF-α, as well as the anti-inflammatory cytokine IL-10. **(c)** Representative images of Masson trichrome staining of infarcted cardiac tissue showing fibrosis on day 14 after MI. **(d)** Quantification of the area of fibrosis in the heart in each treatment group. **(e–f)** Western blot showing the expression of TGF-β on day 3 after MI. The protein level is significantly decreased after treatment with SSSe NPs compared to saline. Reproduced with permission from Ref. [139] © 2022 The Authors.

also show the inhibition property on the activation of the p-44/42, p-SAPK/JNK, and p-p38 MAPK signaling pathways. A novel constructed SeNPs can effectively suppress the activation of the p-44/42, p-SAPK/JNK, and p-p38 MAPK signaling pathways and significantly reduce the levels of above signaling pathways related inflammatory cytokines such as IL-1β, IL-6, IL-17A, IL-22, and TGF-β [145].

Additionally, SeNPs can regulate inflammation by modulating the apoptosis signaling pathways related to oxidative stress responses and DNA damage. For instance, Lentinus edodes polysaccharides (LNT) modified SeNPs are synthesized to form SeNPs@LNT. Western blot results indicate that these particles could inhibit apoptosis induced by human adenovirus (HAdV) in cells by regulating the expression of apoptotic proteins Bcl-xL, Bcl-2, and Bad in the Bcl-2 signaling pathway, while also modulating DNA damage proteins p53, PARP, c-PARP, p-ATM, and p-ATR in the p53 signaling pathway, thereby comprehensively regulating the p53/Bcl-2 apoptotic signaling pathway. This regulation helps in treating lung inflammation caused by HAdV infection (Fig. 20) [146].

Conclusion and Future Perspectives

SeNPs play a significant role in modulating inflammatory diseases. Se, an essential trace element, has been recognized for its antioxidant properties and its ability to alleviate oxidative stress, which are key factors in inflammatory process. Compared with traditional Se forms, SeNPs offer unique advantages, including a big specific surface area and high biocompatibility, exhibiting lower toxicity and enhanced anti-inflammatory activity. The synthesis methods for SeNPs, including physical, chemical, and biological approaches, have been diverse and continually evolving, allowing for the production of SeNPs with tailored properties suited to specific biomedical applications. The anti-inflammatory effects of SeNPs are primarily mediated through their ability to modulate redox balance, affect signaling pathways such as NF-κB, and modulate the expression of selenoproteins, which are crucial in controlling inflammation. Studies have demonstrated that SeNPs can reduce the production of inflammatory cytokines like IL-6 and IL-1, and enzymes such as iNOS, thereby alleviating inflammatory responses. Furthermore, SeNPs hold promise for the treatment of inflammatory associated diseases, including myocardial infarction, nephrotoxicity, neuroinflammation, and colitis, among others (Scheme 1).

As research on SeNPs continues to deepen, innovative particle designs are gradually emerging. In

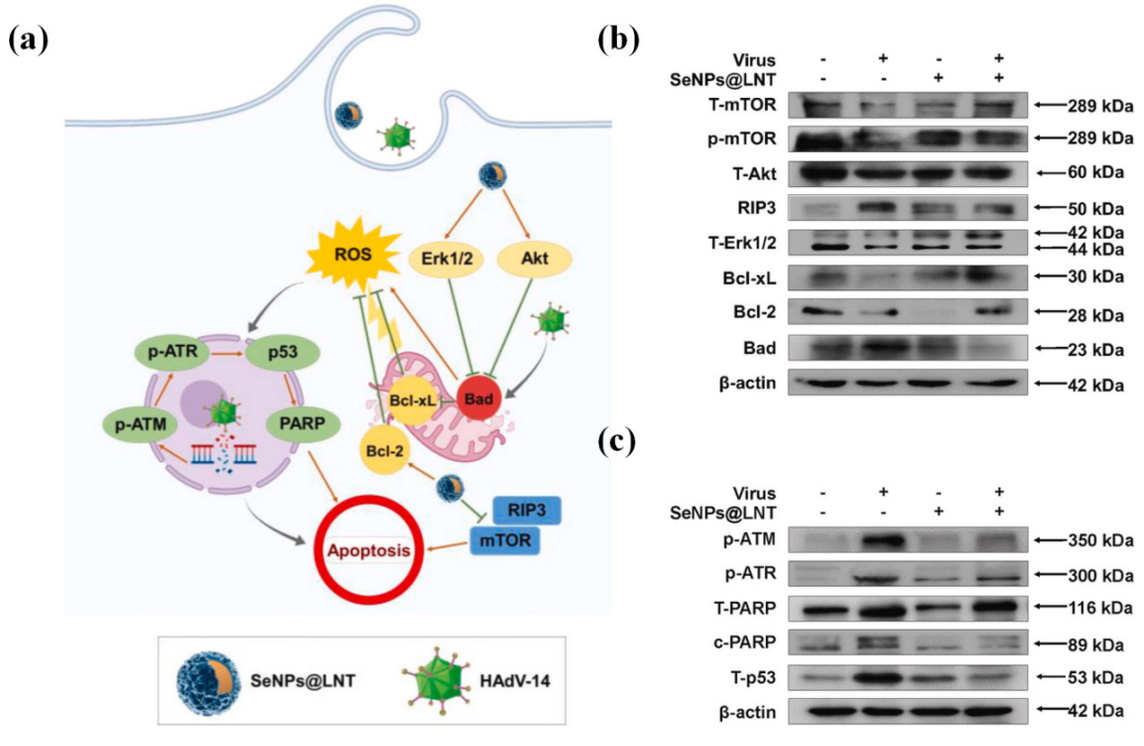
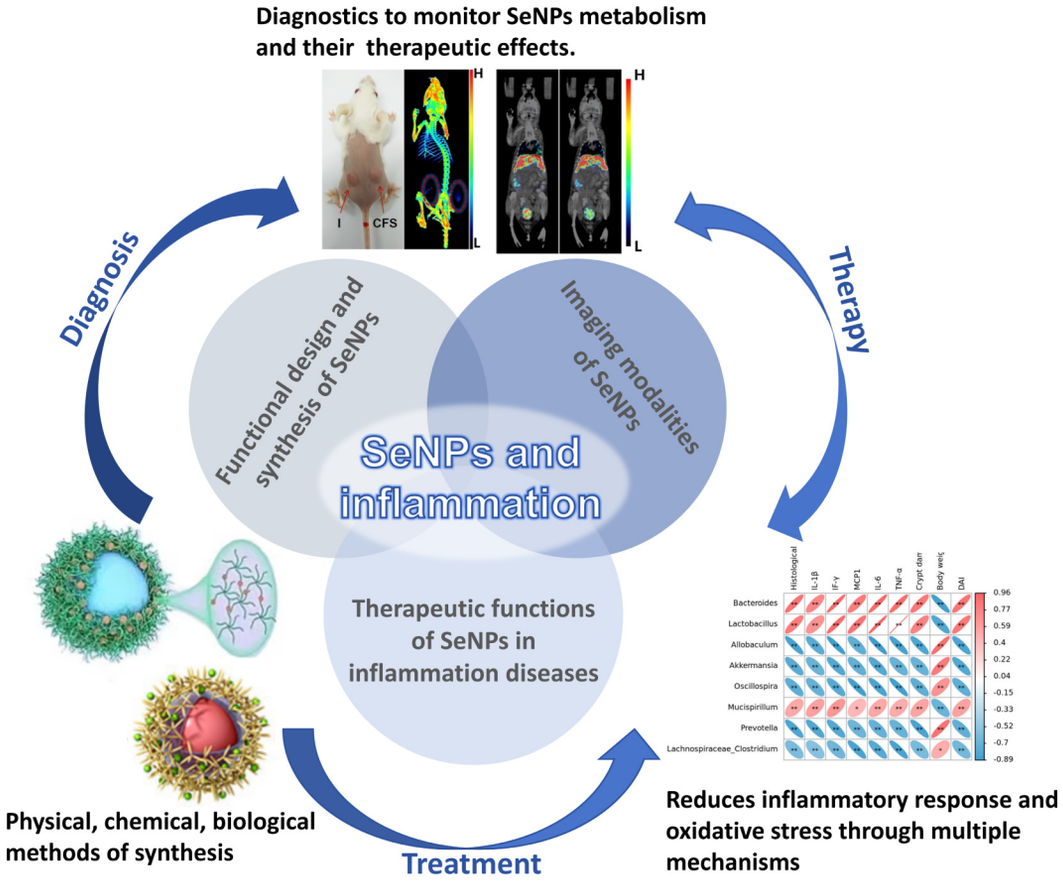


Fig. 20 Translational selenium nanoparticles boost GPx1 activation to reverse HAdV-14 virus-induced oxidative damage. **(a)** The sketch of apoptotic signaling pathways participated in the antiviral activities of HAdV-14 by SeNPs@LNT. **(b)** Regulation of apoptotic proteins in the Bcl-2 signaling pathways by SeNPs@LNT. **(c)** Regulation of DNA damage proteins in the p53 signaling pathways by SeNPs@LNT. The A549 cells were treated with 8 M SeNPs@LNT for 48 h. Reproduced with permission from Ref. [146] © 2024 The Authors.



Scheme 1 Synthesis and application of SeNPs for the modulation of inflammatory diseases.

recent years, diselenide bonds with Se-Se linkers have garnered widespread attention in the design and synthesis of nanomedicines due to their various advantages [147]. Compared to the bond energy of disulfide bonds (268 kJ/mol), diselenide bonds have lower energy (172 kJ/mol), which makes them more susceptible to external stimuli, allowing them to transform from hydrophobic diselenides to hydrophilic selenic acids [148]. Currently, diselenide crosslinkers have been successfully synthesized for NIR-responsive [149], X-ray sensitive [150], and visible light-responsive drug delivery systems [151]. Additionally, the cleavage of diselenide bonds possesses unique biological functions. The Se atoms in organic Se compounds have special electronegativity and atomic radii [152, 153]. Diselenide bonds can be easily oxidized into selenic acid or reduced into seleno alcohols in different redox conditions. Under physiological conditions, seleno alcohols consume ROS and then revert back to diselenide bonds through a dehydration process, thereby alleviating the accumulation of pathological ROS in inflammatory sites. Diselenide-Bridged Hyaluronic Acid Nano-antioxidant has been reported to reduce ROS levels by directly scavenging ROS and upregulating the Nrf2/HO-1 signaling pathway, demonstrating significant therapeutic effects in the treatment of colitis [154]. Another nano-platform based on diselenide bonds (RPZCu), with dual functions of ROS scavenging and neuroprotection, has shown a good therapeutic effect on the rat embolic middle cerebral artery occlusion (MCAO) model [155]. Therefore, Se-Se linkers have potential application value and innovative prospects in the field of nanotech-based anti-inflammatory therapy.

Despite the promising potential of SeNPs in modulating inflammation, several limitations need to be addressed. Firstly, different synthesis methods for SeNPs have various inherent drawbacks that require further optimization [156, 157]. Additionally, the single dosage form of SeNPs, such as oral or injectable administration, reduces adaptability for diverse demands of patients. For instance, acute inflammation necessitates rapid action, whereas chronic inflammation demands sustained effects, highlighting the need for diverse forms to meet specific therapeutic requirements. Secondly, the toxicity, degradation, and metabolic process of SeNPs

Table 2 Challenges in the clinical translation of SeNPs.

Category	Challenges	Ref.
Synthesis	The lack of standardization leads to variability in particle characteristics.	[156,163]
	Residual chemicals limit medical applications.	[60]
	Biosynthesis is difficult to scale up.	[101]
Stability	The storage process is highly reactive and easily oxidized.	[164]
	There are large differences in stability among different synthesis methods.	[96, 165]
Safety	The treatment window is narrow, and low doses may be ineffective, while high doses carry the risk of toxicity.	[101,161,162,166]
	Personalized drug delivery strategies are required.	[167]
Targeting	It is difficult to achieve precise delivery while minimizing damage to non-target tissues, which depends on effective cell uptake and tissue penetration.	[168,169]
Mechanisms	Limited understanding of specific diseases, insufficient research on nanotoxicology and selenoprotein pharmacokinetics.	[161]
Supervision	The complex field of supervision policies.	[170–171]

in vivo remain unclear. Excessive selenium intake can cause prostate cancer and type 2 diabetes [158–160], complicating the precise dosing of selenium-based drugs. Furthermore, the specific organs or tissues targeting effect of SeNPs must be achieved to minimize harm to non-target areas. Thirdly, the mechanisms by which SeNPs regulate inflammation are not yet fully understood [161]. The interactions between SeNPs and immune cells remain unclear, particularly in varying inflammatory microenvironment. The mechanisms of the activation, inhibition, or modulation of immune cells by SeNPs are poorly defined. Additionally, their impact on specific inflammatory related pathways is not comprehensively elucidated. Although SeNPs can regulate apoptotic signaling pathways by influencing proteins such as Bcl-2 and p53 in several disease, much remains unknown about how these processes integrate with the broader inflammatory response [146]. The above limitations present significant challenges for the clinical translation of SeNPs, including lack of standardization in production processes [69], differences in individual treatment for patients with different selenium contents [162], and difficulties in evaluating pharmacokinetic and pharmacodynamic evaluations [163]. These issues complicate efforts to achieve standardized industrial production of SeNPs. Table 2 provides an overview of the current challenges associated with the clinical application of SeNPs. Despite these issues, SeNPs as an emerging nanomedicine also present promising opportunities for development. Compared to other selenium-based drugs, SeNPs exhibit lower toxicity and higher degradability [156]. However, current regulatory policies and experimental rigor reveal gaps, particularly in long-term toxicology studies and direct comparisons with inorganic selenium formulations. For instance, Khurana highlighted the importance of conducting rigorous animal model studies to accelerate the clinical translation of promising SeNP formulations [161]. Designing comparative studies among inorganic selenium, organic selenium, and SeNPs, while thoroughly evaluating their efficacy and long-term effects, represents a pivotal opportunity to advance the research and clinical applications of SeNPs.

CRediT Author Statement

Xinwei Bai: conceptualization, investigation, project administration, supervision, visualization, writing original draft, writing–review, and editing. **Tianchang Zhou:** data curation, investigation, and writing original draft. **Xiao Wu:** data curation, investigation, and writing original draft. **Jin Chang:** funding acquisition, project administration, and supervision. **Xiaoli Wu:** conceptualization, funding acquisition, project administration, supervision, writing–review, and editing.

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Conflict of Interests

The authors declare that no competing interest exists.

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