Review

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The Application of Selenium Nanoparticles in Immunotherapy

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Abstract

Selenium (Se), is an essential trace element that primarily functions in the form of selenoproteins. These selenoproteins play crucial roles in the functioning of the human organism, including anti-inflammatory processes, regulating redox balance, participating in the metabolism of thyroid hormones, and maintaining the proper functioning of the immune system. The synthesis of selenoproteins is a complex process that relies on adequate selenium intake and involves multiple specific factors. A deficiency in selenium can lead to a variety of health issues, such as Keshan disease (cardiomyopathy) and Kashin–Beck disease (osteochondropathy), liver diseases, and cancer. Nanoscale selenium particles exhibit superior conversion and utilization compared to conventional inorganic and organic forms. Surface modifications of Se nanoparticles enable them to perform diverse physiological functions. Thus, the modification of selenium-containing nanomaterials, particularly their surface properties, is crucial for understanding Se's biological roles in antitumor activity, immunotherapy, and inflammatory responses. We summarize the preparation methods and chemical properties of various active selenium nanoparticles (SeNPs), discuss the rational design and biomedical applications of modified selenium nanomaterials in immunotherapy, and propose a network approach for their design and biological effects.

Keywords: Selenium; selenium nanoparticles; biomedical applications; immunotherapy

Introduction

Selenium (Se), a multivalent element from the oxygen group, exists in the environment as both inorganic and organic forms. As an essential trace element, selenium is closely linked to human health and disease progression [1]. Selenium levels are associated with various diseases, including cancer, liver disease, diabetes, neurological disorders, cardiovascular disease, and thyroid-related illnesses [2–4]. Numerous studies have demonstrated that selenium is a critical component of various enzymes in living organisms, with biological functions including cancer prevention, immune enhancement, anti-aging, antibacterial, and anti-inflammatory effects [5]. Selenium is a vital element in numerous biological processes. Selenium's biological functions in the body are closely tied to its various forms of transformation. Different selenium forms are absorbed and metabolized into HSe^-, which is then converted into selenoproteins [6–9]. Of the 25 identified selenoproteins, most regulate redox homeostasis (e.g., GPx and Trx families) [10–14]. Some selenoproteins regulate thyroid hormones (Dio

family) [15, 16], while others are involved in protein folding (e.g., SelN, SelM, SelS) [17–21]. Additionally, selenophosphate synthetase 2 (SPS2) regulates selenocysteine synthesis, and SelP is involved in selenium storage and transport, both crucial for maintaining selenium levels and the biological effects of selenoproteins [22–25]. Some selenoproteins' biological functions remain unclear, and their mechanisms of action require further investigation. Organic and inorganic selenium are widely recognized for their role in regulating cellular redox homeostasis by transforming into various selenoproteins to exert their biological effects.

With the development of nanotechnology, multifunctional composite selenium nanoparticles (SeNPs) have gained increasing attention [26–28]. The unique nanoscale, surface, and quantum effects of nanoparticles offer new possibilities for selenium to perform distinct biological roles in tumor therapy, immune modulation, and inflammatory responses. Compared to traditional inorganic and organic selenium, nano-selenium exhibits better biocompatibility and lower toxicity, making it widely studied in biomedicine. Zhang et al. studied the acute toxicity of red amorphous nano-selenium in mice and found that the LD50 of nano-selenium was 113.0 mg/kg, compared to 15.7 mg/kg for sodium selenite. Experiments on rats and mice demonstrated that the acute, subacute, short-term, and subchronic toxicity of high-dose nano-selenium (≥2 mg/kg body weight) was significantly lower than that of sodium selenite, selenite, selenomethionine, and methyl selenomethionine. Additionally, nano-selenium at supra-nutritional levels (0.2–0.4 mg/kg) showed no significant toxicity in the animals [29]. The modifiable surface properties of SeNPs also enable its functionalization for various disease models, particularly in tumor therapy and immunomodulation. The rapid advancement of nanotechnology in biomedicine has led to increased attention on the synthesis of SeNPs with higher bioavailability and its biomedical applications. The design, controlled synthesis, and functional modification of selenium nanomedicines are crucial in biomedical research. Current research on SeNPs primarily focuses on chemical modifications to explore their diverse biological effects across various fields. This paper reviews the synthesis and modification methods of selenium nanodrugs and their applications in biomedical fields, including cancer therapy, immunomodulation, and inflammatory response (Fig. 1).

Design and Synthesis of SeNPs

Synthesis of SeNPs

The synthesis of SeNPs is broadly categorized into chemical and biosynthesis methods, each with unique techniques and applications. Chemical synthesis of SeNPs involves converting inorganic or organic selenium into zero-valent SeNPs through redox reactions. Shen et al. developed spherical SeNPs using KBH_4 as a reducing agent in an ice bath, utilizing a straightforward one-step method (Fig. 2(a)) [30]. Sodium selenite and L-ascorbic acid are commonly used for reduction in aqueous solutions (Fig. 2(b)) [31]. Despite the effectiveness of this method, the resulting nanoparticles often exhibit instability, necessitating additional stabilizers. For instance, Nie et al. used glucose as both a reducing and modifying agent, facilitating the production of stable SeNPs from sodium selenite at high temperatures [32]. Xiong et al. employed cysteine as a reducing and stabilizing agent to produce chiral SeNPs via the spontaneous reduction of sodium selenite (Fig. 2(c)) [33]. Additionally, phycocyanin from *Spirulina* has been used for reduction, producing SeNPs with potential antioxidant properties [34]. Zheng et al. prepared polyethylene glycol (PEG) to create ultrasmall SeNPs by direct heating and dispersing gray selenium in liquid phase (Fig. 2(d)) [35]. Recent advancements in chemical synthesis focus on optimizing reducing agents and stabilizers to enhance nanoparticle dispersion and stability.

Biosynthesis of SeNPs involves biological processes using various organisms, including bacteria, fungi, viruses, plants, and animals [36]. This method converts inorganic selenium into organic forms and nanoparticles through enzymatic reactions [37]. In 2010, researchers utilized *Klebsiella pneumoniae* to produce elemental SeNPs from selenium chloride, with sizes ranging from 100 to 550 nm and an average of 245 nm [38]. Xu et al. used the aerobic bacterium *Comamonas testosteroni* S44 to produce red SeNPs, highlighting the role of amino acid-enriched proteins in nanoparticle formation and stability [39]. In 2023, Nie et al. synthesized protein corona-encapsulated SeNPs averaging less than

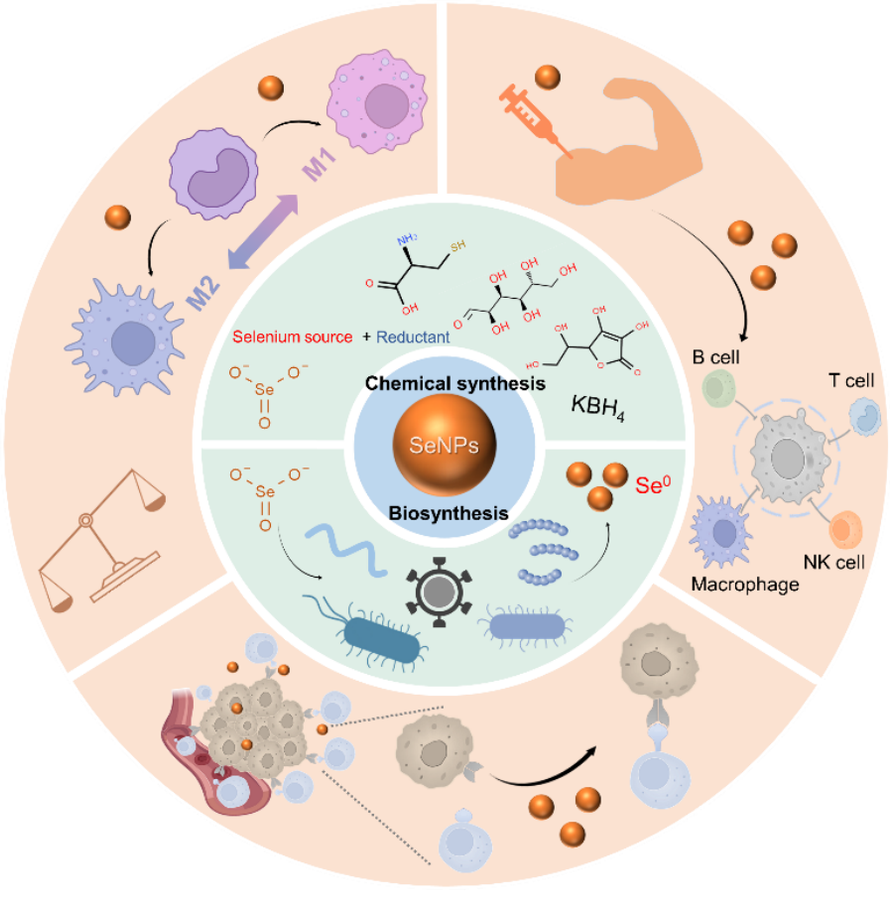

Fig. 1 Synthesis and immunological application of selenium nanoparticles.

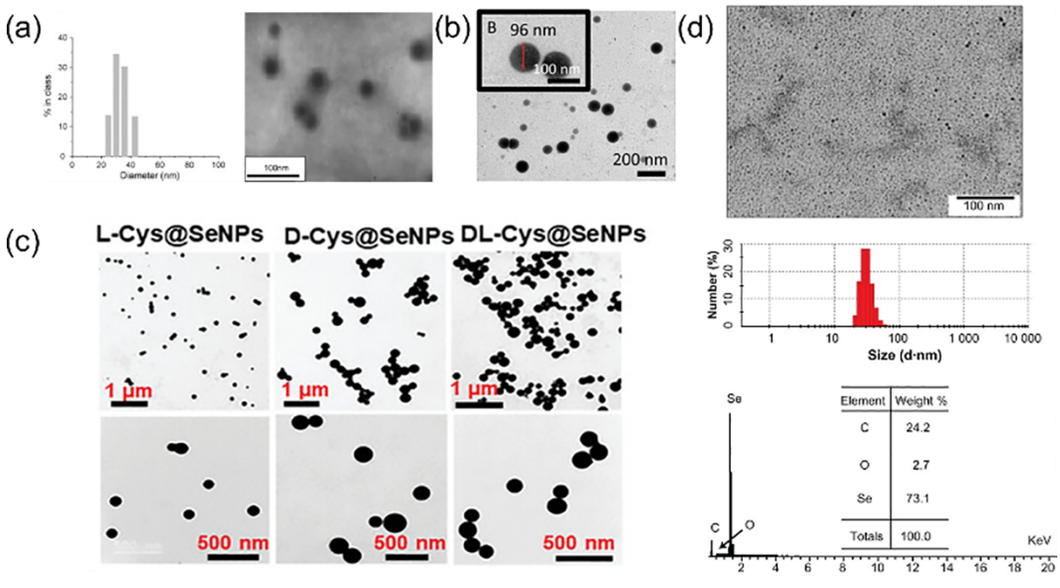

Fig. 2 SeNPs synthesized by different methods. **(a)** Particle size distribution and TEM images of KBH_4-reduced SeNPs. Reproduced with permission from Ref. [30] © 2008 Elsevier B.V. **(b)** TEM images of nano-selenium reduced by vitamin C. Reproduced with permission from Ref. [31] © 2024 Wiley-VCH GmbH. **(c)** TEM images of cysteine-reduced nano-selenium. Reproduced with permission from Ref. [33] © 2023 Wiley-VCH GmbH. **(d)** Nanometer selenium TEM image of heated gray selenium. Reproduced with permission from Ref. [35] © 2012 Zheng et al.

100 nm using *Streptococcus boulardii*, showing that yeast protease A contributed to the assembly of the protein corona [40]. Li et al. synthesized SeNPs with a stable size of 122 nm using the probiotic bacterium *Bifidobacterium animalis* subspecies *lactis* H15, stabilized by the chaperone protein GroEL [41].

Understanding the role of proteins and enzymes in selenium reduction across different organisms could enhance the controlled synthesis of SeNPs with desired sizes and morphologies.

Surface modification of SeNPs

The size of nanomaterials significantly influences their cellular uptake and *in vivo* distribution, impacting their retention and clearance in organisms. Nanoparticles smaller than 10 nm are typically cleared rapidly through the kidneys, while those larger than 200 nm may be cleared by phagocytic cells in the reticuloendothelial system (RES). Particles in the 50–200 nm range can remain in the body longer, with gradual clearance by the liver [42]. Targeted drug delivery, through controlled synthesis and functional modification, enhances the efficacy of SeNPs in biomedical applications.

Polysaccharides are commonly used for modifying SeNPs. Jiang et al. synthesized GLP-SeNPs by functionalizing SeNPs with gibberellic acid polysaccharides (GLPs), which enhanced cellular uptake in glioma cells by targeting integrin αvβ3, thereby activating apoptotic pathways and killing the cells (Fig. 3(a)) [43]. Yan et al. employed carboxy curdlan polysaccharides with different molecular properties and chain conformations (Cur-4, Cur-8, and Cur-24) to stabilize and cap SeNPs. Cur-8-modified SeNPs exhibited the smallest particle size (~ 56 nm) and the greatest stability [44]. Yang et al. constructed SeNPs (L-SeNPs) modified with lichenan from *Usnea longissima*, resulting in stable, monodispersed spherical structures with an average diameter of approximately 96 nm [45]. Zhu et al. used *Ulva lactuca* polysaccharide (ULP) to modify SeNPs, producing nanoparticles with an average diameter of ~ 130 nm, which showed significant protective effects against DSS-induced acute colitis in mice (Fig. 3(b)) [46]. Rao et al. synthesized TSIIA@SeNPs-APS by modifying SeNPs with astragalus polysaccharide (APS) and loading them with tanshinone IIA (TSIIA) for spinal cord injury treatment (Fig. 3(c)) [47].

Chitosan, an aminopolysaccharide, is another attractive carrier for SeNPs due to its biocompatibility, biodegradability, and bioactivity

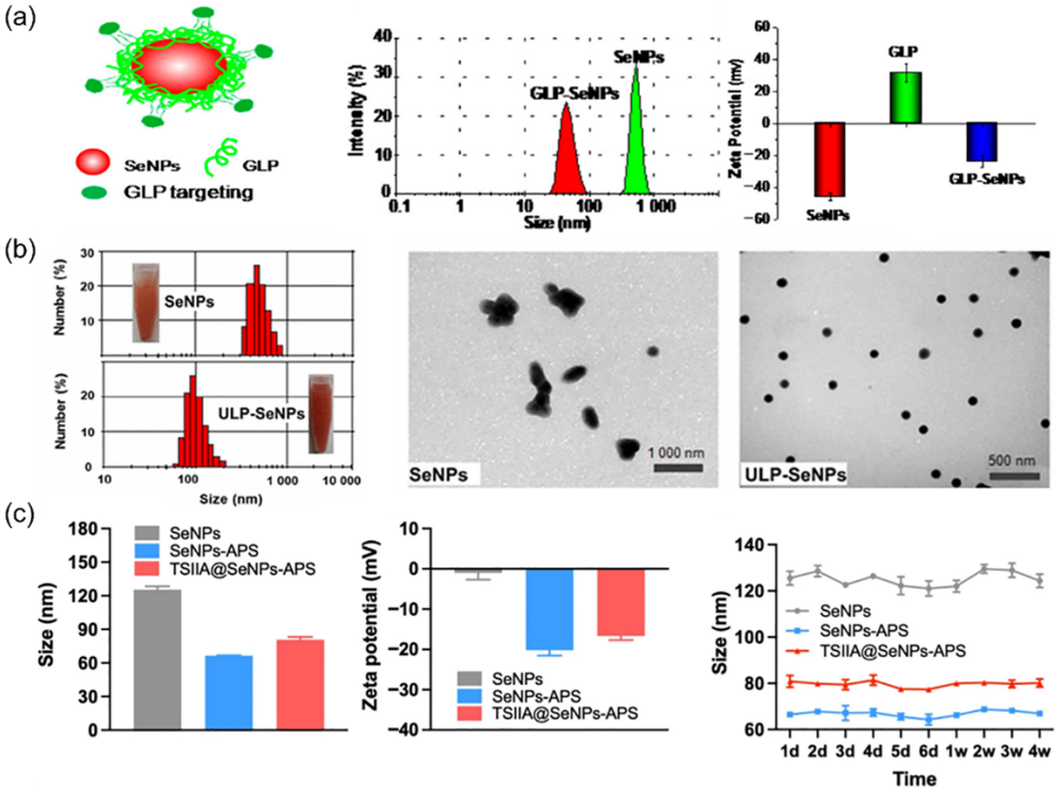

Fig. 3 SeNPs modified by different polysaccharides. **(a)** Schematic structure, size distribution and potential of SeNPs, GLP and GLP-SeNPs. Reproduced with permission from Ref. [43] © 2014 American Chemical Society. **(b)** Size distribution and TEM images of SeNPs and ULP-SeNPs. Reproduced with permission from Ref.[46] © 2017 Zhu et al. **(c)** The size distributions, surface charges, and particle size distributions of SeNPs, SeNPs-APS and TSIIA@SeNPs-APS in aqueous solutions vary with time. Reproduced with permission from Ref. [47] © 2022 Rao et al.

[48]. Lentinan SeNPs have been extensively studied for their antioxidant and anti-inflammatory properties. Liang et al. synthesized Lentinan-functionalized SeNPs (LNT-SeNPs), showing high antioxidant activity and potential for treating postoperative cognitive dysfunction (Fig. 4(a)) [49]. Li et al. found that Lentinan SeNPs exhibited low cytotoxicity and reduced mitochondrial damage and reactive oxygen species (ROS) production induced by human adenoviral infection (Fig. 4(b)) [50]. Liu et al. developed functionalized LNT-SeNPs to enhance NK cell-mediated tumor-killing activity via the TrxR1-IL-18RAP-pSTAT3 pathway [30]. Zou et al. reported that LNT-SeNPs effectively regulated the expression of selenoprotein GPx1, inhibiting osteoclastogenesis and preventing osteolysis [51].

In addition to polysaccharides, other macromolecules are used for modifying SeNPs. Polyethylene glycol (PEG), an amphiphilic molecule, is frequently employed. Liu et al. functionalized SeNPs with PEG [52]. Yu prepared X-ray-responsive SeNPs using PEG as both a surface decorator and template, achieving significant radiosensitizing effects [53]. The cationic polymer polyethyleneimine (PEI) has also been used; Jalalian et al. utilized PEG-conjugated PEI (PEI-PEG) to deliver epirubicin-functionalized SeNPs, enhancing antitumor effects [54]. Feng et al. synthesized SeNPs@AAs using amino acid-modified SeNPs, where NH^{4+} in amino acids stabilized the nanostructures and enhanced cellular uptake by MCF-7 breast cancer cells, leading to increased apoptosis [55]. Bovine serum albumin-stabilized SeNPs (BSA-SeNPs) showed preventive effects on neurological diseases, inhibiting ferroptosis-mediated neurotoxicity and ameliorating cerebral hemorrhage-like pathology [56]. Zhang et al. synthesized ATP-SeNPs by modifying SeNPs with adenosine triphosphate (ATP), enhancing their uptake and inducing apoptosis in HepG2 liver cancer cells [57].

Targeted modification of SeNPs

Targeted drug delivery aims to direct therapeutic agents to specific body regions, including organs, tissues, and cellular or subcellular levels, thereby minimizing the non-specific toxic effects associated with conventional methods [58, 59]. This approach reduces the required therapeutic dose by enhancing nanoparticle aggregation in the target region, often achieved through surface modification with specific receptors [60].

Huang et al. developed a DOX-loaded selenium nanoparticle (SeNP) system using ferritin Tf from *Salvia divinorum* as a targeting ligand. Tf significantly enhanced the cellular uptake of DOX-loaded SeNPs in cancer cells by overexpressing the ferritin receptor. This process occurs via lattice protein-mediated and follicle/lipid raft-mediated endocytosis, improving selectivity between cancerous and normal cells [61].

In another study, Luo et al. designed hyaluronic acid selenium (HA-Se) nanoparticles targeting the CD44 receptor to scavenge ROS and inhibit inflammatory responses in damaged spinal cord tissue [62].

Additionally, Huang synthesized highly homogeneous and stable SeNPs with targeting capabilities towards the epidermal growth factor receptor (EGFR). These nanoparticles were

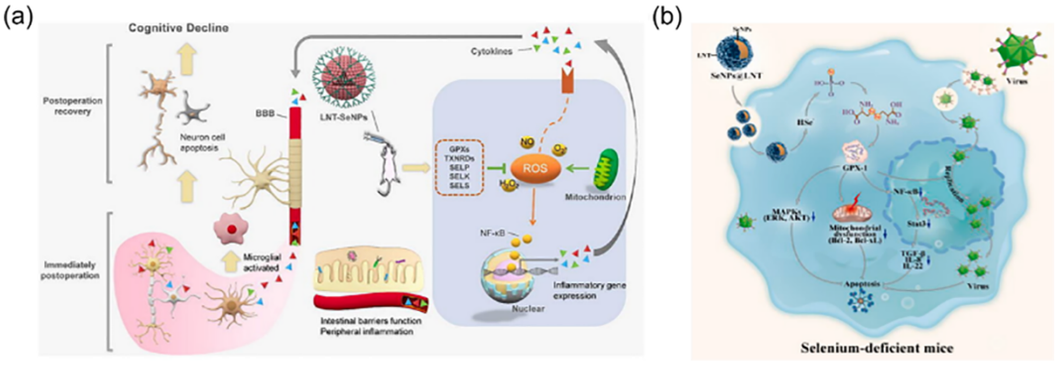

Fig. 4 SeNPs@LNT performs a variety of functions. **(a)** Schematic diagram of SeNPs improve surgery-induced cognitive impairmen. Reproduced with permission from Ref. [49] © 2022 Elsevier B.V. **(b)** Schematic diagram of SeNPs@LNT designed for the treatment of adenovirus pneumonia caused by HAdV-14 infection. Reproduced with permission from Ref. [50] © 2024 Li et al.

responsive to the tumor microenvironment, enhancing their therapeutic efficacy [63].

Folate (FA) has been widely investigated as a ligand for nanoparticle functionalization in cancer therapy due to its frequent overexpression in various cancer types. Liu et al. designed FA-conjugated SeNPs to counteract multidrug resistance in cancer cells, demonstrating the potential of targeted SeNPs in overcoming therapeutic challenges [64].

Selenium and Immune Response

The human immune system relies on various components, including the production of ROS by macrophages and neutrophils, adhesion molecules, and receptors for soluble mediators like arachidonic acid derivatives and cytokines [65]. Selenoproteins play a crucial role in regulating these cellular activities, particularly in managing oxidative stress [66, 67].

ROS are believed to be key mediators of intercellular signaling and communication among various immune cells. The regulation of cellular redox levels involving ROS is closely associated with selenium. Although the precise morphological and biological pathways through which SeNPs are absorbed and function in the body remain unclear, studies in fields such as oncology and inflammation suggest that SeNPs may exert their effects by being converted into selenoproteins [68]. These selenoproteins then play pivotal roles in modulating immune responses, highlighting the potential of selenium in therapeutic applications.

Nano-selenium and immunotherapy

Immunotherapy, which involves modulating the patient's immune system to alleviate or cure diseases, can be categorized into two strategies: activating the immune system to kill abnormal cells or suppressing immune inhibition to enhance the immune system's capacity to eliminate disease [69]. In the context of tumors, which often exhibit low immunogenicity and have mechanisms that help them evade immune surveillance, immunotherapy focuses on increasing the immune system's sensitivity to tumor antigens and blocking immune escape signals to enhance tumor elimination.

Immune cell therapy has emerged as a powerful approach in treating malignant tumors. Liu et al. demonstrated that SeNPs significantly enhanced the cytotoxicity of cytokine-induced killer (CIK) cells from cancer patients against tumor cells by upregulating the expression of the activation receptor NKG2D and its ligands. This strategy also effectively induced the infiltration of natural killer (NK) cells into tumors and polarized tumor-associated macrophages toward the M1 phenotype, triggering a robust immune response [70].

Du et al. found that combining functionalized SeNPs with metformin enhanced the immunotherapeutic effect of NK92 cells against osteosarcoma. This enhancement was attributed to the increased production of ROS in HepG2 cells and the upregulation of cell surface receptor proteins ULBP-3/4, PD-L1, MICA, B, as well as NK92 cell surface receptors PD-1 and FasL [71].

In another study, Liu et al. investigated the effects and mechanisms of functionalized Lentinan SeNPs (LNT-SeNPs) on NK cells in malignant pleural effusions (MPEs). LET-SeNPs enhanced immunotherapy by activating the TrxR1-IL18RAP-pSTAT3 pathway, promoting NK cell activation, which effectively eradicated lung cancer cells and reduced pleural effusion (Fig. 5(a)) [30].

Gao et al. reported a selenium-containing nanoparticle (PSeR/DOX) that exhibited sensitized responses to radiation, showing potential anticancer effects and immune checkpoint inhibitor activity during radiotherapy. In cancer cells treated with these nanoparticles, HLA-E expression was decreased, and co-incubation with NK cells revealed that the downregulation of HLA-E enhanced NK cell activity, primarily by blocking the HLA-E/NKG2A interaction (Fig. 5(b)) [72, 73].

Zhang et al. found that combining an anti-4-1BB antibody with SeNPs attenuated the immunosuppressive effects of regulatory T cells and promoted the proliferation and metastasis of immune cells, synergistically killing tumor cells. This combination also reduced inflammatory damage to normal tissues and mitigated overstimulation of the immune response in the spleen [74].

Overall, current research on SeNPs in immunotherapy focuses primarily on NK cells and the M1/M2 macrophage correlation, while other aspects of its potential in immunotherapy require

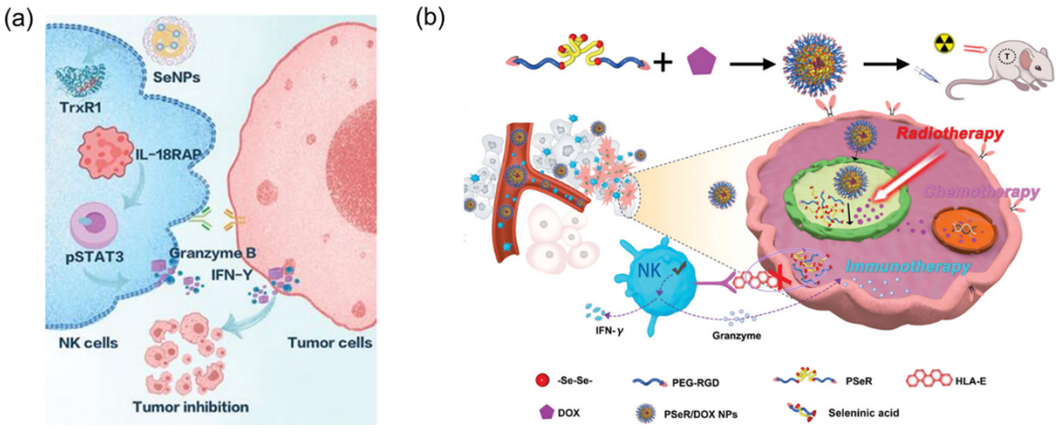

Fig. 5 Nano-selenium enhanced NK cell immunotherapy. **(a)** SeNPs enhance NK cell-mediated tumoricidal activity in malignant pleural effusion via the TrxR1-IL-18RAP-pSTAT3 pathway. Reproduced with permission from Ref. [31] © 2024 Wiley-VCH Verlag. **(b)** Schematic illustration of utilizing selenium-containing nanoparticles to implement combined treatment of chemotherapy, radiotherapy, and immunotherapy. Reproduced with permission from Ref. [72] © 2020 Wiley-VCH Verlag.

further exploration.

Nano-selenium and immune adjuvants

Immune adjuvants enhance the efficacy of cancer vaccines by stimulating the immune system's response to the vaccine to enhance the adaptive immune response [75]. Although there is no universally accepted classification of immune adjuvants so far, their functions can be generally attributed to the following: prolonging the half-life of antigen in the body; stimulating macrophage phagocytosis; promoting lymphocyte contact and lymphocyte proliferation [76, 77]. Most vaccine adjuvants currently in use or development are nanoparticles [78]. Compared to conventional materials, nanomaterials can provide adjuvant activity by enhancing antigen delivery to the immune system or by enhancing innate and/or adaptive immune responses [79]. Common nanomaterials that have been used as vaccine adjuvants can be broadly classified into two types: metal-based nanoadjuvants and polymeric nanoparticles. Among them, the metal-based nanoadjuvants are mainly aluminum-based adjuvants [80, 81], gold nanoparticles [82] and silver nanoparticles [83]. Polymer is a kind of material with easy synthesis, excellent biocompatibility and biodegradability. Polymer adjuvants such as chitosan and polyethylenimine have been widely studied [84, 85].

However, their clinical use is often limited due to short response durations and various side effects. The development of safe and effective vaccine vectors is a key scientific issue to be solved urgently in the field of vaccines. SeNPs, with its excellent antioxidant properties, plays a crucial role in regulating immune cell activity, particularly T-cells, to promote antibody responses, making it a potential candidate as an immune adjuvant. In view of the key role of selenium in the human body and its good safety, researchers have developed SeNPs as vaccine adjuvants with anti-tumor activity, carrier and immune activation functions through the precise design and regulation of selenium nanomaterial [85, 86].

Luo et al. designed two kinds of SeNPs (Selenum-HEP loaded PLGA nanoparticles and selenium modified HEP-PLGA nanoparticles) and evaluated their immunoactivities. It was shown that both SeNPs significantly stimulated macrophage phagocytic activity, CD40 and CD86 expression, and stimulated increased levels of NO, TNF-α, IL-1β, and IL-6 in peritoneal macrophages. This suggests that SeNPs can enhance macrophage activation and may be used as a delivery system to induce robust immune responses [87].

Deng et al. successfully synthesized selenium nano-adjuvants in situ for inactivated viruses, including porcine epidemic diarrhea virus (PEDV), pseudorabies virus (PRV), and porcine reproductive and respiratory syndrome virus (PRRSV). This was achieved by leveraging selenium's role in immune cell function and its biomineralization properties. This facile method for synthesizing selenium nano-adjuvants could be generalized for other inactivated virus vaccines. The nanovaccine efficiently enhanced dendritic cell (DC) uptake of PEDV, PRV, and PRRSV, activated DCs by triggering the TLR4 signaling pathway, and modulated selenoprotein expression. Additionally, it more effectively triggered

macrophage and natural killer cell-mediated innate immunity and T cell-mediated cellular immunity [88].

In another study, bioSeNPs exhibited an enhanced adjuvant effect by improving immune response and survival in a breast cancer mouse model using 4T1 cell antigens as a vaccine. SeNPs activated macrophages into a pro-inflammatory state, thereby enhancing innate immunity. Yazdi et al. intravenously administered SeNPs to 4T1-loaded BALB/c mice, and after twenty days, a significant increase in serum IFN-γ, IL-2, and IL-12 levels was detected, along with a reduction in TGF-β levels, resulting in a stronger delayed-type hypersensitivity reaction. Consequently, SeNPs reduced tumor volume and increased survival rates in treated mice [89].

Lai et al. explored the use of SeNPs in regulating the redox state in DCs after pathogen stimulation, leading to the development of RBD antigen-loaded nanovaccines (RBD@SeNPs) using SeNPs as adjuvants through electrostatic interactions. Selenium nano-adjuvants demonstrated immune-enhancing and redox-shaping activities, regulating the expression of GPX selenoproteins in immune cells, thereby improving their function and responsiveness to vaccination. Beyond activating innate immune cells, Se nano-adjuvant-based vaccines induced Th1-biased immunity and produced high-quality, antigen-specific neutralizing antibodies with high titers and efficacy against pseudoviral infections [90].

Nano-selenium and the inflammatory response

Inflammation is a crucial early event in the pathogenesis of many diseases [91–95], and SeNPs have been shown to play a significant role in anti-inflammatory processes through the activity of selenoproteins.

Deng encapsulated hyaluronic acid-modified SeNPs within calcium alginate (SA) hydrogel protective shells, which facilitated the in situ synthesis of selenoproteins. Specifically, SeNPs up-regulate the expression of selenoproteins GPx1/2/4 and SeLK at the RNA and protein levels, and down-regulate the expression of pro-inflammatory factors such as IL-6 and IL-1β. In the DSS-induced mouse colitis model, SeNPs reduced the proinflammatory index of IL-6 and IL-1β in the colon, significantly reduced the number of pro-inflammatory monocytes and neutrophils, increased the number of immune regulatory T cells, and maintained intestinal immune homeostasis. This sequence of events is attributed to the majority conversion of Se nanoparticles into SeCys2 in mouse tissues, which is one of the keys to the conversion of Se into selenoproteins [96].

Xie et al. found that LET-SeNPs effectively activated the Nrf2-Keap1 signaling pathway, enhanced the expression of antioxidant selenoproteins at both mRNA and protein levels, and inhibited mast cell activation, resulting in pronounced antiallergic effects (Fig. 6). In the Macaca fascicularis model, Se nanoparticles were also verified to achieve anti-allergic dermatitis by reducing the content of IL-6 and TNF-α [97].

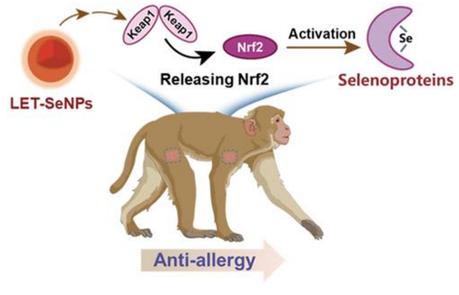

Fig. 6 Nano-selenium is associated with inflammation. Reproduced with permission from Ref. [97] © 2023 American Chemical Society.

Zhu et al. explored the effects of SeNPs modified with *Ulva lactuca* polysaccharides (ULP) in a murine acute colitis model, demonstrating that ULP-SeNPs inhibited macrophage activation by suppressing the nuclear translocation of NF-κB [46].

The pathogenesis of postoperative cognitive dysfunction is based on neuroinflammation caused by oxidative stress induced by surgery. Liang et al. used SeNPs to alleviate oxidative stress and inflammation, reduce neuronal cell death and improve surgery-induced cognitive impairment in mice. This work also examined the uptake, metabolism and transformation SeNPs in mice. Selenium is mainly taken up by the liver, lung and spleen, and most of it is converted to SeCys2 in the digestive tract [49].

Yang et al. used mannose-rich oligosaccharids-functionalized SeNPs to alleviate DSS-induced colitis in mice by promoting macrophages to reprogram M2 polarization [98]. It provides new strategy for successful treatment of inflammatory bowel disease (IBD) and other intestinal diseases.

Conclusion and Future Perspectives

Nanosized selenium has shown significant potential in various biomedical applications, particularly in immunomodulation and inflammatory response.

This review covers the synthesis and modification methods of SeNPs, highlighting its role as an immune adjuvant that stimulates and enhances immune cell activity, especially in anti-tumor therapies. Many scientists have synthesized a series of functionalized SeNPs through different selenium sources, different reducing agents and surface modifiers, which can specifically regulate different sites and different disease models. These studies will provide the direction for the subsequent researchers to study the transformation process and action targets of SeNPs.

SeNPs can also work synergistically with other immune cells, achieving a multifaceted therapeutic effect. Although the benefits of selenium supplementation in pathogen defense, cancer prevention, and immunity enhancement are well-documented, the regulation of individual selenoproteins and their precise mechanisms in immune enhancement and inflammation reduction remain to be fully understood. A deeper exploration of selenoproteins' roles and their molecular mechanisms in regulating immune cell function is essential.

Additionally, although the immune modulatory effects of SeNPs have been demonstrated in mice and the Macaca fascicularis model, their scalability for clinical application needs to be further confirmed. Perhaps the biggest challenge at present is finding out how SeNPs specifically modulate different cells to achieve various effects *in vivo*, and how this process can be safely and controllably done. Future research should prioritize developing more accessible analytical assays to track and study the intracellular pathways of SeNPs, expanding its application in anti-tumor therapies, immune system synergy, and other biomedical fields.

CRediT Author Statement

Yu Yang: conceptualization, writing-original draft, writing-review & editing, visualization. **Ying Liu,Qingxia Yang:** formal analysis, supervision, and validation. **Ting Liu:** conceptualization, methodology, supervision, review structure conception.

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Conflict of Interests

The authors report no conflicts of interest in this work.

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