Review

Nano Biomed Eng

Versatile Copper-Chalcogenide-Based Nanoparticles for the Treatment of Brain Diseases

Shuyang Xie[§], Hualong Liu[§], Ke Yang[§], Tingting Wang, Hao Zhang, Zhen Li

Center for Molecular Imaging and Nuclear Medicine, State Key Laboratory of Radiation Medicine and Protection, School of Radiation Medicine and Protection, Suzhou Medical College, Soochow University, Collaborative Innovation Center of Radiation Medicine of Jiangsu Higher Education Institutions, Suzhou 215123, China

[§] These authors contributed equally to this work.

Corresponding authors. E-mails: Hao Zhang, zhanghaoqf@suda.edu.cn; Zhen Li, zhenli@suda.edu.cn

Received: Dec. 20, 2024; **Revised:** Feb. 2, 2025; **Accepted:** Feb. 10, 2025

Citation: S.Y. Xie, H.L. Liu, K. Yang, et al. Versatile copper-chalcogenide-based nanoparticles for the treatment of brain diseases. *Nano Biomedicine and Engineering*, 2025, 17(1): 91−110.

http://doi.org/10.26599/NBE.2025.9290117

Abstract

Copper chalcogenide nanoparticles, particularly $Cu_{2-x}E$ (E = S, Se, Te; $0 \leq x \leq 1$), have gained significant interest in recent years due to their distinct physical and chemical properties, making them highly versatile for a wide range of applications. Among these, copper selenide nanoparticles (CS NPs) have attracted special attention due to their remarkable characteristics, which can be tailored through various modification strategies, providing significant potential for the diagnosis and treatment of neurological diseases. This review summarizes emerging trends and explores future perspectives on the use of CS NPs for diagnosing and treating central nervous system diseases, including glioblastoma and neurodegenerative disorders.

Keywords: copper chalcogenides; biomimetic nanomaterials; glioblastoma; neurodegenerative diseases; customized treatment

Introduction

With advancements in nanotechnology, copper chalcogenide nanomaterials have found extensive applications in the biomedical field [1]. Copper chalcogenide nanoparticles, including copper oxides, sulfides, selenides, and tellurides, offer distinct advantages due to their unique physical and chemical properties. For instance, CuO nanoparticles are utilized in tumor photothermal therapy (PTT) and chemodynamic therapy (CDT), as well as in addressing bacterial resistance for treating various infectious diseases. Lu et al. developed an ES@CuO nanosystem to induce cuproptosis, suppress B16 melanoma cell growth, and enhance immune responses. This nanosystem also remodeled the tumor microenvironment and improved therapeutic efficacy against murine melanoma when combined with PD-1 [2]. CuS nanoparticles have applications in biomolecule, chemical, and pathogen detection, molecular imaging, and tumor therapy [3]. Likewise, $Cu_{2-x}Te$ nanosheets modified with polyethylene glycol (bio$Cu_{2-x}Te$ NSs) function as multifunctional CDT agents for effective cancer treatment via mild-photothermally enhanced CDT [4]. These examples highlight the significant potential of copper chalcogenide nanoparticles in the biomedical field.

Another copper chalcogenide, copper-deficient cuprous selenide ($Cu_{2-x}Se$), has been extensively studied due to its tunable properties and versatile bioapplications, similar to other copper chalcogenide nanomaterials. Additionally, both copper and selenium are essential trace elements for the human body, playing crucial roles in maintaining overall health [5]. Copper selenide nanoparticles ($Cu_{2-x}Se$ NPs, CS NPs) exhibit strong localized surface plasmon resonance (LSPR) in the second near-infrared (NIR-II) window [6], granting them potential applications in photoacoustic (PA) imaging [7], PTT [8], photodynamic therapy (PDT) [9], and more. CS NPs efficiently convert absorbed light into heat, causing thermal damage to tumor cells or diseased tissues to achieve treatment through thermal effects [10]. They can also generate reactive oxygen species (ROS) via electron transfer and energy transfer mechanisms under NIR-II light irradiation, making them effective for PDT [11, 12]. Without light irradiation, they catalyze the degradation of hydrogen peroxide (H_2O_2) through their Fenton-like properties, producing ROS to induce intracellular oxidative stress and exert cytotoxic effects on tumor cells for CDT [13, 14]. More importantly, their properties are strongly influenced by copper deficiency (i.e., vacancy), which not only enhances their characteristics but also provides space for incorporating other elements to further improve their functionality [15]. These features can be further expanded and explored for disease diagnosis and treatment. Therefore, the unique properties of CS NPs make them highly promising for biomedical applications.

CS NPs can be synthesized through simple and controllable methods, with their size, vacancies, and properties precisely regulated by adjusting synthesis conditions [16, 17]. Additionally, specific surface functional groups can be introduced for further functionalization. Compared to other inorganic nanoparticles, CS NPs can be prepared at extremely small sizes without compromising their intrinsic properties due to their size-independent characteristics [18]. This allows them to be synthesized as small as possible to efficiently cross the blood–brain barrier (BBB) with the assistance of focused ultrasound, a major challenge in treating central nervous system (CNS) diseases such as glioblastoma (GBM) and Parkinson's disease (PD) [19–22]. Under normal circumstances, many therapeutic drugs struggle to reach the lesion site, significantly limiting treatment effectiveness [23]. Moreover, ultrasmall CS NPs exhibit prolonged blood circulation time, facilitating their diffusion into the brain with ultrasound assistance. Furthermore, the ability of CS NPs to cross the BBB can be enhanced through conjugation with targeting peptides and functional cell membranes [24, 25]. These unique properties provide CS NPs with significant advantages and potential for diagnosing and treating CNS diseases.

As a typical CNS disease, GBM can benefit from the enhanced immunotherapeutic efficacy of CS NPs through multiple mechanisms [26, 27]. The ROS generated by CS NPs can induce tumor immunogenic cell death (ICD), thereby activating the antitumor immune response [28]. Additionally, CS NPs help alleviate the immunosuppressive tumor microenvironment by reducing the infiltration of immunosuppressive cells, relieving T cell dysfunction, and ultimately enhancing the overall efficacy of GBM immunotherapy [29, 30].

Beyond GBM immunotherapy, CS NPs also play a crucial role in treating PD. The primary pathological characteristics of PD include the abnormal aggregation of misfolded alpha-synuclein (α-syn) and the degeneration and death of dopaminergic (DA) neurons in the substantia nigra. Additionally, oxidative stress is a key factor in PD pathogenesis [31, 32]. Polyphenol-functionalized CS NPs exhibit antioxidative properties and can effectively scavenge excess intracellular ROS, reducing oxidative stress-induced neuronal damage when combined with reductive drugs [33]. Moreover, CS NPs can inhibit α-syn aggregation through multiple mechanisms, thereby alleviating disease symptoms [34]. Collectively, these mechanisms enable CS NPs to indirectly slow the progressive loss of neurons. Furthermore, CS NPs can directly contribute to neuronal restoration by promoting mitochondrial biogenesis and enhancing the differentiation of neural stem cells (NSCs) into DA neurons, thereby replenishing lost DA neurons [35, 36].

In summary, CS NPs have emerged as a promising biomaterial due to their unique advantages, diverse physical and chemical properties, and significant potential in treating CNS diseases. This review highlights recent advances in CS NPs and their applications in CNS disorders (Fig. 1). We first

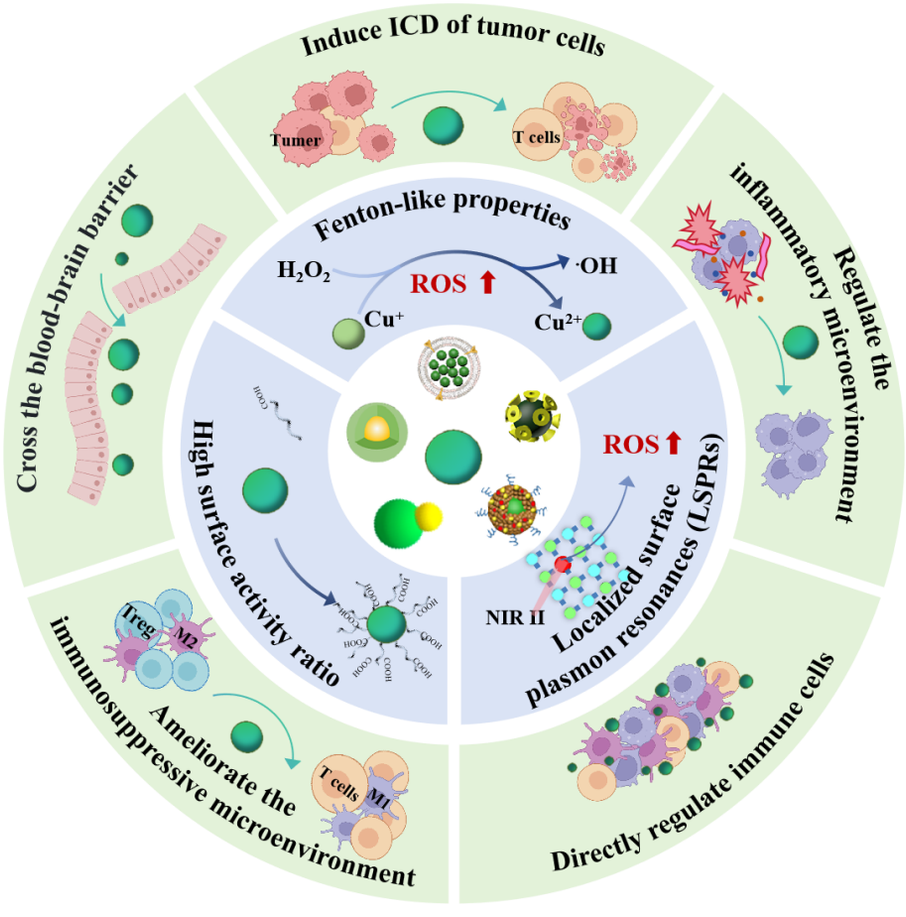

Fig. 1 Properties and applications of $Cu_{2-x}Se$ NPs.

introduce their synthesis methods and intrinsic properties, followed by an overview of how CS NPs enhance the immune response in GBM treatment. Next, we discuss their role in PD therapy. Finally, by analyzing their applications in GBM immunotherapy and neurodegenerative disease treatment, we provide an in-depth discussion on future research directions and clinical applications. These insights are expected to drive innovative breakthroughs in overcoming CNS diseases and advancing personalized treatment strategies.

Syntheses and Properties of the CS NPs

Synthesis of CS NPs

A variety of methods have been developed for synthesizing nanoscale copper chalcogenides, with the dimensions, morphology, and characteristics of the resulting nanostructures being intricately linked to the chosen synthesis approach. Among the different techniques, the most widely employed methods include solvothermal/hydrothermal synthesis, colloidal synthesis, microwave-assisted synthesis, template-directed synthesis, and cation exchange synthesis [18]. In our previous studies, we developed several universal synthesis methods. For example, we used Se powder as a precursor to synthesize CS NPs under ambient conditions. Se powder was reduced by $NaBH_4$ in an aqueous solution under magnetic stirring and nitrogen protection. A mixture of $CuCl_2{\cdot}2H_2O$ and mercaptosuccinic acid (MSA) was fully dissolved in distilled water and then immediately added to the selenium precursor solution, forming a dark green solution, which indicated the formation of copper-deficient $Cu_{2-x}Se$ ($0 \leq x \leq 1$) nanoparticles (denoted as MSA $Cu_{2-x}Se$ NPs) (Fig. 2(a)) [37]. In another method, Se NPs were synthesized via the reduction of SeO_2 by vitamin C. These Se nanoparticles served as sacrificial templates and reacted with Cu ions to produce copper selenide nanoparticles, which were gradually oxidized in the presence of air to form CS NPs (Fig. 2(b)) [38]. Additional synthetic methods have been comprehensively summarized elsewhere [18, 39–44].

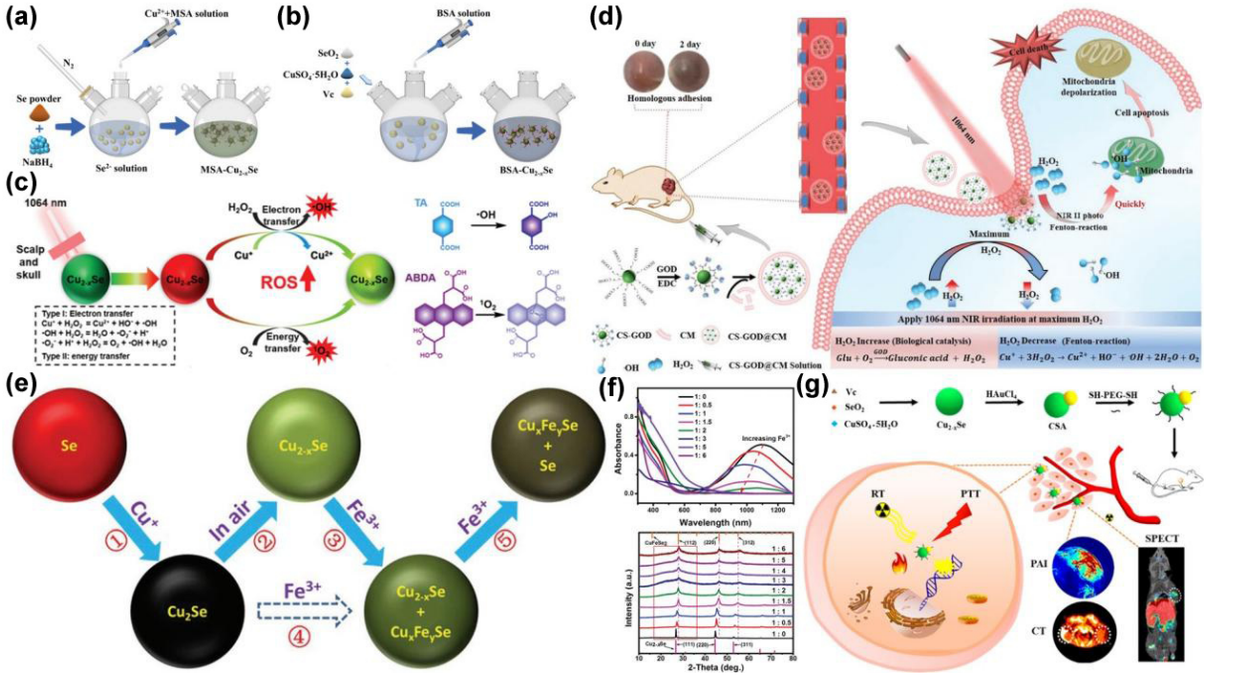

Fig. 2 (a) Schematic illustration of the synthesis of the MSA-stabilized $Cu_{2-x}Se$ nanoparticles. Reproduced from Ref. [37] © 2016 WILEY-VCH Verlag. **(b)** Schematic illustration of the BSA-stabilized $Cu_{2-x}Se$ nanoparticles. Reproduced with permission from Ref. [38] © 2019 American Chemical Society. **(c)** Schematic illustration of the generation of ROS through the electron transfer (·OH radicals) and energy transfer ($^1O_2$ radicals) mechanisms under the NIR-II laser irradiation. Reproduced with permission from Ref. [12] © 2019 Royal Society of Chemistry. **(d)** Schematic illustration of the boosted Fenton reaction through improvement of H_2O_2 concentration within the tumor using cell-membrane-coated CS-GOD nanoparticles (CS, $Cu_{2-x}Se$). Reproduced with permission from Ref. [25] © 2019 WILEY-VCH Verlag. **(e)** Synthesis of Fe^{3+}-doped $Cu_{2-x}Se$ nanoparticles. **(f)** Variation of the absorption and XRD patterns of the nanoparticles prepared from different dopant ratios. Reproduced with permission from Ref. [15] © 2018 Royal Society of Chemistry. **(g)** Schematic illustration of the preparation of Au–CS heterostructured NPs, which can serve as effective radiosensitizers to enhance radiotherapy. Reproduced with permission from Ref. [38] © 2019 American Chemical Society.

Properties of the CS NPs

The copper deficiency endows CS NPs with strong LSPR in the NIR-II window, which could be used for PA imaging and PTT [45]. For example, the CS NPs could produce vast amounts of ROS via electron transfer and energy transfer mechanisms under the irradiation of the NIR-II laser for PDT (Fig. 2(c)) [12]. Apart from the LSPR, CS NPs could react with H_2O_2 to generate ·OH for CDT through their Fenton-like properties (Fig. 2(d)) [25, 46]. Their performance can be enhanced by increasing the concentration of H_2O_2 within the tumor and irradiating with the NIR-II light.

Furthermore, copper deficiency in CS NPs provides vacancies that can be utilized for the incorporation of other elements, enabling multifunctional engineering. For instance, to modulate the vacancy levels of CS NPs, Zhang et al. doped them with magnetic ferric ions (Fe^{3+}) at room temperature. The peak position and intensity of the near-infrared LSPR in the resulting nanostructures were finely tuned by adjusting the Fe^{3+} ion concentration (Figs. 2(e) and 2(f)) [15]. Similarly, gold ions (Au^+) were incorporated into CS NPs, yielding nanoparticles that function as effective and efficient radiosensitizer for enhanced radiotherapy (Fig. 2(g)) [38].

Overall, the diverse physical and chemical properties of CS NPs highlight their immense potential for CNS disease treatment. To improve their aqueous solubility, colloidal stability, and biocompatibility, CS NPs have been surface-functionalized with dimercapto poly(ethylene glycol) (HS-PEG-SH) [37]. Additionally, to further enhance therapeutic efficacy, CS NPs can be functionalized with small-molecule drugs [47], and encapsulated within various cell membranes to construct biomimetic nanoparticles [48–50].

The BBB is an essential structure of the CNS, creating a relatively independent internal environment distinct from other bodily systems, thereby ensuring normal physiological functions [51, 52]. However,

the BBB acts as a double-edged sword. A major challenge in GBM treatment, particularly for immunotherapy, is the presence of the BBB, which obstructs the delivery of most drugs, including immune checkpoint antibodies, preventing their accumulation at the tumor site [53, 54]. Thus, a key challenge in treating GBM and other CNS diseases is how to reversibly and selectively open the BBB on demand. Recently, focused ultrasound has been clinically tested as a method to transiently open the BBB for GBM treatment [55–58]. In our previous study, we synthesized CS NPs of different sizes and used them to evaluate BBB opening and recovery following focused ultrasound treatment. Our findings revealed that polyethylene glycol (PEG)-modified ultrasmall CS NPs exhibited prolonged blood circulation time (Figs. 3(a) and 3(b)) and effectively diffused into the brain with ultrasound assistance, outperforming larger nanoparticles. This was confirmed by strong signals observed in PA imaging and single-photon emission computed tomography (SPECT/CT) imaging (Figs. 3(c)–3(f)). Furthermore, biodistribution studies, blood routine examinations, and histological staining demonstrated that the accumulated ultrasmall CS NPs were excreted from the brain and major organs within 15 days without causing adverse side effects [59].

To further enhance the ability of CS NPs to cross the BBB, they were functionalized with targeting modifiers. In our previous study, biomimetic nanoparticles were designed by functionalizing CS NPs with CD6 and encapsulating them with a tumor cell membrane, resulting in CS-J@CM/6 NPs. The

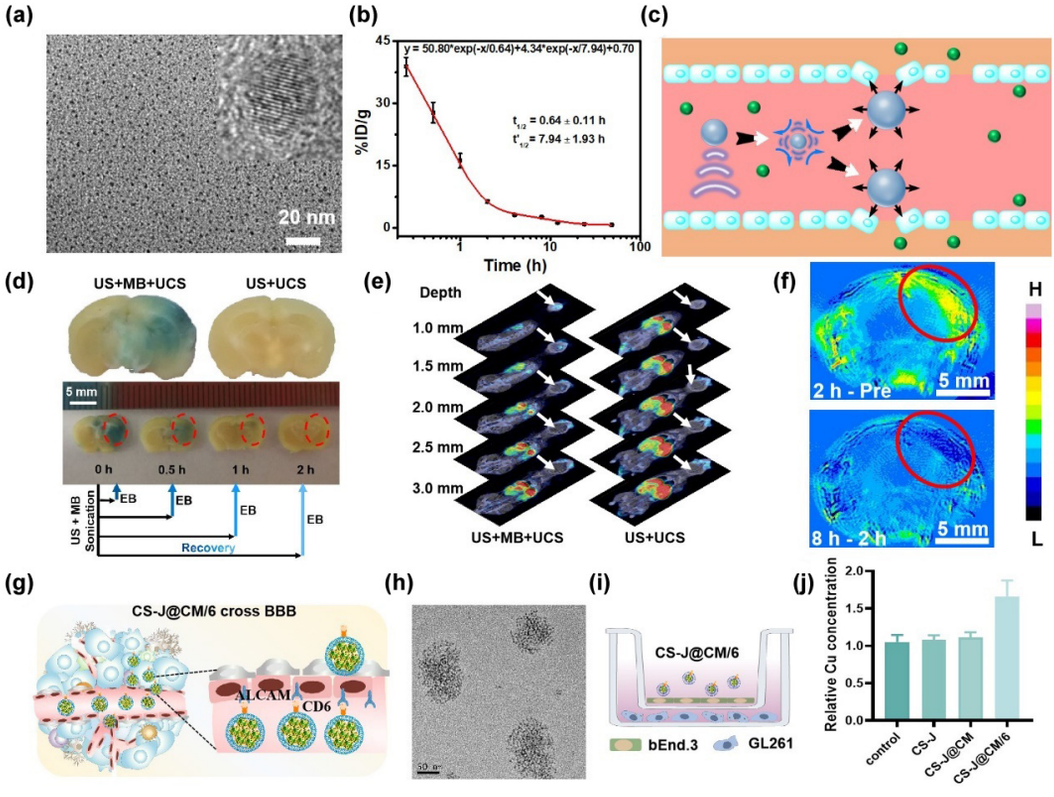

Fig. 3 (a) Transmission electron microscopy (TEM) image of CS NPs. **(b)** Blood circulation half-life of CS NPs in mice, determined by measuring Cu concentration at various time points postinjection using inductively coupled plasma mass spectrometry (ICP–MS) (dose: 5 mg/kg). **(c)** Schematic illustration of the reversible opening of the BBB using focused ultrasound. **(d)** Evans Blue (EB) staining of mouse brain tissues after ultrasound treatment (Left: with microbubbles; Right: without microbubbles). After ultrasound-induced BBB opening, the brains of mice were stained with EB to observe dynamic changes. **(e)** Whole-body single-photon emission computed tomography/computed tomography (SPECT/CT) images of mice from two groups at 2-h postinjection of ^{99m}Tc-labeled CS NPs, with white arrows indicating the sonicated locations. **(f)** Signal enhancement in a mouse brain from the subtraction of PA images before treatment and 2 h after treatment with US+MB+UCS. The subsequent signal decrease from 2 to 8 h is also shown. Reproduced with permission from Ref. [59] © 2018 American Chemical Society. **(g)** Schematic diagram of CS-J@CM/6 NPs actively crossing the BBB. **(h)** TEM image of CS-J@CM/6 NPs. **(i)** Schematic representation of the *in vitro* BBB transwell model setup. **(j)** Cu concentration in GL261 glioblastoma cells from the lower chamber, as detected by ICP-MS, demonstrating nanoparticle penetration across the BBB model. Reproduced from Ref. [60] © 2023 T.T. Wang, et al.

specific interaction between CD6 and the activated leukocyte cell adhesion molecule, which is expressed by endothelial cells, facilitated their passage across the BBB. Once inside the brain, these nanoparticles effectively targeted tumor cells through the homophilic adhesion effect (Figs. 3(g) and 3(h)). Both *in vitro* and *in vivo* experiments confirmed that CS-J@CM/6 NPs could actively cross the BBB without external assistance (Figs. 3(i) and 3(j)). This demonstrates that CS NPs are capable of crossing the BBB through both passive and active mechanisms, enabling their accumulation at tumor sites for GBM immunotherapy and other brain disease treatments [60].

Glioblastoma Immunotherapy Boosted by CS NPs

This section summarizes the applications of CS NPs in enhancing the immune response for GBM treatment. GBM is one of the most common CNS diseases in neurosurgery, characterized by a high recurrence and mortality rate. Despite significant advancements in medicine, the prognosis for high-grade invasive GBM remains poor, with a five-year survival rate of less than 5% [61, 62]. Therefore, developing innovative treatments, such as immunotherapy, is essential to improving therapeutic efficacy [63]. However, immunotherapy has limited effectiveness in GBM due to the following factors: (1) low immunogenicity at the tumor site, leading to a weaker antitumor immune response; (2) a highly immunosuppressive microenvironment caused by an abundance of immunosuppressive cells and a lack of immunostimulatory cells; and (3) dysfunction of immunostimulatory cells, particularly $CD8^+$ T cells, reducing immunotherapeutic efficacy. Therefore, addressing GBM-related immune dysfunction through multifunctional nanoparticles is crucial, as shown in Fig. 4. [64–67].

Immunogenicity increased by CS NPs

The low immunogenicity of GBM contributes to the failure of immunotherapy. However, due to their strong LSPR and Fenton-like properties, CS NPs react with H_2O_2 within the tumor microenvironment to generate ROS. This initiates a vicious cycle between mitochondrial oxidative stress and ER stress, leading to ICD in tumor cells and subsequently enhancing immunogenicity to improve immune response (Fig. 5(a)) [25]. As shown in Figs. 5(b) and 5(c), incubating GL261 cells with CS NPs induces

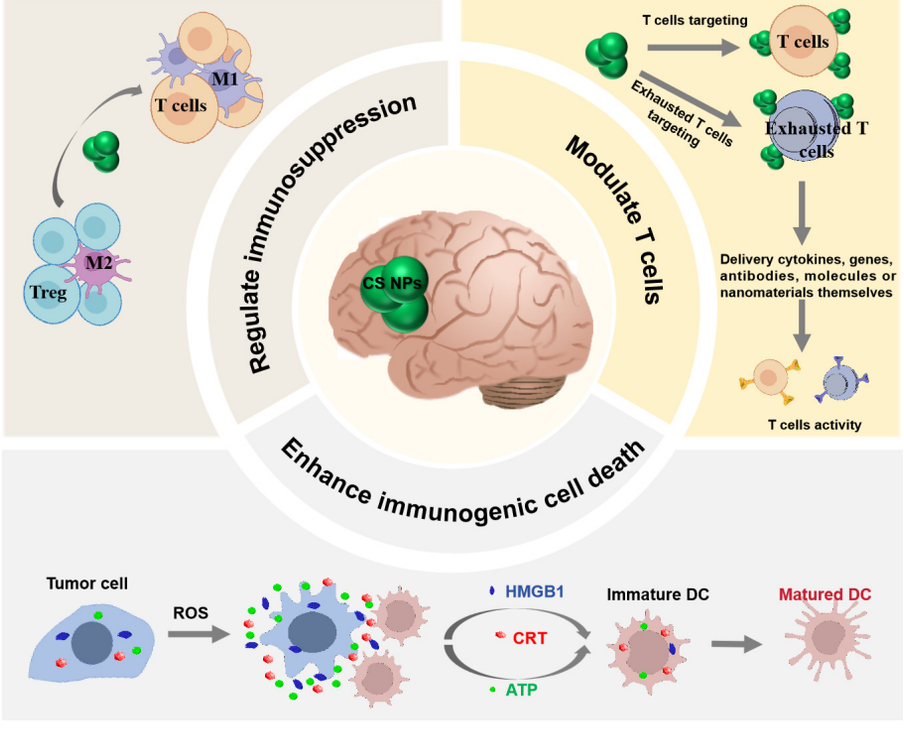

Fig. 4 Schematic illustration of treatment using CS NPs. The diagram highlights how CS NPs enhance immunogenic cell death (ICD), regulate the immunosuppressive tumor microenvironment, and modulate T cell activity to strengthen the antitumor immune response.

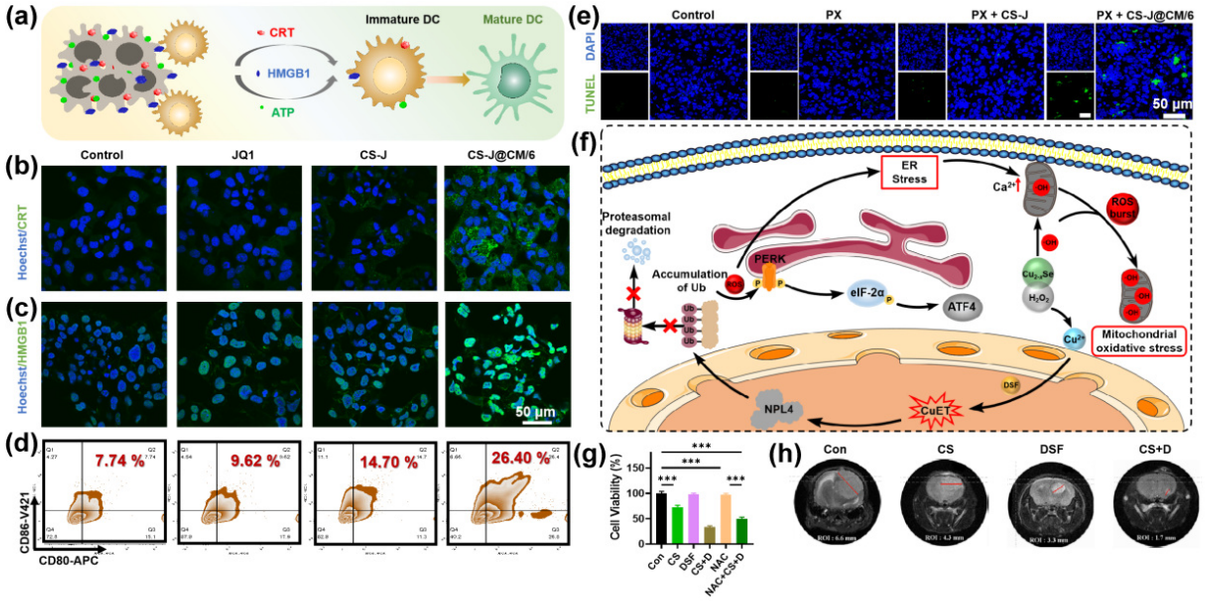

Fig. 5 (a) A schematic representation of the damage-associated molecular patterns, including CRT, ATP, and HMGB1, released from ICD in tumor cells. This process is triggered by the high levels of ROS generated from the degradation of H_2O_2 by CS NPs. **(b)** Immunofluorescence images showing CRT exposure in GL261 cells (scale bar: 50 μm). **(c)** Immunofluorescence images depicting HGBM release from GL261 cells (scale bar: 50 μm). **(d)** Flow cytometry analysis of DCs. **(e)** Immunofluorescence images illustrating PD-L1 expression in tumor slices (scale bar: 25 μm). Reproduced with permission from Ref. [60] © 2023 WILEY-VCH Verlag. **(f)** A schematic representation of how CS NPs and DSF enhance mitochondrial oxidative stress by promoting ER stress through the formation of CuET. Reproduced with permission from Ref. [68] © 2022 Elsevier B.V. **(g)** Cell viability analysis across different treatment groups. **(h)** MRI images showing tumor sizes in mice from different treatment groups. Reproduced with permission from Ref. [27] © 2022 Elsevier B.V.

calreticulin exposure and HMGB1 release. Furthermore, ICD triggered by CS NPs significantly enhances dentritic cell (DC) maturations, which is critical for GBM immunotherapy (Fig. 5(d)). Our findings indicate that CS NPs effectively induce tumor cell apoptosis, which may further increase immunogenicity (Fig. 5(e)). Beyond their LSPR and Fenton-like properties, degradable CS NPs release copper ions, forming high levels of CuET with DSF in tumors. This process induces ICD by exacerbating mitochondrial oxidative stress and promoting ER stress in tumor cells (Fig. 5(f)). Consequently, CS NPs serve as potent nanoparticles for enhancing GBM immunogenicity and improving the efficacy of immunotherapy (Figs. 5(g) and 5(h)) [68].

Infiltration of immunosuppressive cells decreased by CS NPs

The unique tumor immunosuppressive microenvironment (TIME) of GBM contains abundant immunosuppressive cells rather than immunostimulatory cells [69]. TAMs are typical immunosuppressive cells [70, 71]. Interestingly, CS NPs effectively generate ROS in macrophages, triggering the auto-ubiquitination of tumor necrosis factor receptor-associated factor 6 (TRAF6) and subsequently activating interferon regulatory factor 5 (IRF5). This activation promotes the expression of downstream interleukin-23 (IL-23), ultimately reprogramming TAMs from the protumor M2 type to the antitumor M1 type (Figs. 6(a)–6(f)) [72]. Building on this discovery, we fabricated biomimetic nanoparticles CS-I/J@CM. As shown in Fig. 6(g), ultrasmall CS NPs were loaded with IDO inhibitors IND and JQ1 small molecules, then wrapped in tumor cell membranes to construct biomimetic CS-I/J@CM NPs. These nanoparticles regulate the immunosuppressive microenvironment and inhibit immune checkpoint function. They efficiently reach the tumor site, reshaping the TIME by enhancing M1 phenotype macrophages and reducing Treg infiltration through inhibition of tryptophan degradation into kynurenine (Figs. 6(h)–6(j)). Additionally, they suppress PD-L1 expression on tumor cells via JQ1 small molecules, achieving immune checkpoint inhibition (Fig. 6(k)). Ultimately, GBM immunotherapy is enhanced through the synergistic effects of these mechanisms, activating memory T cells and preventing tumor recurrence [29].

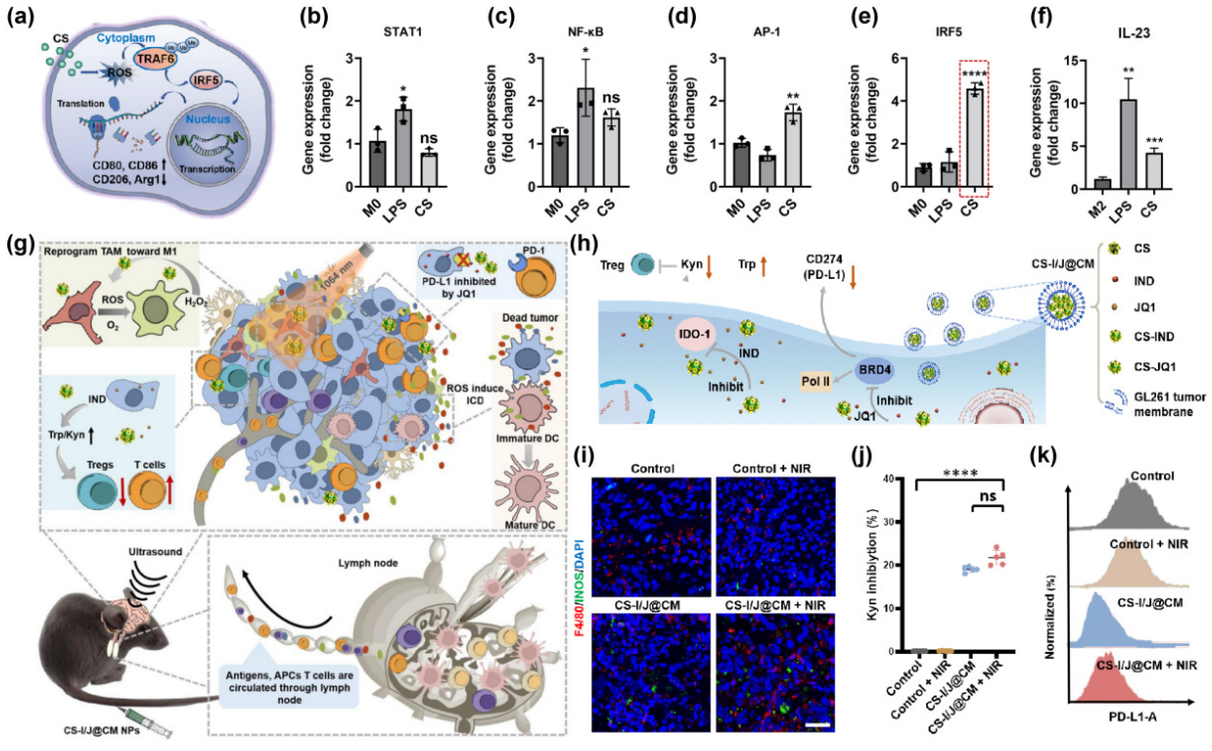

Fig. 6 (a) CS NPs generate ROS to enhance TRAF6 auto-ubiquitination in macrophages, activating the transcription factor IRF5 to reprogram tumor-associated macrophages (TAMs) toward the M1 phenotype. **(b–f)** Gene expressions of the classical M1 polarization signaling pathway in M0-like macrophages (unpolarized RAW 264.7) analyzed by qRT-PCR. Data represent the mean ± standard deviation (SD, $n = 3$). Reproduced with permission from Ref. [72] © 2021 WILEY-VCH Verlag. **(g)** Schematic illustration of remodeling the tumor immunosuppressive microenvironment using all-in-one CS-I/J@CM NPs to improve glioblastoma immunotherapy. **(h)** Schematic illustration of CS-I/J@CM NPs reducing indoleamine 2,3-dioxygenase (IDO) expression to suppress regulatory T cell (Treg) infiltration in tumors and lowering programmed death-ligand 1 (PD-L1) expression on GL261 cells. **(i)** Immunofluorescence images of M1 macrophages ($F4/80^+INOS^+$) at the tumor site (scale bar: 50 μm). **(j)** Kyn inhibition in different tumor groups. **(k)** Flow cytometry analysis of PD-L1 expression on GL261 cells in tumors. Reproduced from Ref. [29] © 2022 T.T. Wang, et al.

Alleviation of T cell dysfunction by CS NPs

The dysfunction of T cells in tumors is a significant challenge for GBM immunotherapy, as GBM not only inhibits T cell infiltration but also induces their dysfunction [73, 74]. Therefore, after reversing the immunosuppressive microenvironment, we alleviated T cell dysfunction caused by GBM. The core–shell Au@$Cu_{2-x}Se$ nanoparticles (ACS NPs) were designed to inhibit CD73 expression, weakening adenosine (ADO)-driven immunosuppression and ultimately enhancing the antitumor activity of T cells (Fig. 7(a)). As shown in Figs. 7(b)–7(d), ACS NPs degrade the high concentration of H_2O_2 in tumors to generate oxygen and improve the hypoxic environment, which reduces HIF-1α overexpression, thereby enhancing the infiltration and activity of antitumor T cells. When combined with radiotherapy, ACS NPs facilitate tumor ICD and recruit more antitumor T cells (Figs. 7(e)–7(h)). Furthermore, IFN-γ^+ $CD8^+$ T cells in the ACS+X+D group of mice increased significantly, demonstrating that ACS NPs not only enhance T cell infiltration but also improve their activity [75].

Our research demonstrates that copper-deficient CS NPs exhibit intrinsic properties and significant potential in GBM immunotherapy. DC vaccines have shown promise in enhancing antigen-specific antitumor immunity within adoptive cell therapy. We treated GBM using CS NPs and dendritic cell (DC)-based nanovaccines. As shown in Fig. 8(a), CS NPs were first used to induce ICD of GL261 cells through ROS generated via their Fenton-like reaction. Next, the membrane debris of apoptotic GL261 cells was loaded with CS NPs. These CS@CM NPs were then used to culture DCs *in vitro* to obtain mature DCs. These DCs not only provided abundant tumor-specific TAAs via MHC I due to lysosomal escape (Figs. 8(b)–8(d)) but also exhibited excellent homing ability to lymph nodes due to the high expression of CCR7 and ICAM-1 (Figs. 8(e) and 8(f)). Finally, CS NPs were coated with the membranes of mature DCs

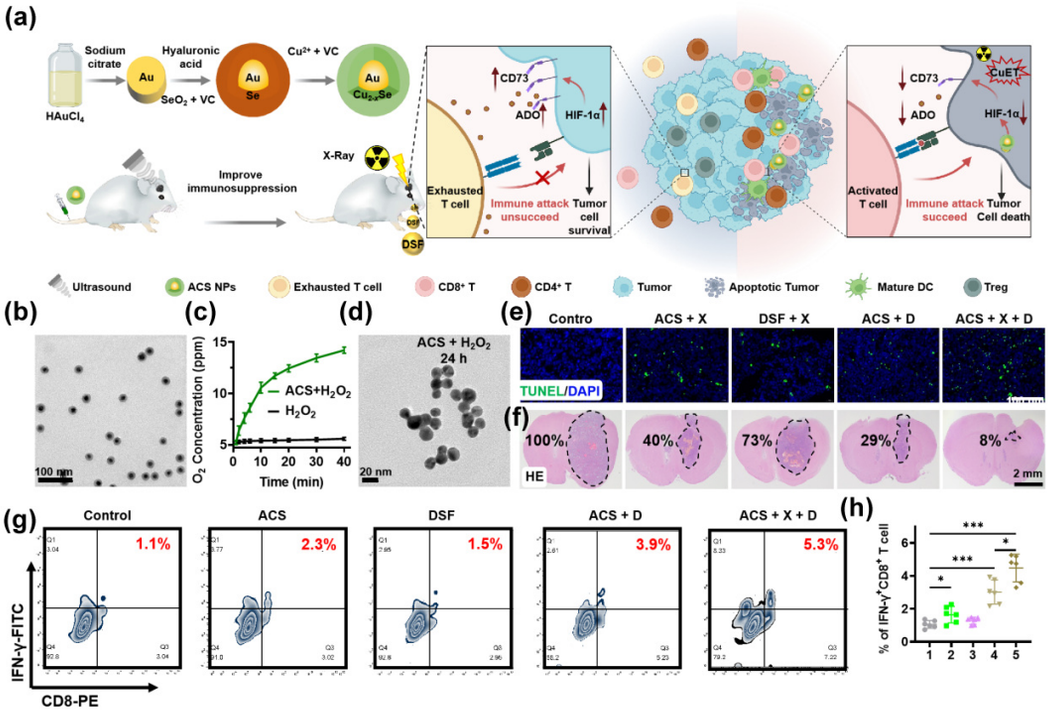

Fig. 7 (a) Schematic illustration of targeting the metabolic immune checkpoint CD73 to enhance glioblastoma (GBM) immunotherapy through the combined use of argentum–copper selenide nanoparticles (ACS NPs), disulfiram (DSF), and radiotherapy. **(b)** Transmission electron microscopy (TEM) image of ACS NPs. **(c)** Generation of O_2 from H_2O_2 and ACS NPs. **(d)** TEM image showing changes in ACS NPs after reaction with an H_2O_2 aqueous solution for 24 h. **(e)** TUNEL staining images of tumor tissues from different groups of mice collected on Day 12. **(f)** Hematoxylin and eosin staining images of tumor tissues from different groups of mice collected on Day 23. **(g–h)** Flow cytometry analysis of IFN-γ^+CD8$^+$T cells and their percentage in tumors from different groups of mice (n = 6). Reproduced with permission from Ref. [75] © 2024 American Chemical Society.

to form DC nanovesicle (named as DCNV (CSD)) nanovaccines, in which CS NPs not only supported the structure of nanovaccines but also enhanced IL-2 expression to facilitate CD8$^+$ T cell proliferation. The generated DCNV nanovaccines could target lymph nodes through their homing ability after subcutaneous injection and activate cytotoxic T lymphocytes (CTLs) via surface-presented tumor-specific TAAs. Ultimately, these DCNV nanovaccines generated memory T cells in the mouse spleen, effectively preventing tumor recurrence (Figs. 8(g)–8(h)) [76].

CS NPs show great potential in the treatment of GBM. A wide range of immunotherapies designed to reverse immunosuppressive pathways has been thoroughly examined to enhance therapeutic efficacy.

Treatment of PD with CS NPs

CS NPs can not only kill tumor cells but also exhibit a remarkable therapeutic effect on neurodegenerative diseases. PD is the second most prevalent progressive neurodegenerative disorder globally, with an increasing incidence [77–79]. According to epidemiological data, PD cases are expected to rise significantly, reaching approximately 12–17 million or more by 2040 [80]. In this section, we summarize the applications of CS NPs in PD treatment.

Currently, several medications are available for PD treatment, including levodopa, dopamine receptor agonists, and anticholinergic drugs [81]. For instance, monoamine oxidase B inhibitors (MAOBIs) [82, 83], catechol-O-methyltransferase inhibitors (COMTIs) [84], amantadine, and istradefylline have been widely used in clinical practice [85, 86]. Although most clinical drugs can alleviate symptoms, they may cause side effects and cannot fundamentally alter the disease onset or halt PD progression [87]. Moreover, these drugs typically lack targeting capabilities, leading to insufficient accumulation in critical brain regions such as the substantia nigra and striatum [88, 89]. Therefore, there is an urgent need to explore novel drugs and treatment methods for PD.

Although the cause of PD remains unclear, it is widely recognized that the abnormal aggregation of misfolded α-syn (Lewy bodies), along with the degeneration of DA neurons in the substantia nigra, constitutes the characteristic pathological features of PD [90]. Interestingly, oxidative stress plays a crucial

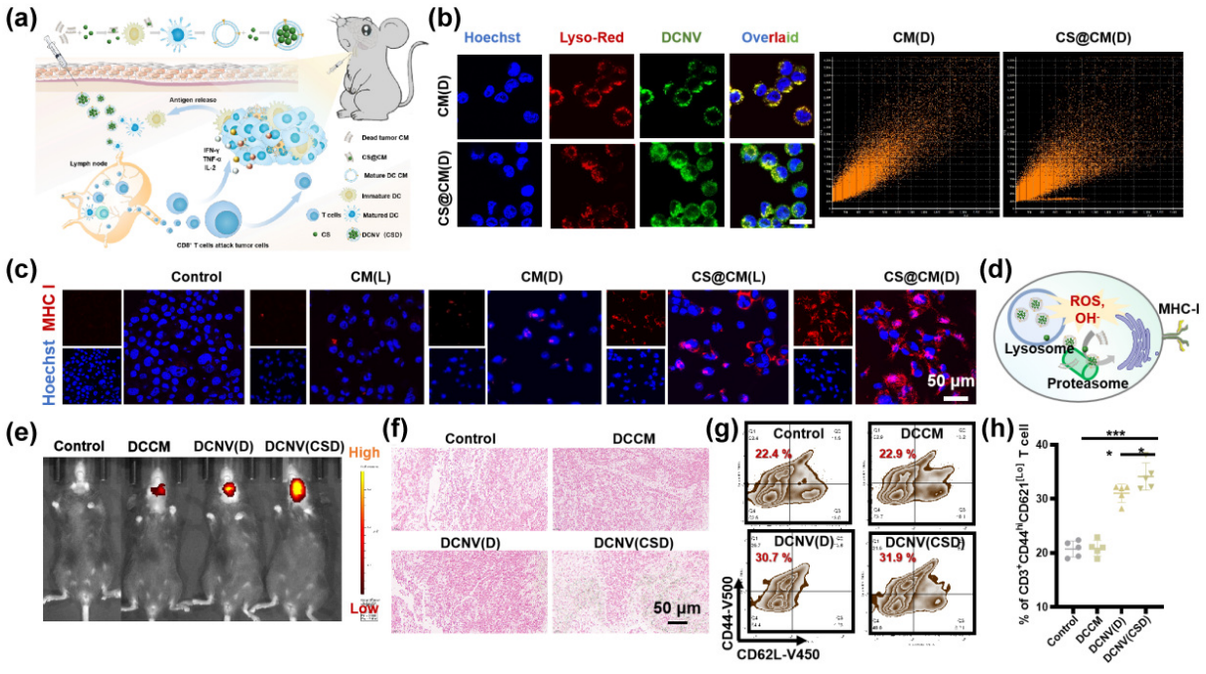

Fig. 8 (a) Schematic illustration of the preparation of personalized DC-based nanovaccines for tumor-specific immunotherapy. **(b)** CLSM images of DC 2.4 cells incubated with CM(D) or CS@CM(D) NPs for 6 h. CM(D) and CS@CM(D) NPs were labeled with Dio (green), nuclei were stained with Hoechst 3342 (blue), and lysosomes were stained with Lyso Tracker-Red (Lyso-Red, red) (scale bar: 20 μm). **(c)** Immunofluorescence images of MHC I on DC 2.4 cells (scale bar: 50 μm). **(d)** Diagram illustrating the escape of nanomaterials from lysosomes. **(e)** Fluorescence images of mice injected with Dil-labeled nanovaccines, recorded using the IVIS Lumina XRMS Series Imaging System. **(f)** Images of tumor slices stained with rubeanic acid from GL261 tumor-bearing mice treated with DCCM, DCNV(D) nanovaccines, or DCNV (CSD) nanovaccines (scale bar: 50 μm). **(g–h)** Flow cytometry analysis of effector memory T cells (T_{EM} cells, $CD3^+CD44^+$ $CD62L^{low}$), their percentage in the spleen of mice from different groups. Reproduced with permission from Ref. [76] © 2024 American Chemical Society.

role in PD pathogenesis [91–93]. Excessive intracellular ROS can lead to neuronal damage and cell death. CS NPs can treat PD through both direct and indirect mechanisms. In our previous work, CS NPs demonstrated antioxidative properties when combined with polyphenols. The modified CS NPs effectively scavenged ROS, thereby reducing the detrimental effects of oxidative stress on neurons [33]. They also inhibited α-syn aggregation by enhancing selective autophagy in neurons [34]. In addition, functionalized CS NPs can be used to treat PD by directly modulating the differentiation of NSCs into DA neurons and promoting neuronal mitochondrial biogenesis [35, 36]. As mentioned earlier, ultrasmall CS NPs exhibit significant advantages in crossing the BBB with the assistance of focused ultrasound. They can be efficiently delivered to brain lesion sites for the treatment of CNS diseases. In the following section, we will specifically elucidate how advanced CS NPs effectively address the challenges associated with PD treatment (Fig. 9).

Inflammatory response reduced by CS NPs

Microglia are essential immune cells in the CNS. In the early stages of PD, most microglia are of the M2-type and can remove harmful substances around neurons through phagocytosis, such as damaged mitochondria and aggregated α-syn [94, 95]. However, as the disease progresses, continuous inflammatory stimulation and oxidative stress may reduce the phagocytic capability of M2-type microglia, preventing the timely removal of harmful substances and increasing neuronal damage. Meanwhile, M1-type microglia continuously release ROS and inflammatory mediators, forming a positive feedback loop that accelerates the degeneration of DA neurons and ultimately leads to neuronal death [96–99]. Therefore, the balance of microglial polarization is disrupted in PD, increasing the M1/M2 microglial ratio. This suggests that PD treatment could involve shifting pro-inflammatory M1 microglia toward the anti-inflammatory M2 phenotype to reduce neuroinflammation [100].

Regulating microglial polarization and reducing neuroinflammation are crucial for the treatment of PD (Figs. 10(a) and 10(b)). In our previous work, ultrasmall CS NPs demonstrated superiority in

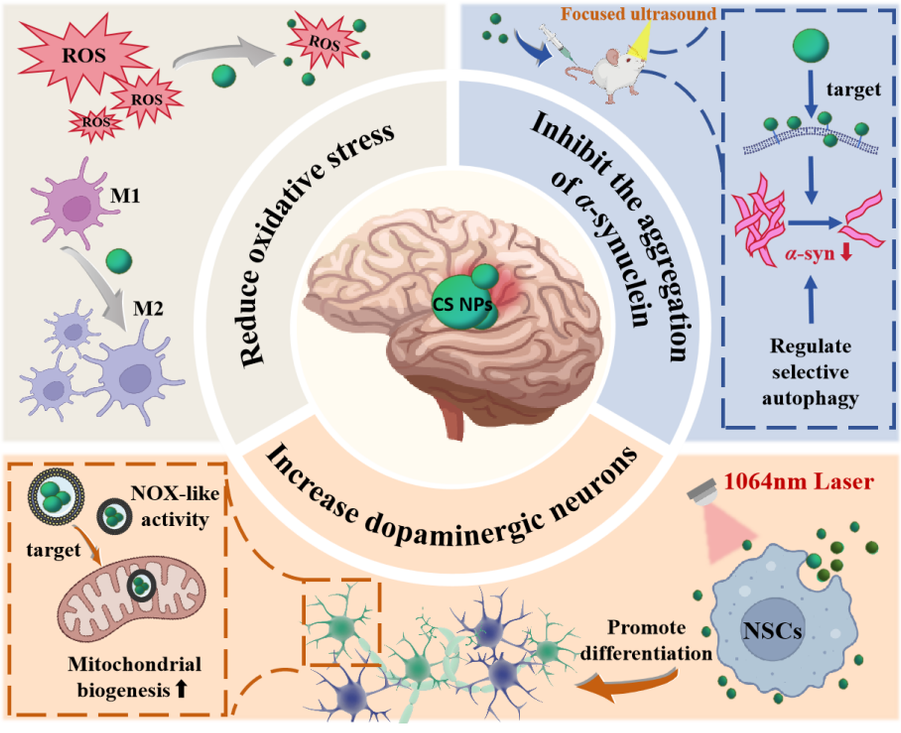

Fig. 9 Treatment of Parkinson's disease (PD) with copper selenide nanoparticles (CS NPs) by reducing oxidative stress in cells, inhibiting α-syn aggregation, and supplementing dopaminergic neurons.

crossing the BBB [24, 25]. They were modified with quercetin (Qe) on their surface (referred to as CSPQ NPs), which not only enhanced the performance of CS NPs but also improved the water solubility, anti-inflammatory, antioxidative, and anti-apoptotic properties of Qe [33]. CSPQ NPs exhibit excellent multi-enzyme activity, including peroxidase (POD), superoxide dismutase (SOD), and catalase (CAT)-like activity, effectively scavenging ROS (Fig. 10(c)). After being coated with the cell membrane of DA neurons (MES23.5 cells), CS NPs efficiently cross the BBB with the assistance of focused ultrasound. Additionally, they effectively target microglia through the specific interaction between ICAM-1 on the MES23.5 cell membrane and $\alpha 4\beta 1$ integrin on the surface of microglia (Figs. 10(d)–10(g)), promoting microglial polarization into the M2-like phenotype with neuroprotective effects. Consequently, CSPQ NPs alleviate oxidative stress in the brain, improve the inflammatory environment, and significantly enhance both motor and memory functions in mice with PD (Fig. 10(h)).

However, the detailed mechanism of microglial polarization mediated by CSPQ@CM NPs remains unclear. Therefore, we further investigated how CSPQ@CM regulates microglial polarization and lipid metabolism [48]. Interestingly, CSPQ@CM specifically targets the TREM2 signaling pathway in microglia, enhancing lipid metabolism and modulating the inflammatory response, ultimately promoting neuronal remyelination. In conclusion, the intrinsic properties of functionalized CS NPs play a crucial role in reducing neurotoxicity and treating neurodegenerative diseases.

α-Syn aggregation inhibited by CS NPs

α-Syn is a naturally expressed unfolded protein in neurons. Under normal circumstances, α-syn exists in a soluble form. However, in PD, it is more prone to misfolding due to genetic and environmental factors. The misfolded α-syn exposes hydrophobic regions, promoting interactions and aggregation. These α-syn aggregates activate the inflammatory response and damage neurons [91, 101–103]. Therefore, the efficient clearance of α-syn aggregates is a key factor in PD treatment.

Autophagy, a self-cleaning mechanism within cells, plays a crucial role in identifying and eliminating damaged proteins, organelles, and other cellular components [104, 105]. Under normal physiological conditions, autophagy effectively degrades pathogenic α-syn, preventing its abnormal aggregation into Lewy bodies and maintaining intracellular stability. Under pathological conditions,

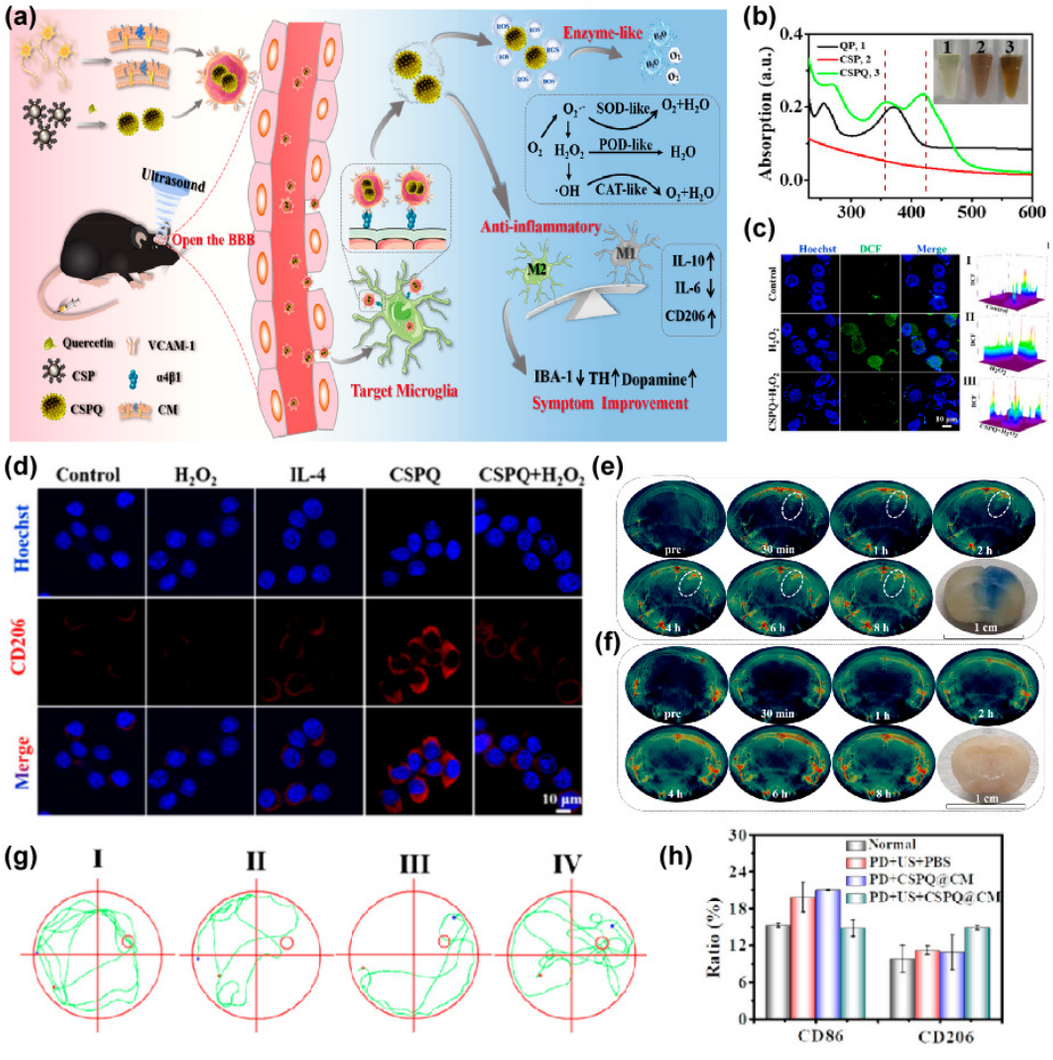

Fig. 10 (a) Schematic illustration of biomimetic copper selenide-polydopamine-quercetin@cell membrane nanoparticles (CSPQ@CM NPs) for targeted modulation of the brain microenvironment in the treatment of Parkinson's disease (PD). **(b)** Ultraviolet–visible (UV–Vis) absorption spectra of the quercetin–polydopamine complex, CSP NPs, and CSPQ NPs. **(c)** Confocal laser scanning microscopy (CLSM) images of BV_2 cells detecting intracellular ROS before and after incubation with H_2O_2 and pretreatment with CSPQ NPs. The fluorescence distribution and intensity in BV_2 cells are shown in I–III. **(d)** CLSM images of BV_2 cells after culturing under different conditions: normal, H_2O_2, interleukin-4 (IL-4), CSPQ NPs, and CSPQ NPs with H_2O_2. **(e)** Photoacoustic (PA) images of the brain of a nude mouse obtained before and after ultrasound treatment, followed by intravenous injection of CSPQ@CM NPs. **(f)** PA images of the mouse brain before and after injection of CSPQ@CM NPs without ultrasound treatment. **(g)** Representative movement paths of mice from different groups (n = 6): (I) normal group; (II) PD+ultrasound (US) + phosphate-buffered saline (PBS) group; (III) PD+CSPQ@CM group; IV) PD+US+CSPQ@CM group. **(h)** Ratios of M2- to M1-like markers, i.e., CD206 and CD86, expressed on microglia in the brains of four groups of mice, were analyzed by flow cytometry. Reproduced with permission from Ref. [33] © 2020 American Chemical Society.

pathogenic α-syn produced by neurons can be cleared by enhancing selective autophagy [106–108]. When excessive pathogenic α-syn is not efficiently and promptly degraded within neurons, it may be exocytosed into the extracellular environment and subsequently removed by microglia [109]. Therefore, regulating autophagy levels in neurons and microglia presents a novel approach for PD treatment [110].

We employed CSPQ NPs to promote the selective autophagic degradation of α-syn aggregates in neurons and improve the treatment efficacy of PD [34]. CSPQ NPs activated the Nrf2/p62 pathway in neurons (Fig. 11(a)). The increased LC3-II/LC3-I ratio confirmed the enhancement of selective autophagy (Fig. 11(b)). *In vivo* experiments demonstrated that CSPQ NPs significantly reduced α-syn aggregate levels (Figs. 11(c) and 11(d)). Finally, motor impairment and exploratory ability in PD mice were drastically improved after treatment, as evidenced by the water maze test and the open field test (Fig. 11(e)).

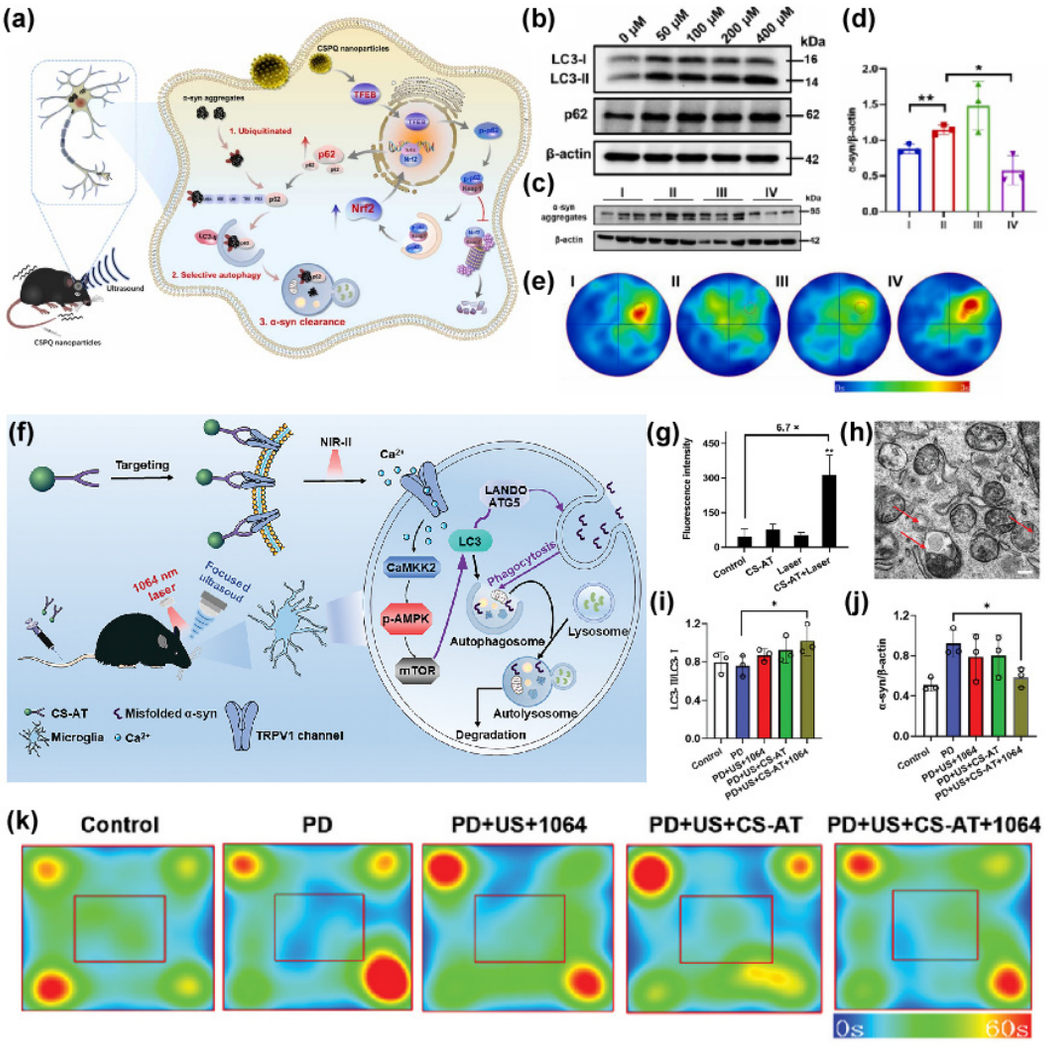

Fig. 11 (a) Schematic illustration of CSPQ NPs activating Nrf2 to regulate SQSTM1/p62-dependent selective autophagy for scavenging α-syn aggregates. **(b)** Expression levels of LC3-II/LC3-I and SQSTM1/p62 in dopaminergic neuronal MES23.5 cells after treatment with different concentrations of CSPQ NPs. **(c)** Western blot assay and **(d)** corresponding quantitative analysis of α-syn aggregates from different groups of mice. **(e)** Fitting diagram of the swimming tracks of five mice per group: (I) Control group, (II) PD+US+PBS group, (III) PD+CSPQ@CM group, (IV) PD+US+CSPQ@CM group. Reproduced with permission from Ref. [34] © 2023 Elsevier B.V. **(f)** Schematic illustration of CS-AT NPs enhancing microglial autophagy to phagocytose and degrade α-syn for PD treatment. **(g)** Fluorescence intensity of Ca^{2+} in BV_2 cells from different groups. **(h)** Representative TEM image of autophagosomes in BV_2 cells incubated with CS-AT NPs and irradiated with a 1 064 nm laser. **(i)** Quantitative analysis of the relative LC3-II/LC3-I ratio. **(j)** α-Syn levels in mice from all groups. **(k)** Open field test results, including representative tracking paths and parameter analysis, showing changes in mean speed, zone transition number, resting total time, and peripheral zone resting time in five groups of mice. Reproduced with permission from Ref. [24] © 2022 WILEY-VCH Verlag.

Additionally, TRPV1 is known to be a temperature-sensitive cation channel [111, 112] and serves as an effective target for the treatment of neurodegenerative diseases. Activation of this channel can enhance autophagy [113]; however, continuous stimulation may lead to an excessive influx of Ca^{2+} into cells, causing mitochondrial damage and even triggering apoptosis [114]. Therefore, it is crucial to regulate TRPV1 activation on demand to modulate intracellular Ca^{2+} levels effectively. Building on this research, we leveraged the high photothermal conversion efficiency of ultrasmall CS NPs to control TRPV1 activation [24]. CS NPs were conjugated with anti-TRPV1 antibodies to form $Cu_{2-x}Se$-anti-TRPV1 nanoparticles (CS-AT NPs). These CS-AT NPs functioned as a photothermal switch, selectively targeting and activating the TRPV1 channel on the microglial membrane under NIR-II irradiation (Fig. 11(f)). This activation induced Ca^{2+} influx, which stimulated the ATG5 and Ca^{2+}/CaMKK2/AMPK/mTOR signaling pathways, promoting the phagocytosis and degradation of α-syn aggregates (Figs. 11(g) and 11(h)). Additionally, CS-AT NPs were efficiently delivered to the striatum of PD mice,

where TRPV1 expression was high. *In vivo* experiments confirmed that enhanced autophagy facilitated efficient phagocytic clearance of α-syn aggregates, significantly improving motor and memory functions in PD mice treated with CS-AT NPs and NIR-II irradiation (Figs. 11(i)–11(k)).

DA neurons increased by CS NPs

Our previous work demonstrated the indirect neuroprotective effects of functional CS NPs on DA neurons. Additionally, combining CS NPs with other therapeutic approaches can directly protect neurons by improving mitochondrial dysfunction and promoting neuronal differentiation.

Mitochondrial dysfunction plays a critical role in neuronal loss. In the neurons of PD patients, mitochondrial impairment leads to insufficient energy supply, increased electron transport chain leakage, and excessive generation of ROS [115]. Moreover, mitochondrial dysfunction disrupts normal calcium signaling, accelerates the misfolding and aggregation of proteins such as α-syn, and ultimately affects neuronal function [116, 117]. Therefore, enhancing mitochondrial function presents a promising strategy for PD treatment [118].

Next, we developed a mitochondrial-targeted nanodelivery system using CS NPs, which effectively coordinates with curcumin through surface copper ions (Fig. 12(a)) [35]. Curcumin-modified $Cu_{2-x}Se$ nanoparticles (CSC NPs) were coated with macrophage cell membranes modified with DSPE-PEG2000-TPP. The coated CSC NPs not only targeted inflamed neurons and their mitochondria but also enhanced mitochondrial biogenesis (Figs. 12(b) and 12(c)) and improved PD treatment outcomes (Figs. 12(d) and 12(e)).

Similarly, we designed $Cu_{2-x}Se$-PVP-SC79 NPs coated with RAW 264.7 cell membranes (CM), referred to as CSS@CM NP [119]. SC79 is a specific Akt phosphorylation agonist that reduces neuronal excitotoxicity, prevents neuronal death, and promotes neurite growth [120]. Additionally, Cu^{2+} ions released from CSS@CM NPs significantly promote neuronal proliferation and cell migration by activating the Akt and ERK signaling pathways. When coated with RAW 264.7 CM, these NPs target neurons, prevent synaptic damage and neuronal apoptosis, and enhance PD treatment efficacy.

When the progressive loss of DA neurons cannot be reversed, an alternative approach is to supplement neurons by controlling the differentiation of NSCs into DA neurons. NSC transplantation has emerged as a promising strategy to generate new DA neurons for PD treatment [121, 122]. NSCs not only possess multidirectional differentiation potential, enabling them to develop into DA neurons, but also secrete a variety of neurotrophic factors [123]. When transplanted into the brains of PD patients, NSCs have the potential to differentiate into mature DA neurons in response to the specific environment. These differentiated neurons can effectively replace damaged or lost neurons and enhance dopamine production in the affected regions [124]. However, precise control over the differentiation pathway of NSCs remains a significant challenge.

Building on previous research, we discovered that the combined use of CS NPs and NIR-II laser irradiation can effectively promote NSC differentiation into neurons [36]. This effect is likely attributed to the intrinsic properties and modifiable surface of CS NPs. The synergistic action of CS NPs and 1 064 nm NIR-II laser irradiation can open voltage-gated calcium channel on the NSC surface, triggering the Ca^{2+}/CaMK/CREB/c-Fos signaling pathway (Figs. 12(f) and 12(g)) and effectively regulating NSC differentiation into DA neurons (Figs. 12(h) and 12(i)). Furthermore, using this approach, we successfully repaired the damaged nigrostriatal neural circuit and improved motor impairment as well as anxiety in PD mice (Fig. 12(j)). These findings highlight the potential of new strategies and methodologiess for PD treatment.

Summary and Future Prospects

Copper chalcogenides, particularly CS NPs, exhibit immense potential in biomedical applications, especially for the treatment of CNS diseases. This potential arises from their unique physicochemical properties, such as strong LSPR in the NIR-II window, Fenton-like catalytic activity, and the ability to be doped with other elements. In the context of GBM treatment, CS NPs enhance immunotherapy efficacy by inducing ICD in tumor cells through ROS generation, reshaping the immunosuppressive tumor microenvironment, and boosting T cell activity. For PD treatment, drug-loaded CS NPs mitigate the inflammatory response by reducing ROS levels and

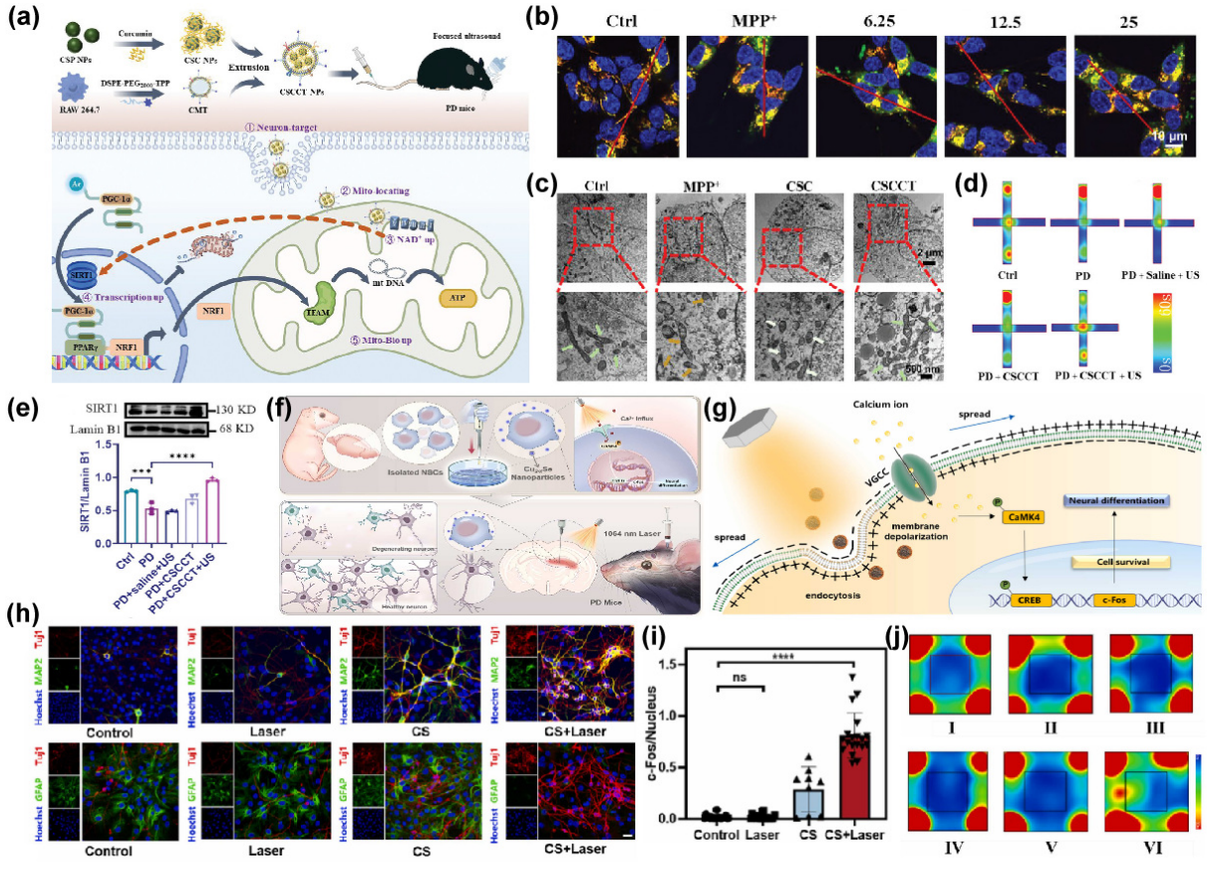

Fig. 12 (a) Schematic illustration of biomimetic targeting nanoparticles ameliorating mitochondrial dysfunction by mediating mitochondrial biogenesis to enhance PD therapy. **(b)** Confocal laser scanning microscopy (CLSM) images showing total and active mitochondria in SH-SY5Y cells pretreated with different concentrations of CSC NPs, followed by incubation with 1-methyl-4-phenylpyridinium (MPP^+). **(c)** Representative TEM images of mitochondria in SH-SY5Y cells treated with MPP^+ after incubation with CSC and CSCCT NPs. **(d)** Elevated plus-maze test: Heat map of tracking paths showing changes in the frequency of open-arm entries in five groups of mice. **(e)** Western blot and quantitative analysis of sirtuin (SIRT) protein levels in five groups of mice. Reproduced from Ref. [35] © 2023 Q. Zheng, et al. **(f)** and **(g)** Schematic illustration of neural stem cell (NSC) transplantation into the striatum of PD mice, promoting their directional differentiation into dopaminergic neurons induced by CS NPs under 1 064 nm NIR-II laser irradiation. **(h)** Representative fluorescence images of NSCs incubated for seven days under different experimental conditions (Control, Laser, CS, CS+Laser). **(i)** Statistical analysis of fluorescence intensity in the representative images of c-Fos expression in NSCs induced by CS NPs and 1 064 nm NIR-II laser irradiation. **(j)** Open field test: Heat maps of tracking paths showing changes in mean speed. Reproduced with permission from Ref. [36] © 2024 Elsevier B.V.

promoting microglial polarization, while also inhibiting α-syn aggregation by modulating the cellular autophagy pathway. In summary, CS NPs, with their unique physicochemical properties, provide novel strategies and methodologies for addressing CNS diseases.

Future research should focus on further optimizing the synthesis and functionalization of CS NPs to enhance their performance and specificity in CNS disease treatment. Additionally, extensive preclinical and clinical trials are essential to validate the efficacy and safety of CS NP-based therapeutics. Although the distribution, degradation, and metabolism of ultrasmall CS NPs have been demonstrated through *in vivo* fluorescence imaging, blood routine tests, blood biochemistry, histological analysis, and characterization of copper transport and binding proteins, results indicate that ultrasmall CS NPs are primarily excreted via feces and urine within 72 h postintravenous injection. Furthermore, the released copper ions did not cause severe toxicity, underscoring the great potential of copper chalcogenide nanoparticles in nanomedicine. However, further *in vivo* studies with larger sample sizes and longer observation periods are necessary to assess the long-term therapeutic effects and potential side effects of CS NPs in CNS disease treatment. Such studies should also be conducted on large animal models and non-human primates. Moreover, the clinical translation of these preclinical findings, alongside the development of advanced drug delivery

systems tailored for CS NPs, is crucial for overcoming CNS diseases and achieving personalized treatment.

CRediT Author Statement

Shuyang Xie: investigation, writing the original draft of the part of introduction and treatment of Parkinson's disease, collecting references. **Hualong Liu**: investigation, writing the original draft of the part of glioblastoma immunotherapy. **Ke Yang**: investigation, writing the original draft of the part of CS NPs syntheses and properties. **Tingting Wang**: formal analysis and supervision. **Hao Zhang**: reviewing and editing the manuscript. **Zhen Li**: conception and modification of the review structure.

Acknowledgements

The authors acknowledge the support from the National Key Research and Development Program of China (No. 2022YFA1104300), the National Natural Science Foundation of China (No. 82472128, 92374113), the Major Basic Research Project of the Natural Science Foundation of the Jiangsu Higher Education Institutions (No. 22KJA310004), Jiangsu Funding Program for Excellent Postdoctoral Talent (No. 318709) and the Interdisciplinary Basic Frontier Innovation Program of Suzhou Medical College of Soochow University (No. YXY2303025). The authors also are grateful for the support from the Suzhou Fundamental Research Project (Nos. SJC2023001 and SYW2024183), the Key Laboratory of Radiation Damage and Treatment of Jiangsu Provincial Universities and Colleges, and the Priority Academic Program Development of Jiangsu Higher Education Institutions (PAPD).

Conflict of Interests

The authors declare that no competing interest exists.

References

[1] S. Goel, F. Chen, W. Cai. Synthesis and biomedical applications of copper sulfide nanoparticles: From sensors to theranostics. *Small*, 2014, 10(4): 631−645. https://doi.org/10.1002/smll.201301174

[2] X. Lu, X. Chen, C. Lin, et al. Elesclomol loaded copper oxide nanoplatform triggers cuproptosis to enhance antitumor immunotherapy. *Advanced Science*, 2024, 11(18): e2309984. https://doi.org/10.1002/advs.202309984

[3] J. Ma, N. Li, J. Wang, et al. *In vivo* synergistic tumor therapies based on copper sulfide photothermal therapeutic nanoplatforms. *Exploration*, 2023, 3(5): 20220161. https://doi.org/10.1002/EXP.20220161

[4] G.Z. Zhou, M. Li. Biodegradable copper telluride nanosheets for redox-homeostasis breaking-assisted chemodynamic cancer therapy boosted by mild-photothermal effect. *Chemical Engineering Journal*, 2022, 450: 138348. https://doi.org/10.1016/j.cej.2022.138348

[5] Y. Yang, Y. Liu, Q.X. Yang, et al. The application of selenium nanoparticles in immunotherapy. *Nano Biomedicine and Engineering*, 2024, 16(3): 345−356. https://doi.org/10.26599/nbe.2024.9290100

[6] O.A. Balitskii, M. Sytnyk, J. Stangl, et al. Tuning the localized surface plasmon resonance in $Cu_{2-x}Se$ nanocrystals by postsynthetic ligand exchange. *ACS Applied Materials & Interfaces*, 2014, 6(20): 17770−17775. https://doi.org/10.1021/am504296y

[7] L. Lin, L.V. Wang. The emerging role of photoacoustic imaging in clinical oncology. *Nature Reviews Clinical Oncology*, 2022, 19(6): 365−384. https://doi.org/10.1038/s41571-022-00615-3

[8] X.S. Li, J.F. Lovell, J. Yoon, et al. Clinical development and potential of photothermal and photodynamic therapies for cancer. *Nature Reviews Clinical Oncology*, 2020, 17(11): 657−674. https://doi.org/10.1038/s41571-020-0410-2

[9] B.W. Sun, J.N. Bte Rahmat, Y. Zhang. Advanced techniques for performing photodynamic therapy in deep-seated tissues. *Biomaterials*, 2022, 291: 121875. https://doi.org/10.1016/j.biomaterials.2022.121875

[10] C.M. Hessel, V.P. Pattani, M. Rasch, et al. Copper selenide nanocrystals for photothermal therapy. *Nano Letters*, 2011, 11(6): 2560−2566. https://doi.org/10.1021/nl201400z

[11] C. Gorrini, I.S. Harris, T.W. Mak. Modulation of oxidative stress as an anticancer strategy. *Nature Reviews Drug Discovery*, 2013, 12(12): 931−947. https://doi.org/10.1038/nrd4002

[12] H. Zhang, T. Wang, H. Liu, et al. Second near-infrared photodynamic therapy and chemotherapy of orthotopic malignant glioblastoma with ultra-small $Cu_{2-x}Se$ nanoparticles. *Nanoscale*, 2019, 11(16): 7600−7608. https://doi.org/10.1039/C9NR01789E

[13] C. Jia, Y. Guo, F.G. Wu. Chemodynamic therapy *via* Fenton and Fenton-like nanomaterials: Strategies and recent advances. *Small*, 2022, 18(6): e2103868. https://doi.org/10.1002/smll.202103868

[14] L. Zhang, C.X. Li, S.S. Wan, et al. Nanocatalyst-mediated chemodynamic tumor therapy. *Advanced Healthcare Materials*, 2022, 11(2): e2101971. https://doi.org/10.1002/adhm.202101971

[15] S.H. Zhang, Q. Huang, L.J. Zhang, et al. Vacancy engineering of $Cu_{2-x}Se$ nanoparticles with tunable LSPR and magnetism for dual-modal imaging guided photothermal therapy of cancer. *Nanoscale*, 2018, 10(7): 3130−3143. https://doi.org/10.1039/C7NR06937E

[16] S.Q. Lie, D.M. Wang, M.X. Gao, et al. Controllable copper deficiency in $Cu_{2-x}Se$ nanocrystals with tunable localized surface plasmon resonance and enhanced chemiluminescence. *Nanoscale*, 2014, 6(17): 10289−10296. https://doi.org/10.1039/C4NR02294G

[17] L.E. Marbella, X.Y. Gan, D.C. Kaseman, et al. Correlating carrier density and emergent plasmonic features in $Cu_{2-x}Se$ nanoparticles. *Nano Letters*, 2017, 17(4): 2414−2419. https://doi.org/10.1021/acs.nanolett.

6b05420
[18] B. Yun, H. Zhu, J. Yuan, et al. Synthesis, modification and bioapplications of nanoscale copper chalcogenides. *Journal of Materials Chemistry B*, 2020, 8(22): 4778−4812. https://doi.org/10.1039/D0TB00182A
[19] Bai X, Zhou T, Wu X, et al. Synthesis and Application of Selenium Nanoparticles for the Modulation of Inflammatory Diseases. *Nano Biomedicine and Engineering*, 2025, https://doi.org/10.26599/NBE.2025.9290111
[20] M.D. Sweeney, A.P. Sagare, B.V. Zlokovic. Blood–brain barrier breakdown in Alzheimer disease and other neurodegenerative disorders. *Nature Reviews Neurology*, 2018, 14(3): 133−150. https://doi.org/10.1038/nrneurol.2017.188
[21] J.B. Xie, Z.Y. Shen, Y. Anraku, et al. Nanomaterial-based blood-brain-barrier (BBB) crossing strategies. *Biomaterials*, 2019, 224: 119491. https://doi.org/10.1016/j.biomaterials.2019.119491
[22] Z. Zhao, A.R. Nelson, C. Betsholtz, et al. Establishment and dysfunction of the blood-brain barrier. *Cell*, 2015, 163(5): 1064−1078. https://doi.org/10.1016/j.cell.2015.10.067
[23] S. Senapati, A.K. Mahanta, S. Kumar, et al. Controlled drug delivery vehicles for cancer treatment and their performance. *Signal Transduction and Targeted Therapy*, 2018, 3: 7. https://doi.org/10.1038/s41392-017-0004-3
[24] J. Yuan, H. Liu, H. Zhang, et al. Controlled activation of TRPV1 channels on microglia to boost their autophagy for clearance of alpha-synuclein and enhance therapy of Parkinson's disease. *Advanced Materials*, 2022, 34(11): e2108435. https://doi.org/10.1002/adma.202108435
[25] T.T. Wang, H. Zhang, H.H.Liu, et al. Boosting H_2O_2-guided chemodynamic therapy of cancer by enhancing reaction kinetics through versatile biomimetic Fenton nanocatalysts and the second near-infrared light irradiation. *Advanced Functional Materials*, 2020, 30(3): 1906128. https://doi.org/10.1002/adfm.201906128
[26] M. Lim, Y.X. Xia, C. Bettegowda, et al. Current state of immunotherapy for glioblastoma. *Nature Reviews Clinical Oncology*, 2018, 15(7): 422−442. https://doi.org/10.1038/s41571-018-0003-5
[27] S. Yang, Y.B. Han, B.L. Bao, et al. Boosting the anti-tumor performance of disulfiram against glioblastoma by using ultrasmall nanoparticles and HIF-1α inhibitor. *Composites Part B: Engineering*, 2022, 243: 110117. https://doi.org/10.1016/j.compositesb.2022.110117
[28] G. Kroemer, C. Galassi, L. Zitvogel, et al. Immunogenic cell stress and death. *Nature Immunology*, 2022, 23(4): 487−500. https://doi.org/10.1038/s41590-022-01132-2
[29] T.T. Wang, H. Zhang, W.B. Qiu, et al. Biomimetic nanoparticles directly remodel immunosuppressive microenvironment for boosting glioblastoma immunotherapy. *Bioactive Materials*, 2022, 16: 418−432. https://doi.org/10.1016/j.bioactmat.2021.12.029
[30] H. Zhang, L. Yang, T.T. Wang, et al. NK cell-based tumor immunotherapy. *Bioactive Materials*, 2024, 31: 63−86. https://doi.org/10.1016/j.bioactmat.2023.08.001
[31] H.R. Morris, M.G. Spillantini, C.M. Sue, et al. The pathogenesis of Parkinson's disease. *The Lancet*, 2024, 403(10423): 293−304. https://doi.org/10.1016/S0140-6736(23)01478-2
[32] H. Ye, L.A. Robak, M. Yu, et al. Genetics and pathogenesis of Parkinson's syndrome. *Annual Review of Pathology*, 2023, 18: 95−121. https://doi.org/10.1146/annurev-pathmechdis-031521-034145
[33] H.H. Liu, Y.B. Han, T.T. Wang, et al. Targeting microglia for therapy of Parkinson's disease by using biomimetic ultrasmall nanoparticles. *Journal of the American Chemical Society*, 2020, 142(52): 21730−21742. https://doi.org/10.1021/jacs.0c09390
[34] H.H. Liu, Q. Zheng, J.X. Yuan, et al. Modulating SQSTM1/p62-dependent selective autophagy of neurons by activating Nrf2 with multifunctional nanoparticles to eliminate α-synuclein aggregates and boost therapy of Parkinson's disease. *Nano Today*, 2023, 49: 101770. https://doi.org/10.1016/j.nantod.2023.101770
[35] Q. Zheng, H. Liu, H. Zhang, et al. Ameliorating mitochondrial dysfunction of neurons by biomimetic targeting nanoparticles mediated mitochondrial biogenesis to boost the therapy of Parkinson's disease. *Advanced Science*, 2023, 10(22): e2300758. https://doi.org/10.1002/advs.202300758
[36] Y.F. Gao, H.H. Liu, Q. Zheng, et al. Modulating efficient differentiation of neural stem cells into neurons by using plasmonic nanoparticles and the NIR II irradiation to boost therapy of Parkinson's disease. *Nano Today*, 2024, 57: 102392. https://doi.org/10.1016/j.nantod.2024.102392
[37] S. Zhang, C. Sun, J. Zeng, et al. Ambient aqueous synthesis of ultrasmall PEGylated Cu_{2-x} Se nanoparticles as a multifunctional theranostic agent for multimodal imaging guided photothermal therapy of cancer. *Advanced Materials*, 2016, 28(40): 8927−8936. https://doi.org/10.1002/adma.201602193
[38] Q. Huang, S. Zhang H., Zhang, et al. Boosting the radiosensitizing and photothermal performance of Cu_{2-x}Se nanocrystals for synergetic radiophotothermal therapy of orthotopic breast cancer. *ACS Nano*, 2019, 13(2): 1342−1353. https://doi.org/10.1021/acsnano.8b06795
[39] H. Zhang, X. Zeng, Z. Li. Copper-chalcogenide-based multimodal nanotheranostics. *ACS Applied Bio Materials*, 2020, 3(10): 6529−6537. https://doi.org/10.1021/acsabm.0c00937
[40] C.Y. Wu, S.-H. Yu, M. Antonietti. Complex concaved cuboctahedrons of copper sulfide crystals with highly geometrical symmetry created by a solution process. *Chemistry of Materials*, 2006, 18(16): 3599−3601. https://doi.org/10.1021/cm060956u
[41] J. Xu, W.X. Zhang, Z.H. Yang, et al. Large-scale synthesis of long crystalline Cu_{2-x}Se nanowire bundles by water-evaporation-induced self-assembly and their application in gas sensing. *Advanced Functional Materials*, 2009, 19(11): 1759−1766. https://doi.org/10.1002/adfm.200801430
[42] S. Goel, C.A. Ferreira, F. Chen, et al. Activatable hybrid nanotheranostics for tetramodal imaging and synergistic photothermal/photodynamic therapy. *Advanced Materials*, 2018, 30(6): 1704367. https://doi.org/10.1002/adma.201704367
[43] R.I. Walton. Subcritical solvothermal synthesis of condensed inorganic materials. *Chemical Society Reviews*, 2002, 31(4): 230−238. https://doi.org/10.1039/B105762F
[44] M.R. Gao, Y.F. Xu, J. Jiang, et al. Nanostructured metal chalcogenides: Synthesis, modification, and applications in energy conversion and storage devices. *Chemical Society Reviews*, 2013, 42(7): 2986−3017. https://doi.org/10.1039/C2CS35310E
[45] N.J. Halas, S. Lal, W.S. Chang, et al. Plasmons in strongly coupled metallic nanostructures. *Chemical Reviews*, 2011, 111(6): 3913−3961. https://doi.org/10.1021/cr200061k
[46] Y. Han, T. Wang, H. Liu, et al. The release and detection of copper ions from ultrasmall theranostic Cu_{2-x}Se nanoparticles. *Nanoscale*, 2019, 11(24): 11819−11829. https://doi.org/10.1039/C9NR02884F

[47] T. Wang, H. Zhang, Y. Han, et al. Light-enhanced O_2-evolving nanoparticles boost photodynamic therapy to elicit antitumor immunity. *ACS Applied Materials & Interfaces*, 2019, 11(18): 16367−16379. https://doi.org/10.1021/acsami.9b03541

[48] W. Li, X. Meng, K. Peng, et al. Boosting microglial lipid metabolism *via* TREM2 signaling by biomimetic nanoparticles to attenuate the sevoflurane-induced developmental neurotoxicity. *Advanced Science*, 2024, 11(10): e2305989. https://doi.org/10.1002/advs.202305989

[49] L. Xu, Z. Xing, J. Yuan, et al. Ultrasmall nanoparticles regulate immune microenvironment by activating IL-33/ST2 to alleviate renal ischemia-reperfusion injury. *Advanced Healthcare Materials*, 2024, 13(13): e2303276. https://doi.org/10.1002/adhm.202303276

[50] X. Zhou, H. Liu, Y. Zheng, et al. Overcoming radioresistance in tumor therapy by alleviating hypoxia and using the HIF-1 inhibitor. *ACS Applied Materials & Interfaces*, 2020, 12(4): 4231−4240. https://doi.org/10.1021/acsami.9b18633

[51] G.C. Terstappen, A.H. Meyer, R.D. Bell, et al. Strategies for delivering therapeutics across the blood–brain barrier. *Nature Reviews Drug Discovery*, 2021, 20(5): 362−383. https://doi.org/10.1038/s41573-021-00139-y

[52] C. Betsholtz. Double function at the blood–brain barrier. *Nature*, 2014, 509(7501): 432−433. https://doi.org/10.1038/nature13339

[53] J.B. Foster, P.J. Madsen, M. Hegde, et al. Immunotherapy for pediatric brain tumors: Past and present. *Neuro-Oncology*, 2019, 21(10): 1226−1238. https://doi.org/10.1093/neuonc/noz077

[54] N.D. Doolittle, R. Fu, P. Ambady, et al. Primary central nervous system lymphoma and the blood-brain barrier. *Blood*, 2016, 128(22): 928. https://doi.org/10.1182/blood.V128.22.928.928

[55] A.R. Kline-Schoder, S. Chintamen, M.J. Willner, et al. Characterization of the responses of brain macrophages to focused ultrasound-mediated blood–brain barrier opening. *Nature Biomedical Engineering*, 2023, 8(5): 650−663. https://doi.org/10.1038/s41551-023-01107-0

[56] K. Piper, J.I. Kumar, J. Domino, et al. Consensus review on strategies to improve delivery across the blood-brain barrier including focused ultrasound. *Neuro-Oncology*, 2024, 26(9): 1545−1556. https://doi.org/10.1093/neuonc/noae087

[57] A.R. Rezai, P.F. D'Haese, V. Finomore, et al. Ultrasound blood–brain barrier opening and aducanumab in Alzheimer's disease. *The New England Journal of Medicine*, 2024, 390(1): 55−62. https://doi.org/10.1056/NEJMoa2308719

[58] Y. Meng, K. Hynynen, N. Lipsman. Applications of focused ultrasound in the brain: From thermoablation to drug delivery. *Nature Reviews Neurology*, 2020, 17(1): 7−22. https://doi.org/10.1038/s41582-020-00418-z

[59] H. Zhang, T. Wang, W. Qiu, et al. Monitoring the opening and recovery of the blood-brain barrier with noninvasive molecular imaging by biodegradable ultrasmall $Cu_{2-x}Se$ nanoparticles. *Nano Letters*, 2018, 18(8): 4985−4992. https://doi.org/10.1021/acs.nanolett.8b01818

[60] T. Wang, H. Zhang, Y. Han, et al. Reversing T cell dysfunction to boost glioblastoma immunotherapy by paroxetine-mediated GRK2 inhibition and blockade of multiple checkpoints through biomimetic nanoparticles. *Advanced Science*, 2023, 10(9): e2204961. https://doi.org/10.1002/advs.202204961

[61] N. Sanai, M.S. Berger. Surgical oncology for gliomas: The state of the art. *Nature Reviews Clinical Oncology*, 2017, 15(2): 112−125. https://doi.org/10.1038/nrclinonc.2017.171

[62] M. Weller, P.Y. Wen, S.M. Chang, et al. Glioma. *Nature Reviews Disease Primers*, 2024, 10: 33. https://doi.org/10.1038/s41572-024-00516-y

[63] J.L. Jiang, X.Y. Cui, Y.X. Huang, et al. Advances and prospects in integrated nano-oncology. *Nano Biomedicine and Engineering*, 2024, 16(2): 152−187. https://doi.org/10.26599/nbe.2024.9290060

[64] R. Medikonda, G. Dunn, M. Rahman, et al. A review of glioblastoma immunotherapy. *Journal of Neuro-Oncology*, 2021, 151(1): 41−53. https://doi.org/10.1007/s11060-020-03448-1

[65] G.P. Dunn, A.T. Bruce, H. Ikeda, et al. Cancer immunoediting: From immunosurveillance to tumor escape. *Nature Immunology*, 2002, 3(11): 991−998. https://doi.org/10.1038/ni1102-991

[66] A.R. Dix, W.H. Brooks, T.L. Roszman, et al. Immune defects observed in patients with primary malignant brain tumors. *Journal of Neuroimmunology*, 1999, 100(1-2): 216−232. https://doi.org/10.1016/S0165-5728(99)00203-9

[67] J.F. Zhao, A.X. Chen, R.D. Gartrell, et al. Immune and genomic correlates of response to anti-PD-1 immunotherapy in glioblastoma. *Nature Medicine*, 2019, 25(3): 462−469. https://doi.org/10.1038/s41591-019-0349-y

[68] H. Zhang, T.T. Wang, H.H. Liu, et al. Boost therapy of hepatocellular carcinoma by amplifying vicious cycle between mitochondrial oxidative stress and endoplasmic reticulum stress *via* biodegradable ultrasmall nanoparticles and old drug. *Nano Today*, 2022, 46: 101601. https://doi.org/10.1016/j.nantod.2022.101601

[69] S. Lakshmanachetty, S.S. Mitra. Mapping the tumor-infiltrating immune cells during glioblastoma progression. *Nature Immunology*, 2022, 23(6): 826−828. https://doi.org/10.1038/s41590-022-01223-0

[70] N. Nagarsheth, M.S. Wicha, W.P. Zou. Chemokines in the cancer microenvironment and their relevance in cancer immunotherapy. *Nature Reviews Immunology*, 2017, 17(9): 559−572. https://doi.org/10.1038/nri.2017.49

[71] P. Zhang, Y. Zhai, Y. Cai, et al. Nanomedicine-based immunotherapy for the treatment of cancer metastasis. *Advanced Materials*, 2019, 31(49): e1904156. https://doi.org/10.1002/adma.201904156

[72] Y.H. Zheng, Y.B. Han, T.T. Wang, et al. Reprogramming tumor-associated macrophages *via* ROS-mediated novel mechanism of ultra-small $Cu_{2-x}Se$ nanoparticles to enhance anti-tumor immunity. *Advanced Functional Materials*, 2022, 32(12): 2108971. https://doi.org/10.1002/adfm.202108971

[73] D.M. Pardoll. The blockade of immune checkpoints in cancer immunotherapy. *Nature Reviews Cancer*, 2012, 12(4): 252−264. https://doi.org/10.1038/nrc3239

[74] K.I. Woroniecka, K.E. Rhodin, P. Chongsathidkiet, et al. T-cell dysfunction in glioblastoma: Applying a new framework. *Clinical Cancer Research*, 2018, 24(16): 3792−3802. https://doi.org/10.1158/1078-0432.CCR-18-0047

[75] H. Zhang, L. Yang, M. Han, et al. Boost infiltration and activity of T cells *via* inhibiting ecto-5'-nucleotidase (CD73) immune checkpoint to enhance glioblastoma immunotherapy. *ACS Nano*, 2024, 18(34): 23001−23013. https://doi.org/10.1021/acsnano.4c04553

[76] T. Wang, M. Han, Y. Han, et al. Antigen self-presented personalized nanovaccines boost the immunotherapy of highly invasive and metastatic tumors. *ACS Nano*, 2024, 18(8): 6333−6347. https://doi.org/10.1021/acsnano.3c11189

[77] L.M.L. de Lau, M.M.B. Breteler. Epidemiology of

Parkinson's disease. *The Lancet Neurology*, 2006, 5(6): 525−535. https://doi.org/10.1016/S1474-4422(06)70471-9

[78] C.L. Ma, L. Su, J.J. Xie, et al. The prevalence and incidence of Parkinson's disease in China: A systematic review and meta-analysis. *Journal of Neural Transmission*, 2014, 121(2): 123−134. https://doi.org/10.1007/s00702-013-1092-z

[79] B. Brakedal, L. Toker, K. Haugarvoll, et al. A nationwide study of the incidence, prevalence and mortality of Parkinson's disease in the Norwegian population. *NPJ Parkinson's Disease*, 2022, 8: 19. https://doi.org/10.1038/s41531-022-00280-4

[80] E.R. Dorsey, T. Sherer, M.S. Okun, et al. The emerging evidence of the parkinson pandemic. *Journal of Parkinson's Disease*, 2018, 8(s1): S3−S8. https://doi.org/10.3233/JPD-181474

[81] T. Simuni, M.S. Okun. Adjunctive therapies in parkinson disease-have we made meaningful progress. *JAMA Neurology*, 2022, 79(2): 119−120. https://doi.org/10.1001/jamaneurol.2021.4140

[82] R. Gray, S. Patel, N. Ives, et al. Long-term effectiveness of adjuvant treatment with catechol-O-methyltransferase or monoamine oxidase B inhibitors compared with dopamine agonists among patients with parkinson disease uncontrolled by levodopa therapy: The PD MED randomized clinical trial. *JAMA Neurology*, 2022, 79(2): 131−140. https://doi.org/10.1001/jamaneurol.2021.4736

[83] PD MED Collaborative Group. Long-term effectiveness of dopamine agonists and monoamine oxidase B inhibitors compared with levodopa as initial treatment for Parkinson's disease (PD MED): A large, open-label, pragmatic randomised trial. *The Lancet*, 2014, 384(9949): 1196−1205. https://doi.org/10.1016/S0140-6736(14)60683-8

[84] A.J. Lees, J. Ferreira, O. Rascol, et al. Opicapone as adjunct to levodopa therapy in patients with parkinson disease and motor fluctuations: A randomized clinical trial. *JAMA Neurology*, 2017, 74(2): 197−206. https://doi.org/10.1001/jamaneurol.2016.4703

[85] O. Rascol, M. Fabbri, W. Poewe. Amantadine in the treatment of Parkinson's disease and other movement disorders. *The Lancet Neurology*, 2021, 20(12): 1048−1056. https://doi.org/10.1016/S1474-4422(21)00249-0

[86] J. Jankovic. Are adenosine antagonists, such as istradefylline, caffeine, and chocolate, useful in the treatment of Parkinson's disease. *Annals of Neurology*, 2008, 63(3): 267−269. https://doi.org/10.1002/ana.21348

[87] K. McFarthing, S. Buff, G. Rafaloff, et al. Parkinson's disease drug therapies in the clinical trial pipeline: 2024 update. *Journal of Parkinson's Disease*, 2024, 14(5): 899−912. https://doi.org/10.3233/JPD-240272

[88] D. Furtado, M. Björnmalm, S. Ayton, et al. Overcoming the blood-brain barrier: The role of nanomaterials in treating neurological diseases. *Advanced Materials*, 2018, 30(46): e1801362. https://doi.org/10.1002/adma.201801362

[89] W.J. Gordián-Vélez, D. Chouhan, R.A. España, et al. Restoring lost nigrostriatal fibers in Parkinson's disease based on clinically-inspired design criteria. *Brain Research Bulletin*, 2021, 175: 168−185. https://doi.org/10.1016/j.brainresbull.2021.07.016

[90] D.M. Wilson, M.R. Cookson, L. Van Den Bosch, et al. Hallmarks of neurodegenerative diseases. *Cell*, 2023, 186(4): 693−714. https://doi.org/10.1016/j.cell.2022.12.032

[91] R.Y. Zhang, X.T. Chen, Y.Y. Cheng, et al. Recent advances of nanomaterials for intervention in Parkinson's disease in the context of anti-inflammation. *Coordination Chemistry Reviews*, 2024, 502: 215616. https://doi.org/10.1016/j.ccr.2023.215616

[92] C. Olanow, W. Tatton. Etiology and pathogenesis of Parkinson's disease. In: *Annual Review of Neuroscience*, 1999, 22: 123−144. https://doi.org/10.1146/annurev.neuro.22.1.123

[93] M. Abdelmonem, N. Saad, H.F. Teh, et al. Curcumin-loaded PEG-coated magnetite nanoparticles synthesized from *Theobroma cocoa*: Neuronal biocompatibility and anti-inflammatory properties in SH-SY5Y and RAW 264.7 cells. *Nano Biomedicine and Engineering*, 2024, 16(3): 386−401. https://doi.org/10.26599/nbe.2024.9290099

[94] S.P. Yun, T.I. Kam, N. Panicker, et al. Block of A1 astrocyte conversion by microglia is neuroprotective in models of Parkinson's disease. *Nature Medicine*, 2018, 24(7): 931−938. https://doi.org/10.1038/s41591-018-0051-5

[95] T. Bartels, S. De Schepper, S. Hong. Microglia modulate neurodegeneration in Alzheimer's and Parkinson's diseases. *Science*, 2020, 370(6512): 66−69. https://doi.org/10.1126/science.abb8587

[96] H.Y. Yu, Q. Chang, T. Sun, et al. Metabolic reprogramming and polarization of microglia in Parkinson's disease: Role of inflammasome and iron. *Ageing Research Reviews*, 2023, 90: 102032. https://doi.org/10.1016/j.arr.2023.102032

[97] M. Guo, J. Wang, Y. Zhao, et al. Microglial exosomes facilitate α-synuclein transmission in Parkinson's disease. *Brain*, 2020, 143(5): 1476−1497. https://doi.org/10.1093/brain/awaa090

[98] C. Roodveldt, L. Bernardino, O. Oztop-Cakmak, et al. The immune system in Parkinson's disease: What we know so far. *Brain*, 2024, 147(10): 3306−3324. https://doi.org/10.1093/brain/awae177

[99] V. Joers, M.G. Tansey, G. Mulas, et al. Microglial phenotypes in Parkinson's disease and animal models of the disease. *Progress in Neurobiology*, 2017, 155: 57−75. https://doi.org/10.1016/j.pneurobio.2016.04.006

[100] X.M. Hu, R.K. Leak, Y.J. Shi, et al. Microglial and macrophage polarization—New prospects for brain repair. *Nature Reviews Neurology*, 2014, 11(1): 56−64. https://doi.org/10.1038/nrneurol.2014.207

[101] M. Vidović, M.G. Rikalovic. Alpha-synuclein aggregation pathway in Parkinson's disease: Current status and novel therapeutic approaches. *Cells*, 2022, 11(11): 1732. https://doi.org/10.3390/cells11111732

[102] J.N. Wang, L.J. Dai, S.C. Chen, et al. Protein–protein interactions regulating α-synuclein pathology. *Trends in Neurosciences*, 2024, 47(3): 209−226. https://doi.org/10.1016/j.tins.2024.01.002

[103] B.N. Li, X. Xiao, M.X. Bi, et al. Modulating α-synuclein propagation and decomposition: Implications in Parkinson's disease therapy. *Ageing Research Reviews*, 2024, 98: 102319. https://doi.org/10.1016/j.arr.2024.102319

[104] N. Mizushima, M. Komatsu. Autophagy: Renovation of cells and tissues. *Cell*, 2011, 147(4): 728−741. https://doi.org/10.1016/j.cell.2011.10.026

[105] K.H. Kim, M.S. Lee. Autophagy—a key player in cellular and body metabolism. *Nature Reviews Endocrinology*, 2014, 10(6): 322−337. https://doi.org/10.1038/nrendo.2014.35

[106] B.N. Lizama, C.T. Chu. Neuronal autophagy and mitophagy in Parkinson's disease. *Molecular Aspects of Medicine*, 2021, 82: 100972. https://doi.org/10.1016/j.mam.2021.100972

[107] S. Engelender. Ubiquitination of α-synuclein and autophagy in Parkinson's disease. *Autophagy*, 2008, 4(3): 372−374. https://doi.org/10.4161/auto.5604

[108] M. Xilouri, T. Vogiatzi, K. Vekrellis, et al. Alpha-synuclein degradation by autophagic pathways: A potential key to Parkinson's disease pathogenesis. *Autophagy*, 2008, 4(7): 917−919. https://doi.org/10.4161/auto.6685

[109] I. Choi, Y.X. Zhang, S.P. Seegobin, et al. Microglia clear neuron-released α-synuclein *via* selective autophagy and prevent neurodegeneration. *Nature Communications*, 2020, 11: 1386. https://doi.org/10.1038/s41467-020-15119-w

[110] M.A. Lynch-Day, K. Mao, K. Wang, et al. The role of autophagy in Parkinson's disease. *Cold Spring Harbor Perspectives in Medicine*, 2012, 2(4): a009357. https://doi.org/10.1101/cshperspect.a009357

[111] M.J. Caterina, M.A. Schumacher, M. Tominaga, et al. The capsaicin receptor: A heat-activated ion channel in the pain pathway. *Nature*, 1997, 389(6653): 816−824. https://doi.org/10.1038/39807

[112] B.H. Li, Y.W. Yin, Y. Liu, et al. TRPV1 activation impedes foam cell formation by inducing autophagy in oxLDL-treated vascular smooth muscle cells. *Cell Death & Disease*, 2014, 5(4): e1182. https://doi.org/10.1038/cddis.2014.146

[113] F.A. Iannotti, V. Di Marzo, S. Petrosino. Endocannabinoids and endocannabinoid-related mediators: Targets, metabolism and role in neurological disorders. *Progress in Lipid Research*, 2016, 62: 107−128. https://doi.org/10.1016/j.plipres.2016.02.002

[114] A.M. Bode, Z.G. Dong. The two faces of capsaicin. *Cancer Research*, 2011, 71(8): 2809−2814. https://doi.org/10.1158/0008-5472.can-10-3756

[115] S.R. Subramaniam, M.F. Chesselet. Mitochondrial dysfunction and oxidative stress in Parkinson's disease. *Progress in Neurobiology*, 2013, 106: 17−32. https://doi.org/10.1016/j.pneurobio.2013.04.004

[116] S. Mullin, A. Schapira. α-synuclein and mitochondrial dysfunction in Parkinson's disease. *Molecular Neurobiology*, 2013, 47(2): 587−597. https://doi.org/10.1007/s12035-013-8394-x

[117] K.C. Ryan, J.T. Laboy, K.R. Norman. Deregulation of mitochondrial calcium handling due to presenilin loss disrupts redox homeostasis and promotes neuronal dysfunction. *Antioxidants*, 2022, 11(9): 1642. https://doi.org/10.3390/antiox11091642

[118] Q. Zheng, H.H. Liu, Y.F. Gao, et al. Ameliorating mitochondrial dysfunction for the therapy of Parkinson's disease. *Small*, 2024, 20(29): 2311571. https://doi.org/10.1002/smll.202311571

[119] J.X. Yuan, L.Y. Xu, Y.B. Han, et al. Boosting neurite outgrowth and anti-oxidative stress for treatment of Parkinson's disease by biomimetic ultrasmall nanoparticles. *Sustainable Materials and Technologies*, 2024, 39: e00807. https://doi.org/10.1016/j.susmat.2023.e00807

[120] Y. Xu, Y.W. Gao, Y. Yang. SC79 protects dopaminergic neurons from oxidative stress. *Oncotarget*, 2018, 9(16): 12639−12648. https://doi.org/10.18632/oncotarget.23538

[121] S. Jiang, H. Wang, C. Yang, et al. Phase 1 study of safety and preliminary efficacy of intranasal transplantation of human neural stem cells (ANGE-S003) in Parkinson's disease. *Journal of Neurology Neurosurgery and Psychiatry*, 2024, 95(12): 1102−1111. https://doi.org/10.1136/jnnp-2023-332921

[122] Y. Sun, J. Kong, X. Ge, et al. An antisense oligonucleotide-loaded blood-brain barrier penetrable nanoparticle mediating recruitment of endogenous neural stem cells for the treatment of Parkinson's disease. *ACS Nano*, 2023, 17(5): 4414−4432. https://doi.org/10.1021/acsnano.2c09752

[123] L.S. Mendonça, C. Nóbrega, H. Hirai, et al. Transplantation of cerebellar neural stem cells improves motor coordination and neuropathology in Machado-Joseph disease mice. *Brain*, 2015, 138(2): 320−335. https://doi.org/10.1093/brain/awu352

[124] D. Ziavra, G. Makri, P. Giompres, et al. Neural stem cells transplanted in a mouse model of Parkinson's disease differentiate to neuronal phenotypes and reduce rotational deficit. *CNS & Neurological Disorders Drug Targets*, 2012, 11(7): 829−835. https://doi.org/10.2174/1871527311201070829