

Research progress in synergistic multimechanism of nanomaterial-mediated neuroinflammatory therapy (Review)

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Abstract. Neuroinflammation treatment faces notable challenges such as low blood-brain barrier (BBB) penetration, poor targeting and systemic toxicity, limiting traditional therapies due to inefficient drug delivery and bioavailability. Nanomaterials have innovatively reshaped this paradigm through multiple mechanisms. The present review elaborates core strategies in immunocyte phenotype regulation, oxidative stress intervention and targeted delivery, focusing on modulating microglia transition from pro-inflammatory to repair states, constructing systems for reactive oxygen species regulation and developing biomimetic carriers for BBB penetration and lesion targeting. The present review highlights technical bottlenecks in long-term biosafety evaluation, cross-organ metabolic mechanism analysis and clinical translation standardization.

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1. Introduction

Neuroinflammation is a central nervous system (CNS) response to injury, infection or deposition of abnormal proteins (1), and its triggering mechanism primarily involves a synergistic interaction between the major glial cells (microglia and astrocytes) and peripheral immune cells (such as monocytes, neutrophils and lymphocytes) within the

CNS. Inflammatory responses are triggered between cells by the release of inflammatory mediators such as cytokines, histamine and reactive oxygen species (ROS). Microglia, as resident immune cells in the CNS, exert neuroprotective effects and maintain an anti-inflammatory environment by releasing neurotrophins under normal physiological conditions (2,3). When an imbalance of immune homeostasis in the CNS and its association with neurodegenerative lesions occurs, microglia move toward the site of injury and after recognizing pathological molecules through pattern recognition receptors (such as Toll-like receptor 4), activate the NF- κ B signaling pathway and the NLRP3 inflammasome, triggering the sustained secretion of proinflammatory factors, such as IL-1 β , TNF- α and other proinflammatory factors, which are rendered as a proinflammatory phenotype (4). An inflammatory microenvironment is formed locally in the lesion area, which directly induces neuronal mitochondrial dysfunction and promotes synaptic phagocytosis through activation of the complement system, thus leading to neuronal death and progression of neurodegenerative diseases. Astrocytes present a dual role in inflammation (5), amplifying the inflammatory response through upregulation of IL-6, C3 complement and chemokines (CXCL10) via the Sig-1 receptor/NF- κ B pathway (6); on the other hand, they support neuronal survival through the secretion of glial cell-derived neurotrophic factor and antioxidant enzymes (7). Peripheral immune cells invade the CNS through the damaged blood-brain barrier (BBB) or choroid plexus, where monocyte-differentiated macrophages migrate towards the site of inflammation and participate in the removal of pathogens and cellular debris, but over-activation may lead to neuronal damage (8). The BBB protects the CNS from foreign substances through its tight junction structure and efflux transporters; however, it also severely impedes the effective delivery of >98% of small-molecule drugs and the vast majority of macromolecular therapeutics (9). Even for the few drugs capable of passive diffusion into the brain, non-specific distribution and rapid metabolic clearance often result in drug concentrations at the lesion site far below the therapeutic threshold, leading to low bioavailability (10). To achieve effective therapeutic concentrations in the CNS, systemic increases in dosage are often required, which in turn exacerbates drug accumulation in non-target tissues and organs, causing systemic toxic side effects and potentially directly inhibiting neuronal function (11). Furthermore, even if traditional small-molecule drugs manage to cross the BBB,

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they generally lack retention capacity within brain tissue and specificity for targeting diseased cells, making it difficult to exert sustained effects within the inflammatory microenvironment; their efficacy is thus transient and limited (12). *In situ* injection at the injury site, while bypassing the BBB, can cause physical injury to the neural microenvironment during the procedure, increasing the risks of glial scar formation, oxidative stress and even secondary infection, thereby limiting their clinical application (13). Collectively, these factors constitute the core dilemma in neuroinflammatory drug therapy; the difficulty in balancing delivery efficiency with therapeutic effectiveness.

Nanomaterials have unique advantages over conventional drugs in anti-neuroinflammatory therapy. Nanomaterials have unique physicochemical properties; in terms of size effect, nanomaterials with a particle size of 5-200 nm can achieve efficient transmembrane transport through receptor-mediated transcytosis, while modulation of the particle size of nanomaterials can markedly affect the kinetics of endothelial cellular uptake (14), which can notably improve the bioavailability of drugs. The surface of nanomaterials is modifiable for precise targeted delivery, and specific binding to specific inflammatory cells or molecules, such as microglia and astrocytes, can be achieved through surface modification, thus improving therapeutic precision (15-17). Charge modification can also be achieved through molecular engineering to modulate the electrostatic interactions of nanocarriers with vascular endothelial or glial cells or through targeted modification of functional groups (such as amino and carboxyl groups) on the surface of nanomaterials to provide molecular anchoring sites for the coupling of targeted ligands to prolong systemic cycling time (18). Nanomaterials are also biocompatible and do not trigger notable immune responses or inflammation, helping to minimize adverse effects during treatment (19). These synergistic mechanisms provide precise molecular interventions to modulate glial cell polarization, inhibit inflammatory vesicle activation and block pro-inflammatory signaling pathways. A schematic diagram (Fig. 1) illustrating the multifaceted mechanisms of nanomaterials in treating neuroinflammation (including immunophenotype modulation, oxidative stress intervention and targeted BBB drug delivery) is presented.

The mechanisms and etiologies of neuroinflammation vary across different CNS diseases, making it important to clarify the disease spectrum addressed in this article. The present review focused on conditions where neuroinflammation acts as a core pathological driver or aggravating factor. Neurodegenerative diseases, such as Alzheimer's disease and Parkinson's disease, represent one domain, with core features involving the interplay between chronic inflammation and pathological protein aggregates, mediated by microglia and astrocytes. Another domain includes acute CNS injuries, such as ischemic stroke and traumatic brain or spinal cord injury, which are characterized by intense and temporally organized inflammatory cascades. The third domain comprises autoimmune-mediated demyelinating diseases, such as multiple sclerosis and its experimental models, where neuroinflammation is predominantly driven by peripheral immune cell infiltration and attacks on central myelin. The studies cited in the present review are based on *in vitro* cellular models or *in vivo* animal models relevant to human diseases. By defining

this scope, the present article aimed to associate classifications of nanomaterials with their mechanisms of action within clear pathological contexts, providing a logical framework for analyzing their translational potential and existing challenges.

2. Classification and characterization of nanomaterials

Based on the chemical composition and structural features, there are a large variety of nanomaterials for biomedical use (20). Nanomaterials have a wide range of applications in drug delivery and therapeutic systems, especially in improving the stability and bioavailability of drugs (21). The therapeutic efficacy and safety can be markedly improved by selecting appropriate nanomaterials and designing rational delivery systems. In biomedical applications, nanomaterials often form composite systems with biomaterials. This composite nature makes it difficult to classify them using the traditional organic/inorganic binary framework. This multidimensional classification system effectively reflects the development of interdisciplinary integration and functional integration of bio-nanomaterials.

Inorganic nanomaterials can be carriers for delivery due to their unique physicochemical properties (22). Metallic nanomaterials can be altered in shape and size depending on the therapeutic need and can be modified to attach various types of chemical functional groups (23). This allows the metal nanomaterials section to attach and bind a variety of ligands, including drugs, antibodies, peptides and polymers, showing marked potential. These nanoparticles include iron oxide nanoparticles, silver nanoparticles, cerium oxide nanoparticles, zinc oxide nanoparticles (ZnONPs), gold nanoparticles (AuNPs) and platinum nanoparticles (24). For example, AuNPs can be modified on the surface of the piezoelectric material barium titanate (BaTiO_3) by *in situ* growth to construct Schottky heterojunctions (Au@BT), which can catalyze the reduction of H^+ for continuous hydrogen production, selectively scavenge ROS to alleviate the oxidative stress, effectively protect neuronal cells from hydroxyl radical damage and maintain cell viability (25). ZnONPs have neuroprotective properties, and ZnONPs can notably reduce the level of oxidative stress at biologically safe concentrations, enhance the antioxidant capacity by upregulating the expression of superoxide dismutase (SOD)1 and SOD2 and effectively inhibit the decrease of mitochondrial membrane potential and improve the function of mitochondrial energy metabolism (26). Fe_3O_4 nanoparticles are well biocompatibility, providing a physical basis for CNS drug delivery Fe_3O_4 integrates ferulic acid and simvastatin through disulfide bonds, synergistically exerting antioxidant, anti-inflammatory and neurotrophic functions, which effectively improves cognitive deficits and enhances memory retention in Alzheimer's disease (AD) model rats (27).

Quantum dots (QDs), which are nanoscale semiconductor particles with size-tunable optical and electronic properties, as nanomaterials show unique advantages in medical diagnostics and therapeutics. QDs can be efficient imaging probes and drug carriers due to their tunable optical properties, small sizes, and the ability to be chemically modified on the surface (28). QDs can be engineered with surface-conjugated targeting ligands to specifically recognize and bind to receptors on brain endothelial cells. This triggers receptor-mediated

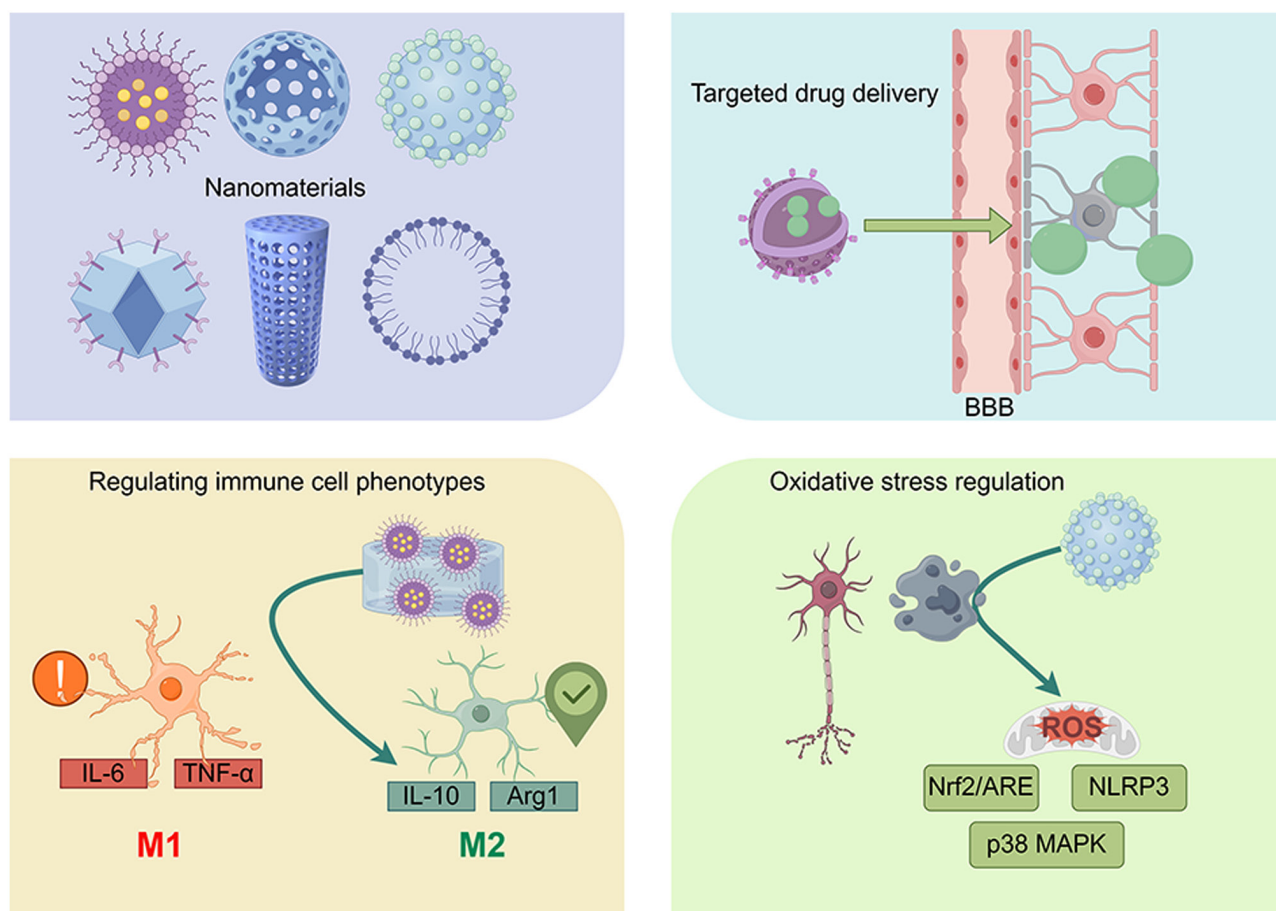


Figure 1. Mechanisms of nanomaterial-based therapy for neuroinflammation. Schematic illustrates the multi-faceted therapeutic actions of nanomaterials, which include modulating immune cell phenotypes, intervening in oxidative stress pathways and facilitating targeted drug delivery across the blood-brain barrier. The figure was prepared using www.figdraw.com). BBB, blood brain barrier.

transcytosis, enabling the targeted delivery of drugs across the BBB into the brain (29). The composite system of QDs with superparamagnetic iron oxide nanoparticles showed synergistic effects in intraoperative navigation and photothermal therapy and enhanced the uptake efficiency of glioma cells through magnetic targeting guidance (30). QDs can be modified by surface functionalization to develop multifunctional nanoparticles, for example, covalently attaching β -cyclodextrins via aminobenzeneboronic acid cross-linking to the QDs surface and utilizing its hydrophobic cavity for efficient loading of dexamethasone to notably improve the efficiency of inducing osteogenic differentiation of human mesenchymal stem cells (31). As a novel semiconductor material, black phosphorus QDs (BP-QDs) can be used to achieve efficient delivery of small interfering RNA (siRNA) to human ovarian teratocarcinoma PA-1 cells by designing polyelectrolyte polymer-modified BP-QDs nanocarriers, which can markedly inhibit the mRNA expression of lysine-specific demethylase 1 in PA-1 cells, confirming the use of BP-QDs as a gene delivery system (32). Although QDs exhibit unique optical properties and surface functionalization advantages in therapeutic areas such as drug delivery and bioimaging, their potential neurotoxicity mechanisms and trans-organ biological effects still need to be evaluated, and it has been reported in the literature that carbon QDs (CQDs) can adversely affect organisms through respiratory exposure. Intranasal administration

of CQDs induced neurobehavioral deficits in mice, which manifested as reduced motor activity, anxiety-like behaviors and impaired spatial learning and memory abilities, and the mechanism was closely related to neuronal death in the cortex and hippocampus. It was also found that low-level accumulation of CQDs in brain tissue could cause neurological damage through metabolic reprogramming rather than direct neurotoxicity, highlighting the specificity of its indirect mechanism of action (33).

Carbon nanomaterials show unique potential in the treatment of neurological diseases, mainly including carbon nanotubes (CNTs) and graphene and their derivatives. CNTs can be categorized into single-walled CNTs and multi-walled (MWCNTs) based on their structural differences; they possess marked electrical conductivity, mechanical strength and a high specific surface area with tunable surface chemistry. Owing to these properties, they have been widely used in the diagnosis and treatment of neuropathological diseases, particularly in drug delivery (34). However, the hydrophobicity and potential toxicity of CNTs limit their biomedical applications and need to be modified by surfactants to reduce cytotoxicity and improve solubility (35). A study has shown that metal-catalyzed CNTs may trigger free radical generation, DNA damage and inflammatory responses, and their long-term biosafety needs to be further evaluated (36). The physicochemical properties of MWCNTs influence their transcriptomic profiles. In

particular, aspect ratio (length-to-diameter ratio) and specific surface area correlate with activation of inflammatory and acute phase response signaling pathways, revealing the critical role of these parameters in MWCNT-induced inflammatory responses (37).

Dendrimers (dendritic macromolecules) are nanoscale polymers consisting of branched layered structures with morphology similar globular proteins, with an outer layer enriched with functional groups, low dispersibility, size controllability and high surface modification capabilities, making them ideal drug delivery vehicles and imaging tools in neuroscience (38). Carbon polyamidoamine (PAMAM) is a widely studied class of dendritic macromolecules with diameters of 1–14 nm, markedly controllable nanostructures and modifiable surface functional groups (39). The surface functional groups of PAMAM can be chemically modified to adjust hydrophilicity, thereby adapting to physiological environments, enhancing the efficiency of drug delivery (40) and notably enhance drug bioavailability (41). Furthermore, PAMAM can also be used as a small interfering (si)RNA delivery system to inhibit specific protein expression in neurons (42). Surface-engineered modified G4-type PAMAM dendrimers reduce cytotoxicity through hydroxylation, penetrate the BBB barrier, load curcumin and exhibit anti-inflammatory effects by inhibiting astrocyte over-activation to achieve synergistic efficacy between drug delivery and its own therapeutic effects (43). A study developed a macrophage membrane biomimetic modified phosphorus dendrimer nano-delivery system, which integrates anti-inflammatory, antioxidant and vascular regeneration strategies through the synergistic delivery of fibronectin and edaravone, effectively regulating microglia polarization, inhibiting neuronal apoptosis and remodeling the ischemic brain microenvironment (44). Tailored peptide dendritic polymers can build multifunctional nano-delivery systems with unique star-shaped geometries, which markedly enhance neuronal membrane interactions and BBB penetration and exhibit potent neuroprotective effects with synergistic multi-mechanisms in multiple models of neurodegenerative pathologies, including Parkinson's disease and Alzheimer's disease (45).

Polymeric nanomaterials are nanocarriers prepared from natural or synthetic polymers that are biocompatible and biodegradable, and their design needs to be selected based on therapeutic target properties (46). Polymeric nanomaterials have demonstrated notable advantages in CNS drug delivery by prolonging drug duration of action through slow-release mechanisms, markedly increasing drug bioavailability and enhancing BBB penetration, which protects drugs from enzymatic degradation and facilitates targeted delivery of active molecules (47). Poly(ethylene glycol)-poly(lactic acid hydroxyacetic acid) [PEG-poly(lactic acid hydroxyacetic acid)] copolymer was used as a carrier to achieve synergistic efficacy between photodynamic therapy and anti-angiogenic therapy by loading photosensitizer and multi-target tyrosine kinase inhibitor, effectively inhibiting glioblastoma cell proliferation and angiogenesis (48). PEG-polycaprolactone block copolymer nanoparticles can form biomaterials with bifunctional targeting properties by covalently modifying the cell-penetrating peptide, Tat, and the targeting drug. Using PEG hydrophilic chain segments to reduce immunogenicity

and prolong *in vivo* circulation time, the Tat peptide facilitates nanoparticle penetration of the BBB through electrostatic interaction and energy-dependent transmembrane transport, and after *in vivo* intranasal administration, it can be efficiently delivered to the tumor region of the brain via the olfactory nerve pathway (49). In one study, a chitosan-based cationic polymer nanoparticle system was constructed, and rivastigmine was encapsulated in the hydrophobic core formed by chitosan and sodium tripolyphosphate by ionic gelation, and Tween 80 was introduced as a surfactant to optimize the performance of the formulation. By utilizing the mucosal adhesion of chitosan and the passive targeting properties of nanoparticles, effective delivery of the drug to CNS after oral and intranasal administration was achieved, modulating tau protein phosphorylation, NF- κ B inflammatory pathway and Nrf-2 antioxidant pathway and alleviating the Alzheimer's-like pathological process, such as neuronal loss, tau protein aggregation, and associated inflammatory and oxidative stress responses (50).

Liposomes are spherical vesicular nanocarriers composed of phospholipid bilayers with high biocompatibility and modifiability, which can effectively encapsulate hydrophilic and hydrophobic drugs and optimize drug release properties by modulating the lipid components, making them a notable tool for CNS drug delivery (51). The bilayer phospholipid structure of liposomes can effectively encapsulate pro-drugs and achieve targeted delivery through surface modification (52). Liposomes modified with specific peptides can notably improve drug accumulation efficiency in diseased tissues and prolong *in vivo* circulation time by binding to notably expressed receptors at inflammatory sites. Functionalized liposomes can facilitate drug crossing the BBB and improve therapeutic efficacy in CNS disease models (53). Some researchers have used dipalmitoyl phosphatidylcholine with cholesterol as a base and curcumin co-solubilized with lipids in organic solvents to form a homogeneous film for the development of liposomal drug-carrying system. The efficient encapsulation of drug molecules in the hydrophobic region within the phospholipid bilayer was realized, and the phospholipid bilayer structure effectively protected curcumin from hydrolysis and photodegradation (54). In addition, liposomes have good nasocerebral delivery efficiency and can be modified by PEG to modulate the spatial distribution. Surface charge regulates the targeted accumulation of drugs in specific brain regions via electrostatic interactions. Positively-charged liposomes demonstrate enrichment in the forebrain and olfactory bulb regions, whereas negatively-charged liposomes exhibit a predilection for distribution within the hindbrain and spinal cord pathways. The PEG modification markedly enhances the brain and spinal cord distribution efficiency by decreasing the macrophage clearance rate and prolonging the mucosal retention time (55).

The diverse categories of aforementioned nanomaterials are systematically summarized in Fig. 2.

3. Nanomaterial-based therapeutic strategies

Immune cell phenotypic regulation. In the pathological process of neuroinflammation, the regulation of immune cell phenotypes is a notable determinant of disease outcomes (56). CNS-resident microglia and peripherally infiltrated

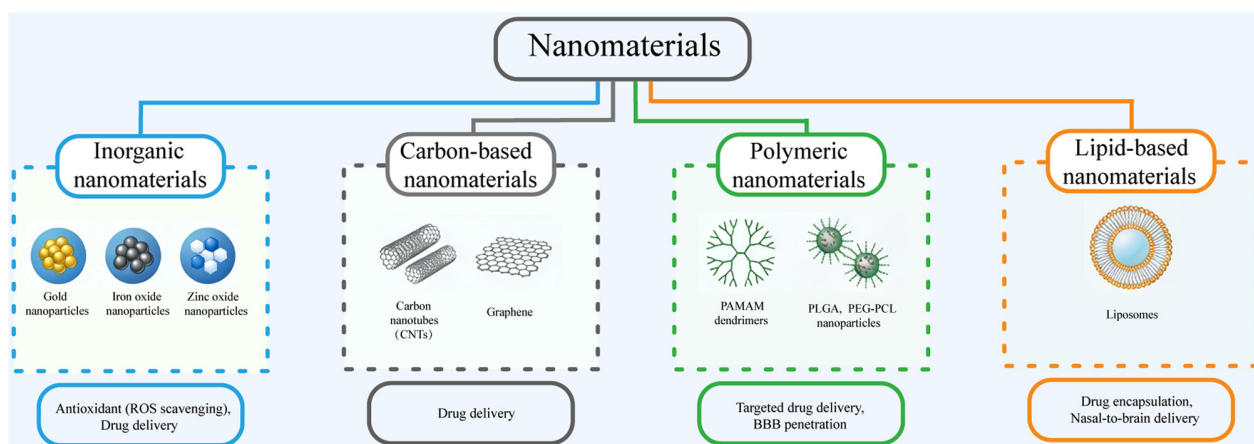


Figure 2. Main classifications of nanomaterials. Schematic diagram lists the key categories of nanomaterials discussed in the present review, including inorganic nanomaterials, carbon-based nanomaterials, polymer nanomaterials and lipid-based nanomaterials. The figure illustrates the typical structures, representative examples and primary application directions of each type. BBB, blood brain barrier; ROS, reactive oxygen species; PAMAM, polyamidoamine; PLGA, poly(lactic-co-glycolic acid); PEG-PCL, Poly(ethylene glycol)-polycaprolactone.

macrophages exhibit notable phenotypic plasticity, and their polarization direction influences the inflammatory balance within the local microenvironment (57). Microglia exist as a continuum with marked disease-stage specificity and spatial heterogeneity. In Alzheimer's disease models, the synergistic effects of A β and tau pathology induce disease stage-specific microglial subtypes. Among these, a distinct population termed late-stage AD-associated microglia emerges in the advanced stages of the disease. This subtype is characterized by a unique molecular signature that distinguishes it from other microglial populations activated during the disease process (58). Spatial multi-omics analysis further reveals that the functional state of microglia is closely linked to their precise anatomical location in the brain. Differences in microglial spatial distribution are notably associated with specific immune functions (59). Pro-inflammatory phenotypes exacerbate BBB disruption and neuronal degeneration by releasing inflammatory mediators such as TNF- α and IL-6, whereas anti-inflammatory phenotypes promote tissue repair and restoration of immune homeostasis through the secretion of molecules such as IL-10 and Arg1. Therefore, microglia present as a complex continuum that dynamically evolves with disease progression, spatial location and developmental stage. A recent study found that nanocarrier-based targeted delivery systems can cross CNS barriers to specifically modulate immune cell phenotypic polarization in lesion areas, achieving precise balance in the pro-inflammatory/anti-inflammatory cytokine microenvironment. This phenotype-specific intervention offers advantages over traditional broad-spectrum immunosuppressive therapies, as it avoids the risk of secondary infections associated with systemic immunosuppression (60).

The innovation in the design of nanomaterial delivery systems lies not only in the physical delivery ability to break through the central barrier, but also in the dynamic regulation of immune cell phenotype through the integration of biomimetic structures and molecular signals. Current research focuses on how nanomaterials can remodel the neuroinflammatory immune microenvironment through the integration of biomaterials and immunology. In the following section,

systematically analyzed how nanomaterials can remodel the pathological process of neuroinflammation through regulatory mechanisms by combining the design principles of various delivery systems.

Liposomes can be combined with hydrogels to construct a quercetin-based nanogel delivery system, which uses liposomes as drug carriers to enhance the ability of drug targeting and enrichment in the injured region, forming a long-lasting and slow-release platform, where the functionalized liposomes enable targeted drug delivery to the injury site, and the hydrogel ensures its sustained local release. This combined approach effectively induces microglia polarization towards the M2 anti-inflammatory phenotype, leading to the inhibition of pro-inflammatory factor secretion, upregulation of anti-inflammatory mediator expression and promotion of axonal regeneration (61). Intranasal administration of curcumin, which is self-assembled into pure drug nanoparticles and then encapsulated within a liposomal nano-delivery system, circumvents the BBB barrier restriction and releases the active component at the site of the lesion to synergistically modulate microglia reprogramming and inhibit pro-inflammatory factor secretion (62). Liposomes can be loaded with lactoferrin (Lf)-coupled astaxanthin (ASX) via a thiol-maleimide click chemistry to construct Lf-ASX-LPs, a nano-delivery system with brain-targeting properties. Functionalization of lactoferrin markedly enhances the liposomes' ability to penetrate across the BBB and the efficiency of neuronal cell uptake. It was found that Lf-ASX-LPs inhibited the release of pro-inflammatory factors mediated by the NF- κ B pathway in microglia, effectively reducing neuro-inflammatory responses. The mechanism of action involves Lf receptor-mediated transcellular transport to achieve brain-targeted delivery, as well as through the regulation of microglia microenvironmental homeostasis (63). Liposomes, modified with a platelet-neutrophil hybrid membrane coating, allow precise delivery of neutrophil elastase inhibitors to focal areas. By inhibiting elastase activity, the formation of neutrophil extracellular traps (NETs) is effectively blocked, which in turn inhibits the activation of the AIM2

inflammatory vesicle pathway by DNA components released from NETs. This immunomodulatory effect notably reduced the M1 polarization tendency of microglia by down-regulating the caspase-1-dependent inflammatory signaling pathway, breaking the cycle of neuroinflammation and providing ideas for immunometabolic reprogramming therapy (52). The study used bilayer phosphatidylserine-cholesterol/phosphatidylserine (PScho/PS) liposomes as the main material, carrying myelin basic protein peptide fragments. PScho/PS can notably inhibit the secretion of innate immune factors such as IL-1 β by pro-inflammatory macrophages and remodel immune homeostasis by promoting regulatory T cell (Treg) expansion while suppressing the differentiation of Th1/Th17 effector cells. Mechanistic studies have revealed that PScho/PS, by mimicking phospholipid signals on the surface of apoptotic bodies, is preferentially internalized by M2 anti-inflammatory macrophages, triggering immune tolerance-related pathways. During the recruitment phase of the immune response, PScho/PS inhibits the expression of the M1-associated chemokine receptor CCR7, reducing the recruitment of pro-inflammatory cells to inflammatory sites. In the activation phase, it suppresses the activation of Th1/Th17 cells by down-regulating the secretion of pro-inflammatory factors such as IL-1 β and IL-6; in the resolution phase, it promotes M2 phenotypic markers like CD206 and enhances Treg cell function to induce immune tolerance and inflammation resolution (64,65).

The hydroxyl-terminated polyamide-amine dendrimer (G4-PAMAM-OH) has BBB barrier penetration properties and can covalently couple the PPAR α/γ dual agonist, tesaglitazar (Tesa), to the surface of this nanocarrier via ester bonding, to construct a pH/esterase-responsive drug delivery system (D-Tesa). D-Tesa can target neuroinflammatory sites by enhancing the recruitment of microglia to lesion areas. During the activation phase, D-Tesa not only markedly inhibits the secretion of pro-inflammatory factors, such as nitric oxide in microglia, but also significantly upregulates the expression of anti-inflammatory factors, including interleukin-10 and interleukin-4. Furthermore, it enhances the expression of phagocytosis-related proteins, such as the scavenger receptor CD36, which is functionally correlated with an increased capacity for β -amyloid clearance. Its mechanism of action involves the synergistic activation of dual PPAR α/γ signaling pathways. By inhibiting NF- κ B nuclear translocation, it reduces the inflammatory cascade response, and by upregulating molecules such as Arg1 and CD36, it promotes the polarization of microglia toward an M2 phenotype (66). The PEG dendritic polymer PEGOL-60, featuring a high-density hydroxyl surface constructed via click chemistry, can penetrate the impaired BBB. Following systemic administration, it specifically accumulates in lesion areas, enhancing targeted recruitment of microglia and macrophages. The surface hydroxyl groups improve affinity for receptors on activated immune cells through charge interactions, promoting nanocarrier endocytosis. Additionally, PEGOL-60 itself exhibits marked antioxidant activity, reducing the secretion of inflammatory factors TNF- α and IL-6 in microglia while upregulating the expression of M2 phenotype markers, such as CD206, Arg1 and IL-4 (67).

Poly(lactic acid)-hydroxyacetic acid copolymer can be loaded with the antioxidant celastrol to construct a biomimetic

nanoplatform, which can achieve the precise regulation of the microenvironment in the injured area, and effectively remodel the neuroinflammatory microenvironment by scavenging excessive ROS and inducing the macrophage polarization from the M1 phenotype to the M2 phenotype. *In vitro* experiments have shown that it can reverse inflammation-induced mitochondrial dysfunction and promote neuronal synaptic regeneration, and *in vivo* studies have confirmed that it notably improves the recovery of motor function by inhibiting pro-inflammatory factor storms, decreasing glial scarring and promoting axonal myelin regeneration (68).

The mitochondria-targeted nanozyme triphenylphosphonium (TTP)-MoS₂ QDs, formed by covalently conjugating and distearoylphosphatidylethanolamine-PEG 2000 (DSPE-PEG-TTP) onto the surface of molybdenum disulfide QDs, possesses the ability to cross the BBB and exhibits mitochondrial targeting properties. It preferentially accumulates in lesion areas and influences the recruitment of microglia. During the inflammatory activation process, TPP-MoS₂ QDs target mitochondria to block ROS-mediated pro-inflammatory signaling pathways, downregulate the expression of pro-inflammatory factors IL-1 β , IL-6 and TNF- α , while upregulating the anti-inflammatory factor TGF- β . This promotes the shift of microglia from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype. In the inflammation resolution phase, M2-type microglia further alleviate neuroinflammation and promote neuronal survival by enhancing A β phagocytic clearance and secreting neuroprotective factors, forming a positive feedback regulatory loop that facilitates effective inflammation resolution (69).

Neuroinflammation not only involves resident glial cells within the CNS but also represents a dynamic process in which the continuous infiltration of the peripheral immune system plays a notable role (70). Disruption or dysfunction of the BBB provides a gateway for peripheral immune cells, such as monocyte-derived macrophages, neutrophils and lymphocytes, to enter the CNS, where they interact with microglia to form a complex neuroimmune network. For example, infiltrated monocytes/macrophages exhibit functional states in lesion areas that are similar yet heterogeneous to those of microglia, and their phenotype and activity directly influence inflammatory outcomes (71). T cell subsets further polarize glial cell phenotypes through the secretion of specific cytokines. Innovative design of nanomaterials offers novel strategies for precisely intervening in this immune axis. Through surface functionalization modifications, nanocarriers can specifically target adhesion molecules or selectins markedly expressed on BBB endothelial cells under inflammatory conditions, thereby competitively inhibiting the initial adhesion and rolling of immune cells and reducing infiltration at its source (72). Drug-loaded nanomaterials not only deliver therapeutics to lesions but can also interact directly with already infiltrated immune cells by mimicking apoptotic cell membranes or carrying specific ligands, promoting their shift toward anti-inflammatory or reparative phenotypes and accelerating inflammation resolution (73).

Oxidative stress regulation. Nanomaterials demonstrate unique neuroprotective mechanisms by regulating oxidative stress pathways, with their primary targets focusing on the

modulation of redox balance and inflammatory signaling pathways. By targeting key molecules involved in ROS metabolism, nanomaterials can effectively activate endogenous antioxidant defense systems. Under physiological conditions, ROS serve as notable secondary messengers, and their pathological role is defined by context-dependent thresholds, spatiotemporal dynamics and impaired cellular compensatory mechanisms (74). Therefore, the therapeutic goal of nanomaterials is to interrupt these maladaptive cycles in a cell-specific manner within critical time windows, not by completely eliminating ROS but by precisely targeting the sources of oxidative stress and its signaling consequences to restore redox homeostasis. Key pathological mechanisms intertwined with oxidative stress include mitochondrial dysfunction, ferroptosis, and the ROS-NLRP3 inflammasome amplification loop. This amplification loop constitutes a cycle central to neuroinflammation: Mitochondrial dysfunction or NADPH oxidase activation generates excessive ROS, which act as damage-associated molecular patterns (DAMPs) to activate the NLRP3 inflammasome (75). The activated NLRP3 inflammasome recruits and cleaves pro-caspase-1 into active caspase-1, which in turn processes pro-inflammatory cytokines IL-1 β and IL-18 into their mature, secreted forms, exacerbating the inflammatory response (76). Nanomaterials that target and scavenge mitochondrial ROS or inhibit NADPH oxidase can directly block the upstream ROS-mediated activation of NLRP3, severing this signaling cascade and achieving concomitant antioxidant and anti-inflammatory effects. Specifically, this oxidative stress is closely linked to inflammatory signaling, where extracellular ATP serves as a potent DAMP. ATP signaling can exacerbate mitochondrial ROS production and propagate inflammatory cell death cascades, forming a vicious cycle within the neuroinflammatory microenvironment (77). Moreover, nanocarriers notably reverse lipid peroxidation by re-establishing redox homeostasis. This re-establishment is achieved through synergistic mechanisms, including the activation of endogenous antioxidant pathways (for example, Nrf2/ARE), direct scavenging of reactive oxygen species (ROS), and suppression of key ROS generation sources, such as mitochondrial dysfunction. Lipid peroxidation, a major consequence of oxidative stress, leads to structural and functional damage to cell membranes, subsequently triggering neuronal degeneration. By modulating redox balance, nanomaterials effectively inhibit lipid peroxidation, enhance the activity of endogenous antioxidant enzymes and reduce the accumulation of oxidative stress byproducts.

By constructing a functionalized nanodelivery system, neuroinflammatory lesions can be precisely targeted; therefore, efficiently achieving delivery of antioxidant molecules. This strategy can markedly reduce ROS-mediated oxidative damage, restore neuronal redox homeostasis and inhibit glial cell hyperactivation, thereby alleviating the oxidative stress cascade in the neuroinflammatory microenvironment. The nanocarrier enhances the endogenous antioxidant defense system by modulating the Nrf2/ARE antioxidant signaling pathway, while selectively scavenging mitochondria-derived excess ROS and inhibiting NADPH oxidase activity, thereby blocking the positive feedback loop of oxidative stress-inflammation. In addition, the nanomaterials formed a therapeutic model of synergistic regulation of oxidative stress

and immune microenvironment by modulating immune cell phenotypic polarization (78). The antioxidant mechanism of Prussian blue-based nanoparticles (PBK NPs) originates from the electron transfer network of the iron-based catalytic center, which selectively neutralizes neurotoxic mediators such as superoxide anions and hydrogen peroxide. The near-infrared photothermal effect can induce local heating, which not only disrupts amyloid protein aggregates but also activates the cellular heat shock pathway, thereby enhancing the endogenous antioxidant defense system and alleviating neuroinflammation (79). Prussian blue analogues (Pb-Zr) show advantages in neuroinflammation regulation; Pb-Zr notably enhances active site exposure and free radical scavenging by introducing zirconium ions to optimize the crystal structure. Pb-Zr is able to improve the oxidative stress microenvironment by modulating zinc ion deposition and nucleation via Zr cations and by enhancing ROS scavenging through its nanozyme activities. Pb-Zr reduces the levels of lipid peroxidation products by mimicking the synergistic effects of SOD, catalase (CAT) and glutathione peroxidase (GPx). This antioxidant property down-regulated IL-6 and up-regulated arginase-1 to achieve immune homeostatic remodeling. In addition, Pb-Zr affected neuronal mitochondrial function by modulating zinc ion deposition behavior and notably reduced apoptosis-related protein expression (80). Human serum albumin (HSA)-embedded copper nanoclusters (CuNCs@HSA) based on HSA have a composite structure with ultra-small size and negative electrical surface properties. Its therapeutic effect stems from the regulation of the dynamic balance of oxidative stress, which synergistically scavenges ROS through SOD, CAT and GPx-like activities, while inhibiting the process of β -amyloid (A β) fibrosis. The antioxidant activity of CuNCs@HSA enhances endogenous antioxidant defenses through the modulation of the Nrf2/ARE signaling pathway and effectively reduces the microglia-activation-mediated neuroinflammatory factor storm (81). A research team constructed ROS-responsive liposomes based on thioether bond-modified phospholipids (specifically, 1,2-diarachidonoyl-sn-glycero-3-phosphocholine). Through TPP cation-mediated mitochondria-targeted delivery of quercetin, it can effectively enhance the release of antioxidant molecules at the lesion site, scavenge excessive mitochondrial ROS to maintain the redox balance of neuronal cells and inhibit energy metabolism disorders and apoptosis triggered by mitochondrial dysfunction. The nanosystem activates the SIRT1/FOXO3A signaling pathway, enhances the endogenous antioxidant system and at the same time blocks the p38 MAPK-mediated oxidative stress-inflammation effect, realizing the synergistic intervention of transcriptional regulation and kinase signaling pathway (82). PAMAM dendritic macromolecules can be selectively enriched in activated glial cells by modification with drug conjugation via disulfide bonds and achieve controlled drug release, activating endogenous antioxidant defense mechanisms through inhibition of glutamate carboxypeptidase II, reduction of extracellular glutamate and increase in anti-inflammatory cytokine TGF- β 1 to achieve synergistic alleviation of oxidative stress injury and neuroinflammatory responses (83). In addition, QDs can be enriched in microglia mitochondria through nano-enzymatic design to target and scavenge mitochondria-derived ROS, thereby inhibiting oxidative stress, with the mechanism involving

exerting nanozyme antioxidant activity to scavenge ROS and thereby inhibit the ROS-NLRP3 inflammasome signaling axis (84). However, surface functionalization is a key strategy for optimizing the biosafety of QDs. For example, molybdenum disulfide (MoS₂) QDs can be covalently modified with (3-carboxypropyl) TPP and 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[amino(PEG)-2000] (DSPE-PEG-NH₂) to form a composite material. The DSPE-PEG chains provide excellent water dispersibility and anti-protein adsorption capabilities, enhancing biocompatibility, reducing cytotoxicity and mitigating potential neurotoxicity risks associated with QDs (69).

Targeted drug delivery. Nanomaterials can effectively penetrate the BBB by leveraging their unique physicochemical properties, enabling targeted delivery to neuroinflammatory sites. Traditional systemic administration suffers from low efficiency and a high risk of systemic toxicity due to the selective permeability of the BBB and non-specific biodistribution (85). Nanomaterial-based targeted delivery strategies offer an innovative direction to address this issue by precisely regulating the spatiotemporal distribution characteristics of drugs. Under the trigger of pathological microenvironments, nanosystems can achieve controlled drug release through molecular structural rearrangement and cross cell membranes via endocytosis. Their surface modification and size regulation can markedly enhance their accumulation capability within the inflammatory microenvironment, increasing the local drug concentration (86). The synergistic effect of this precise delivery and regulation mechanism provides an innovative strategy for neuroinflammation therapy.

During receptor-mediated transcytosis, specific receptors can be utilized for directional transport, where nanocarriers modified with specific ligands are suitable material types. For instance, transferrin -modified brain-targeting liposomes can specifically recognize transferrin receptor 1, which is overexpressed on BBB endothelial cells under pathological conditions. They achieve efficient BBB crossing via receptor-mediated transcytosis, thereby delivering biologics such as monoclonal antibodies to the CNS (87). These nanocarriers encapsulate and preserve the bioactivity of monoclonal antibodies, enabling intra-neuronal drug release, inhibiting pathological protein fibril formation, consequently alleviating neuroinflammation and improving neuronal survival rates. This nanosystem can notably enhance the biodistribution of antibodies within the CNS, regulating proteostasis and glial cell activation states through multiple pathways, ultimately achieving neuroprotective effects and demonstrating favorable biocompatibility. Similarly, liposomes modified with leukocyte chemotactic peptides can achieve specific targeting to inflammatory sites by leveraging high affinity for formyl peptide receptors on immune cells such as neutrophils. Utilizing vascular leakage and active cell migration within inflammatory regions, these nanocarriers are targeted to the CNS. A study combined the use of C16 and Ang-1; C16 focuses on blocking the initial stage of immune cell infiltration, while Ang-1 focuses on repairing damaged BBB function. Although C16 possesses defined anti-inflammatory activity, its low solubility at physiological pH limits bioavailability, necessitating intervention from a nano-delivery system. By loading the complex onto leukocyte

chemotactic peptide-modified liposomal carriers, the drug solubility issue was resolved. This active targeting strategy enables the drug to cross the intact BBB and achieve a locally high concentration at demyelinating lesion sites (55).

Beyond active targeting, the inherent physicochemical properties of nanocarriers are also required for crossing the BBB via adsorption-mediated transcytosis or passive targeting mechanisms based on pathological microenvironments. Key factors include nanoscale size and surface charge, and suitable material types are represented by PAMAM dendrimers. Hydroxyl modification reduces the positive charge of the dendrimer, avoiding non-specific interactions with negatively charged components of the BBB, thereby promoting entry into the brain parenchyma through the compromised endothelial gaps of the damaged BBB and accumulation within the inflammatory microenvironment (88). Regarding drug selection, triptolide is a natural compound with marked immunomodulatory activity, but its clinical application is limited by toxicity and poor water solubility (89). Fourth-generation hydroxyl-terminated PAMAM dendrimers possess small size and near-neutral surface charge, which are key physical properties enabling passive crossing of the damaged BBB. This carrier is conjugated with retinoic acid via ester bonds and utilizes the low pH and esterase microenvironment within tumor cells to trigger drug release, thereby precisely regulating the STAT3 signaling pathway to inhibit pro-inflammatory phenotypic transformation (90). This delivery system can notably improve drug accumulation efficiency at lesion sites, remodel the neuroinflammatory microenvironment by reprogramming immune cell phenotypes, while reducing non-specific drug distribution in peripheral organs, effectively mitigating the toxicity associated with traditional administration. Sinomenine is a natural alkaloid with notable anti-inflammatory and antioxidant activities. One study covalently conjugated sinomenine to a PAMAM dendrimer carrier via an enzyme-sensitive linker, constructing a sinomenine nanoconjugate (D-Sino) (91). Leveraging its nanoscale size and neutral charge, this conjugate can reduce non-specific interactions with plasma proteins or healthy tissues, facilitating easier crossing through compromised BBB regions. Within the traumatic brain injury microenvironment, the enhanced phagocytic capacity of activated microglia enables further active uptake of this nanoconjugate. After cellular internalization, the conjugate can downregulate the expression of pro-inflammatory cytokines such as TNF- α and IL-1 β and alleviate oxidative stress damage by inhibiting NF- κ B signaling pathway activation (92). Animal model experiments showed that this system possesses good neuroinflammation targeting capability and can markedly mitigate acute-phase inflammatory responses (93).

After successful entry into brain tissue, further cell membrane penetration and intracellular delivery are key to exerting therapeutic efficacy. The key target cells are activated microglia and astrocytes. Carriers such as PAMAM dendrimers can diffuse rapidly within the brain and are ultimately specifically taken up by activated phagocytic glial cells. For example, a glutamate carboxypeptidase II (GCPII) inhibitor conjugated to a dendrimer can specifically target activated microglia and astrocytes in neuroinflammatory regions, leveraging the overexpression of GCPII on the glial

cell surface to enhance accumulation at the lesion site (91). Similarly, D-Sino can utilize the inflammation-targeting property of the nanocarrier to enhance active uptake of the drug by activated microglia, notably increasing the effective drug concentration within target cells (93).

Furthermore, intranasal administration offers a unique pathway that can directly bypass the BBB, the nose-to-brain pathway, enabling brain-targeted delivery via this route. When administered intranasally, nanoparticles can be delivered directly to the brain parenchyma bypassing the BBB via the olfactory nerve pathway. A short hairpin RNA plasmid based on RNA interference can specifically silence the key inflammatory mediators CCL20 and its receptor CCR6, precisely regulating the neuroimmune microenvironment. Using a PAMAM dendrimer polymer as the delivery carrier, combined intranasal and intravenous administration can achieve dual regulation targeting both the brain and peripheral immune organs. This delivery system effectively downregulated the expression of CCL20/CCR6 in brain tissue and the circulatory system, notably inhibited microglial activation and pro-inflammatory cytokine release and synergized with human mesenchymal stem cell transplantation to promote neuroregeneration by enhancing the activity of brain-derived neurotrophic factor and the neural stem cell proliferation marker Ki67 (94).

Integrated analysis of multi-mechanism synergistic therapy for neuroinflammation using nanomaterials. Neuroinflammation is a central pathological link in CNS diseases, the regulation of which requires multi-target intervention strategies. Although nanomaterials have demonstrated distinct advantages in immunomodulation, intervention of oxidative stress and targeted delivery, treatments relying on a single mechanism are often limited by the complexity of the pathological microenvironment. The research focus has gradually shifted from parallel mechanisms toward multi-mechanism synergy, achieving therapeutic advances through the integration of different pathways using nanomaterials. Such synergy is manifested not only through the physical co-delivery of therapeutic agents, but notably, by initiating crosstalk between upstream and downstream biological pathways to achieve systemic remodeling of neuroinflammation. The present section provides an in-depth analysis of the synergistic network of multi-mechanism actions mediated by nanomaterials in the treatment of neuroinflammation, with emphasis on the cross-talk between oxidative stress and immunomodulation, and on how targeted delivery enhances synergistic effects.

Oxidative stress and neuroinflammation form a tightly coupled positive-feedback loop, mutually driving each other and exacerbating neural damage (95). Excessive production of ROS can activate pro-inflammatory pathways such as NF- κ B, while inflammatory cytokines can further induce ROS bursts. Nanomaterials break this loop by mimicking antioxidant enzymes to directly scavenge ROS, while simultaneously modulating endogenous antioxidant pathways. Notably, this regulation of oxidative stress does not act in isolation but is closely linked to phenotypic switching of immune cells (96). A study has shown that cerium oxide nanoparticles <5 nm in diameter can efficiently eliminate multiple ROS species, including H_2O_2 , O_2^- and $\cdot\text{OH}$, through $\text{Ce}^{3+}/\text{Ce}^{4+}$

valence-state conversion, thereby blocking the NF- κ B inflammatory signaling pathway, inhibiting I κ B phosphorylation and degradation as well as P65 nuclear translocation (97). Ultimately this promotes the reversal of microglia from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype, achieving re-balancing of the immune microenvironment. This indicates that ROS not only serve as mediators of oxidative damage but also act as core signaling molecules regulating the functional plasticity of immune cells, offering precise intervention targets for remodeling the neuroinflammatory microenvironment via nano-antioxidant materials (97). Pb-Zr materials, while scavenging ROS, can down-regulate the pro-inflammatory cytokine IL-6 and up-regulate the anti-inflammatory cytokine TGF- β , promoting the conversion of microglia from M1 to M2 phenotype (80). The underlying synergistic mechanism lies in the fact that Pb-Zr regulates mitochondrial ROS production through zinc ions, inhibits activation of the ROS-NLRP3 inflammasome axis and thereby reduces caspase-1-mediated maturation and release of IL-1 β ; moreover, activation of the Nrf2 pathway can indirectly suppress NF- κ B transcription, achieving pathway-level synergy between antioxidant and anti-inflammatory signals and blocking amplification of inflammatory signaling (69,80). Similarly, mitochondria-targeted liposomes loaded with quercetin can scavenge mitochondrial ROS, inhibit p38 MAPK phosphorylation, reduce expression of M1 phenotypic markers and enhance transcription of M2-related genes via the SIRT1/FOXO3A pathway (82). This antioxidant-anti-inflammatory synergy has also been validated in Parkinson's disease models (98).

The spatiotemporal precision offered by targeted delivery is fundamental to realizing multi-mechanism synergy, as it ensures that therapeutic agents co-localize and act in concert at the lesion site. Targeted delivery systems enable precise localization to the lesion site, avoiding off-target effects while enhancing local synergistic concentrations through controlled release. For example, triptolide-loaded PAMAM dendrimers can target activated microglia via surface modifications, with ester-bond cleavage in acidic lysosomal environments leading to drug release, thereby specifically inhibiting the STAT3 pathway (99). Such targeting not only improves drug bioavailability but, by ensuring that different drug components reach effective therapeutic concentrations in the lesion area, achieves precise spatiotemporal synergy of mechanisms. Multifunctional nanozymes integrated with an IRF-5 siRNA system not only mimic the cascade reactions of natural antioxidant enzymes to efficiently scavenge ROS, but also, via the loaded IRF-5 siRNA, directly silence IRF-5 to block the polarization pathway of macrophages toward the pro-inflammatory M1 phenotype, promoting their conversion to the reparative M2 phenotype (100). This targeting ensures synchronous enrichment of antioxidant nanozymes and immunomodulatory siRNA in the lesion area, enabling direct regulation of macrophage phenotypes in the damaged region through the delivery system and thereby achieving precise spatiotemporal synergy of the two mechanisms. In Alzheimer's disease models, liposomes co-loaded with C16 peptide and Ang-1 can simultaneously block leukocyte infiltration and repair the BBB by enhancing endothelial junctions via the Ang-1/Tie2 pathway and inhibiting integrin-mediated leukocyte adhesion,

synergistically reducing neurovascular unit inflammation (53). Furthermore, stimuli-responsive nanocarriers can further optimize the timing of synergy. ROS-responsive disulfide-bond phospholipid (Di-S-PC) liposomes rapidly release quercetin in high-ROS environments; their release kinetics match the peak of inflammation, ensuring that antioxidant intervention exerts maximal efficacy during the inflammation-initiation phase (82). PBK NPs leverage near-infrared photothermal effects to simultaneously disaggregate A β fibrils and induce heat-shock-protein expression, achieving synergy between physical clearance and biochemical regulation (79).

The core of the synergistic effect lies in the interaction of signaling pathways. Nanomaterials such as TPP-MoS₂ QDs can restore electron-transport-chain function by targeting mitochondria, reducing ROS generation while promoting the expression of M2-related metabolic enzymes, thereby achieving metabolic-immune synergy (69). This synergistic effect extends beyond a single cell type, encompassing the complex intercellular communication network within the neuroinflammatory microenvironment, involving interactions among microglia, astrocytes, neurons and peripheral immune cells (6). Dysregulation of this communication exacerbates the inflammatory cascade, whereas nanomaterials can remodel this process through precise intervention. Biomimetic liposomes, via surface modifications that specifically bind to receptors on inflammatory cell surfaces, block pro-inflammatory signal transmission, inhibit neutrophil extracellular trap (NETosis)-mediated AIM2 inflammasome activation and thus reduce caspase-1-dependent inflammatory pathway activation, regulating microglial polarization (52). Moreover, dendritic polymer-based drug-delivery systems can modulate glutamate homeostasis between neurons and glial cells, promote the expression of anti-inflammatory factors and ultimately establish a multicellular synergistic anti-inflammatory network (83).

Therefore, the synergistic effects of nanomaterials are inherently a multi-level, dynamic process, resulting from the integration of multiple signaling pathways, including metabolic reprogramming, immune phenotypic switching and intercellular communication networks. Based on the distinct design of various nanocarrier systems, they have demonstrated marked potential for the targeted modulation of neuroinflammation across multiple CNS disease models. Their material types, loaded drugs, targets, associated disease models, administration routes and primary mechanisms are detailed in Table I. These multi-level therapeutic strategies are integrated in Fig. 3.

4. Discussion

Neuroinflammation, as a notable mechanism in the pathological process of the CNS, requires innovative therapeutic strategies to address the limitations of traditional therapies, such as BBB penetration efficiency, toxicity control and targeted delivery (87). Nanomaterials, with their unique physicochemical properties and modifiable biological functions, have reshaped the therapeutic approach to neuroinflammation through multiple mechanisms. At the fundamental mechanistic level, the surface modification of nanomaterials enables specific binding to certain cell types and molecular

targets (94), while their biocompatibility reduces the risk of treatment-related immune activation. Nanomaterials achieve precise regulation of the neuroinflammatory microenvironment through multi-level intervention strategies. At the level of immune cell phenotype regulation, dendritic macromolecules, liposomes and polymeric nanocarriers, by delivering gene-regulatory elements or small-molecule drugs, target and regulate the polarization of microglia/macrophages, inhibiting the expression of pro-inflammatory M1 phenotype markers, while simultaneously activating M2 anti-inflammatory phenotype-related pathways (101). This phenotype-specific intervention overcomes the limitations of traditional immunosuppressive therapies (102). At the level of oxidative stress regulation, nanomaterials clear ROS by mimicking the catalytic activity of endogenous antioxidants, while activating the Nrf2/ARE signaling pathway to enhance the antioxidant defense system of cells (103). Mitochondria-targeted nanocarriers precisely regulate mitochondrial membrane potential and energy metabolism, blocking the amplification effect of the ROS-NLRP3 inflammasome signaling axis (4,81). At the level of targeted delivery, nanomaterials construct multi-functional systems through molecular engineering-receptor-mediated BBB transport, pathology microenvironment-responsive drug release and biomimetic modification, markedly enhancing drug accumulation efficiency at the central lesion, while their sustained-release properties extend the therapeutic window and reduce systemic toxicity. The systematic integration of these innovative strategies marks the shift in neuroinflammation treatment from single-target inhibition to global regulation of the microenvironment, providing a new theoretical framework and technical pathway for interventions in CNS diseases such as neurodegenerative disorders, stroke and spinal cord injury.

Nanomaterials have shown marked potential in regulating neuroinflammation, yet their translation from basic research to clinical application faces notable challenges. The long-term safety and toxicity of nanomaterials, particularly their potential accumulation risk within the CNS, constitute a pivotal issue that drives the translation of this field from basic research toward clinical applications. Surface modification and the introduction of biocompatible coatings represent strategies for reducing their toxicity and optimizing biocompatibility. Surface coatings such as PEG, polyvinylpyrrolidone or biopolymers (such as chitosan) can be applied to nanoparticle surfaces through electrostatic interactions, covalent bonding or physical adsorption, thereby reducing nonspecific protein adsorption and immune recognition and avoiding rapid clearance by the mononuclear phagocyte system (104). For instance, PEGylated gold nanoparticles can notably prolong blood circulation half-life and promote brain-specific delivery (105). Functionalization through the conjugation of targeting ligands enhances tissue specificity and minimizes off-target effects in healthy tissues (106). These modifications not only optimize the pharmacokinetics of nanoparticles but also enable controlled degradation to prevent long-term accumulation. However, personalized design considering material type, coating thickness and physiological context is essential to ensure safe translation.

Furthermore, bioinspired functionalization represents another cutting-edge direction, such as the use of cell membrane-coated nanomaterials to confer homologous

Table I. Summary of nano-carrier systems for targeted modulation of neuroinflammation.

Material type	Drug/agent loaded	Target	Disease model	Administration route	Mechanism/action	(Refs.)
PEG-based dendrimer	-	Activated microglia/macrophages	Cerebral palsy/glioblastoma/macular degeneration	Intravenous injection	Specifically accumulates at the lesion site in activated glial cells, exerting antioxidant and anti-inflammatory effects.	(67)
Ditelluride-containing liposomes	Sivelestat	Neutrophil elastase	Ischemic stroke	Intravenous injection	Inhibits neutrophil elastase activity, effectively reduces NETs formation, blocks AIM2 inflammasome activation, modulates microglial phenotype and suppresses neuroinflammation.	(52)
fMLP-modified liposomes	C16 peptide and angiopoietin 1 compound	$\alpha v\beta 3$ integrin on endothelial cells (C16 peptide), Tie2 receptor (Ang-1)	Acute model of multiple sclerosis	Intravenous injection	Alleviates neuroinflammation, reduces demyelination and axonal injury, decreases neuronal apoptosis, increases surviving neuron count, improves BBB integrity and modulates microglial phenotype.	(53)
Liposome-hydrogel hybrid system	Quercetin	Chondroitin sulfate proteoglycans (targeted by CAQK peptide)	Mouse spinal cord injury model	Local <i>in-situ</i> injection	Enhances water solubility and bioavailability of quercetin while reducing cytotoxicity. Prolongs drug retention at the injury site. Effectively promotes polarization of microglia/macrophages towards the anti-inflammatory M2 phenotype, reduces neuronal apoptosis and inhibits glial scar formation.	(61)
ROS-responsive cardiolipin liposomes	Curcumin nanoparticles	A β aggregation/microglial TLR4/NF- κ B signaling pathway	Alzheimer's disease mouse model	Intranasal administration	Efficiently inhibits A β aggregation, promotes A β clearance, modulates microglial polarization, alleviates neuroinflammation and reduces neuronal damage.	(62)
Lactoferrin-modified liposomes	Astaxanthin	Lactoferrin receptors on BBB endothelial cells	Parkinson's disease mouse model	Intravenous injection	Improves water solubility and chemical stability of hydrophobic astaxanthin. Lactoferrin modification markedly enhances BBB penetration and brain accumulation. Inhibits the activation of astrocytes and microglia in the striatum and substantia nigra.	(63)
Phosphatidylserine-based liposomal nanoparticles	MBP peptide	Monocyte/macrophage system	Human multiple sclerosis (<i>in vitro</i>)	<i>In vitro</i> cell culture	Modulates macrophage phenotype and T-cell responses. PSCho/PS- MBP loaded with MBP peptide enhances Treg response to MBP while suppressing pro- inflammatory Th1/Th17 responses.	(64)

Table I. Continued.

Material type	Drug/agent loaded	Target	Disease model	Administration route	Mechanism/action	(Refs.)
PAMAM dendrimer	Tesaglitazar	Activated microglia	LPS-stimulated BV2 cells (<i>in vitro</i>)	<i>In vitro</i> cell culture	Induces microglial phenotypic switch, mitigates inflammatory damage, enhances microglial phagocytosis of A β , improves solubility of poorly water-soluble Tesaglitazar, and enables targeted release at the lesion site.	(66)
Biodegradable poly(lactic-co-glycolic acid) nanoparticles	Celastrol	Macrophages	Mouse spinal cord injury model	Oral administration	Scavenges ROS, modulates macrophage polarization, promotes neurite outgrowth, suppresses neuroinflammation and scar formation and facilitates motor function recovery.	(68)
TPP-MoS ₂ QDs	-	Mitochondria/microglia	Alzheimer's disease mouse model	Intravenous injection	Accumulates in the brain of Alzheimer's disease mice, specifically targets mitochondria, scavenges ROS, regulates cytokines and inflammation, induces microglial M2 phenotype, reduces A β deposition and provides neuroprotection.	(69)
PEGylated nanoliposomes	Berberine chloride	NLRP3/Caspase-1/GSDMD-mediated pyroptosis pathway	Imidacloprid-induced neurotoxicity rat model	Intravenous injection	Mitigates histopathological damage, exerts antioxidant effects, modulates microglial polarization, inhibits the pyroptosis pathway, reduces A β deposition and upregulates Nephrilysin expression.	(78)
Peptide-functionalized Prussian blue nanomaterials	-	RAGE receptors on the BBB	Alzheimer's disease mouse model	Intravenous injection	Scavenges ROS, penetrates the BBB, alleviates oxidative damage, reduces cerebral A β plaque deposition, mitigates neuroinflammation and repairs neuronal damage.	(79)
Zr-doped Prussian blue analogue nanomaterials	-	-	Mouse spinal cord injury model	Intraperitoneal injection	Scavenges ROS, inhibits expression of pro-inflammatory factors, promotes macrophage polarization towards the M2 phenotype, exerts anti-apoptotic effects, protects neurons and promotes functional recovery.	(80)
Human serum albumin-encapsulated copper nanoclusters	-	-	Alzheimer's disease cell model	<i>In vitro</i> culture	Possesses multiple antioxidant enzyme activities, inhibits A β aggregation and alleviates A β -induced oxidative stress and cytotoxicity.	(81)
ROS-responsive, mitochondria-targeted liposomes	Quercetin	Mitochondria/transcription factor FOXO3A	Rat retinal ischemia-reperfusion injury model	Intravitreal injection	Enables intelligent drug release at the lesion site, provides targeting and prolonged retention, exerts antioxidant and mitochondrial protective effects,	(82)

Table I. Continued.

Material type	Drug/agent loaded	Target	Disease model	Administration route	Mechanism/action	(Refs.)
					lowers levels of pro-inflammatory factors in retinal tissue, provides anti-apoptotic and neuronal protection, improves retinal function, upregulates the SIRT1/FOXO3A pathway and inhibits phosphorylation of the p38 MAPK pathway.	
Fourth-generation hydroxyl-terminated PAMAM dendrimer	2-(3-Mercaptopropyl) pentanedioic acid	Activated astrocytes and microglia	Rabbit cerebral palsy model	Intravenous injection	Enhances brain targeting and retention, inhibits glutamate excitotoxicity, promotes release of anti-inflammatory factors, improves microglial morphology and enhances neurobehavioral scores.	(83)
PAMAM nano-dendriplex	Plasmid DNA encoding shRNA to silence CCL20 and/or CCR6 genes	CCL20 chemokine and its receptor CCR6	Mouse repetitive traumatic brain injury model	Combined intranasal and intravenous injection	Dual-route administration ensures delivery of nanoplexes to the brain and spleen, achieving local and systemic gene silencing, which suppresses neuroinflammation, alleviates pathological damage, reduces neuronal degeneration, creates a reparative microenvironment, promotes neurotrophism and proliferation and improves behavioral function.	(93)
Fourth-generation hydroxyl-terminated PAMAM dendrimer	Sinomenine	Activated microglia/macrophages	Neonatal rabbit traumatic brain injury model	Intravenous injection	Enhances intracellular drug delivery, inhibits the NF-κB pathway, suppresses acute inflammation and enables controlled sustained drug release.	(91)
PEGylated liposomes	Fingolimod	-	Mouse neurovascular inflammation model	Intravenous injection	Reduces drug-induced erythrocyte toxicity, achieves targeted delivery, enhances therapeutic efficacy and improves pharmacokinetics.	(94)
PEG-coated cerium nanoparticles	-	ROS/NF-κB inflammatory signaling/microglial polarization balance	BV-2 cell oxygen-glucose deprivation/reperfusion model (<i>in vitro</i>)	<i>In vitro</i> cell culture	Efficiently scavenges multiple ROS, localizes to mitochondria and lysosomes, drives microglial M2 phenotype, modulates inflammatory factors, provides neuroprotection and inhibits the NF-κB pathway.	(97)
Neutrophil membrane-coated Mn ₃ O ₄	IRF-5 siRNA	ROS/macrophage polarization	Rat spinal cord injury model	Local implantation	Scavenges ROS, specifically targets inflammatory cells, reprograms macrophage phenotype, alleviates	(101)

Table I. Continued.

Material type	Drug/agent loaded	Target	Disease model	Administration route	Mechanism/action	(Refs.)
nanoflower-siRNA complex					neuroinflammation and scarring, promotes nerve regeneration and angiogenesis and improves motor function recovery.	

A β , Beta-amyloid; AIM2, Absent in melanoma 2; Ang-1, Angiopoietin-1; BBB, Blood-brain barrier; CAQK, a peptide sequence targeting chondroitin sulfate proteoglycans; CCL20, Chemokine (C-C motif) ligand 20; CCR6, CC chemokine receptor type 6; fMLP, N-Formylmethionyl-leucyl-phenylalanine; GSDMD, Gasdermin D; IRF-5 siRNA, small interfering RNA targeting interferon regulatory factor 5; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; MBP, myelin basic protein; NETs, neutrophil extracellular traps; NF- κ B, Nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP3, NOD-, LRR- and pyrin domain-containing protein 3; PAMAM, poly(amidoamine); PEG, polyethylene glycol; PSCho, phosphatidylserine; RAGE, receptor for advanced glycation end products; ROS, reactive oxygen species; shRNA, short hairpin RNA; TLR4, toll-like receptor 4; TPP-MoS2 QDs, triphenylphosphonium-modified molybdenum disulfide quantum dots; Treg, regulatory T cell.

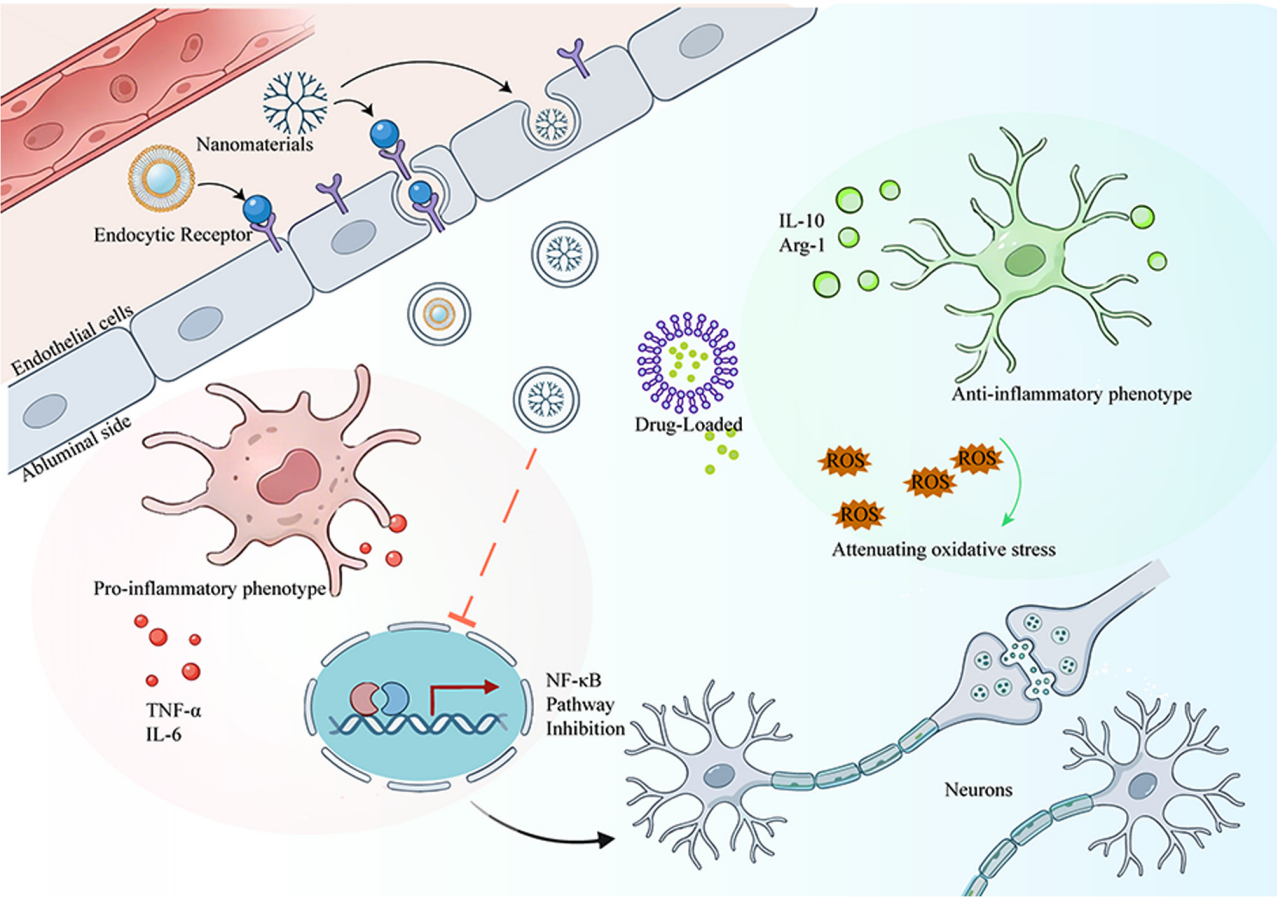


Figure 3. Schematic Diagram of the anti-inflammatory and neuroprotective mechanisms of nanomaterials. The schematic summarizes the key action pathways of drug-loaded nanomaterials in neuroinflammation. ROS, reactive oxygen species.

targeting and immune-evasion capabilities. This approach may offer new pathways for achieving long-term, safe circulatory monitoring and intervention of nanomaterials within the CNS. Endowing nanomaterials with microenvironment responsiveness, enabling them to react to specific signals at neuroinflammatory sites, is key to achieving precise therapeutic action while lowering off-target toxicity. Under

neuroinflammatory conditions, the CNS microenvironment undergoes a series of characteristic changes, including altered ATP concentrations and overexpression of specific proteases. Building on this, ROS-responsive nanomaterials can be designed; these materials or their functionalized shells remain stable in normal tissue but degrade rapidly around inflamed sites, releasing encapsulated drugs (107). Such a

mechanism-based strategy can greatly circumvent the risks of long-term and widespread metabolic interference.

Looking forward, the assessment and investigation of the long-term neuro-safety of nanomaterials should advance toward more systematic and prospective dimensions. Traditional approaches relying on measuring metal element content or histopathological observation are inadequate to dynamically track the real-time distribution, transformation status and long-term interactions of nanomaterials with various neural cell types in living brains. Emerging techniques such as isotope labeling, Raman imaging and *in vivo* imaging based on the intrinsic fluorescence of carbon materials will provide data for understanding their long-term biological behaviors (108). Current toxicity evaluations mostly focus on indicators like cell viability, oxidative stress and inflammatory cytokines (109). However, whether long-term retention of nanomaterials subtly influences neuronal electrophysiological properties, synaptic plasticity or even overall neural network function is central to assessing their long-term cognitive safety. This calls for in-depth exploration using techniques such as patch-clamp recording, multi-channel electrophysiology and *in vivo* calcium imaging. By fostering interdisciplinary collaboration among materials chemistry, nanotoxicology and neuroscience, and through proactive and intelligent material design strategies, it is the goal to ultimately enable the safe and successful application of nanomaterials in the clinical treatment of major CNS disorders, including neurodegenerative diseases and brain injuries.

For instance, carbon-based materials (such as carbon dots and carbon nanotubes), despite their excellent BBB penetration ability, have been found to interfere with the mitochondrial electron transport chain upon chronic low-dose exposure. This interference can lead to oxidative phosphorylation disorder and subsequent neuronal energy metabolism dysfunction (110), highlighting the need for long-term safety studies. The ion release behavior of metal nanoparticles may destroy the steady-state balance of essential trace elements such as zinc and copper and then affect synaptic plasticity (111). At present, there are few studies on the systematic evaluation of the immunogenicity of molecules modified on the surface of nanocarriers and the potential interaction between dendrimers and complement system has not been discussed. Although some studies have verified the cellular compatibility of PAMAM dendrimers, there is no experimental analysis on the possible risk of non-specific immune activation, and the related immunogenicity control mechanism and long-term biological safety have not been clearly clarified in the study (112). Moreover, the limited depth of mechanistic investigation hinders the achievement of precise treatment. At the level of mechanism research, most of the existing achievements focus on phenotypic observation (M1/M2 polarization characterization of macrophages and analysis of inflammatory factors), but there is a lack of systematic research on molecular pathways regulated by nanomaterials. The existing research has not effectively established the interaction between the physical and chemical characteristics of nanomaterials (such as particle size and ζ potential) and cell response mechanisms (such as endocytosis pathway selection and autophagy regulation). The causal relationship between the systematic effects (such as neurovascular unit remodeling, neural network regulation, neuroinflammatory

microenvironment regulation) produced by the combination of nano-materials and cells has not yet been clarified, and the transformation mechanism needs experimental verification. In addition, the clinical transformation of nanomaterials faces multiple technical problems. The existing preparation process is difficult to realize large-scale standardized production of nanomaterials, and the difference of particle size distribution between batches may lead to the change of biological distribution characteristics, so controlling particle size and particle size distribution is an important goal for the production of medical nanomaterials (113). Conventional nanofabrication methods, such as ionotropic gelation, thin-film hydration and emulsion solvent evaporation, typically rely on batch operations. Their mixing processes are constrained by laminar diffusion and the uncontrollability of manual handling, resulting in broad particle size distributions and inconsistent encapsulation efficiency. These inherent limitations notably hinder the clinical transformation of nanomedicines. Fortunately, emerging microfluidic technology offers a promising solution to address batch-to-batch variability in nanomaterial preparation. This technology enables precise manipulation of fluids within microscale channels with defined dimensions, markedly improving batch-to-batch consistency in attributes such as particle size, morphology and drug loading capacity (114). Research indicates that transitioning from traditional batch-based ionotropic gelation to microfluidic-based production processes not only yields drug-loaded nanoparticles with improved monodispersity but also maintains notably stable physicochemical properties and biological activity across different production batches (115), offering potential to overcome current translational bottlenecks. Pharmacokinetics of carrier-drug complex system needs systematic exploration (116); for example, the sustained-release characteristics of nanomaterials need to match the drug concentration needed in the focus area, and the drug concentration needed to be maintained in the focus area needs more in-depth research. The design of multi-mechanism synergistic therapy system is still in the primary stage, and it is difficult for single functional nanomaterials to cope with the multi-channel regulation of neuroinflammation. However, the differences in physical and chemical properties between components (such as hydrophilicity, hydrophobicity, surface charge and degradation rate) often lead to the differences in delivery efficiency *in vivo*. Finally, the lack of integration of interdisciplinary methodology limits the innovation breakthrough; the cross-study of materials science and neuroimmunology mostly stays at the level of phenotypic verification and fails to deeply explore the regulatory potential of nano-materials on neuroelectrical activity and immune signal transduction. The application of artificial intelligence and Qualcomm screening technology in the rational design of nano-carriers is still in its infancy, and it is difficult to realize the systematic modeling of the relationship between material characteristics and biological effects. These problems need to be solved through interdisciplinary cooperation and technological innovation.

To advance research in this field from basic studies toward clinical translation, the primary task is to establish a minimal safety dataset that surpasses traditional toxicity assessments. Concurrently, it is essential to evaluate the potential interference of material components with the homeostasis of trace

elements *in vivo*. The standardization process for clinical translation must be deeply aligned with regulatory logic. At the product level, standards such as endotoxin control, sterility assurance and formulation stability should be adopted in accordance with drug evaluation requirements. Regarding the strategic selection of the translational pathway, focus should be placed on the indications most likely to achieve proof-of-concept success first. Disease models characterized by focal lesions and suitable for local or regional administration, such as spinal cord injury or focal cerebral ischemia, hold distinct advantages. These models can partially circumvent the complexities of the BBB through strategies like intrathecal or intranasal administration, thereby enabling a more direct validation of the targeting and efficacy of the nanocarriers themselves. This approach provides a solid foundation for the design of subsequent clinical trials.

Facing the key bottleneck of current research, it is necessary to achieve breakthroughs in the future around biosafety optimization, in-depth analysis of action mechanism, clinical transformation and innovation and multi-mechanism coordination. First, in the aspect of material development, a new nano-system with high therapeutic function and biological safety should be studied and constructed, and establish a long-term toxicity evaluation platform for organ-like, so as to systematically track the influence of nano-materials on nerve metabolism. Secondly, it is necessary to deepen the study of molecular mechanism, reveal the interaction mode between nanocarriers and immune cell surface receptors and clarify the regulation mechanism of physical and chemical properties of materials on signal pathways. In the field of multi-mechanism collaboration, it is necessary to develop multi-functional integrated nano-systems to realize the synergy of anti-inflammatory, anti-oxidation and nerve regeneration. At the same time, the bionic delivery strategy is explored to improve the efficiency of lesion enrichment and reduce the risk of immune clearance. In addition, interdisciplinary cooperation should be strengthened, artificial intelligence should be used to screen new nanomaterials with specific immune regulation function and real-time dynamic regulation of treatment process should be realized by using optical signals or electrical signals through material science design. Finally, through the innovation of preclinical research paradigm, the development of individualized delivery scheme is developed and verified and the practical application transformation of nanomaterials in the treatment of neuroinflammation is promoted.

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Authors' contributions

HW conceptualized and designed the study, developed the methodology, including the literature search strategy and inclusion criteria, secured funding, performed the literature search, screening and formal analysis, prepared the figures and tables, and drafted the initial manuscript. PY participated in methodological design and validation of the search strategy, assisted in literature screening and formal analysis, and contributed to writing and critically reviewing the original draft. WL supervised the project and acquired funding, contributed to drafting the introduction and discussion, and performed thorough review and editing to enhance the intellectual content and clarity of the manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Sochocka M, Diniz BS and Leszek J: Inflammatory response in the CNS: Friend or Foe? *Mol Neurobiol* 54: 8071-8089, 2017.
2. Maugeri G, D'Agata V, Magri B, Roggio F, Castorina A, Ravalli S, Di Rosa M and Musumeci G: Neuroprotective Effects of physical activity via the adaptation of astrocytes. *Cells* 10: 1542, 2021.
3. Mesci P, LaRock CN, Jeziorski JJ, Nakashima H, Chermont N, Ferrasa A, Herai RH, Ozaki T, Saleh A, Snethlage CE, *et al*: Human microglial cells as a therapeutic target in a neurodevelopmental disease model. *Stem Cell Reports* 19: 1074-1091, 2024.
4. Barry-Carroll L and Gomez-Nicola D: The molecular determinants of microglial developmental dynamics. *Nat Rev Neurosci* 25: 414-427, 2024.
5. Ramos-García NA, Orozco-Ibarra M, Estudillo E, Elizondo G, Gómez Apo E, Chávez Macías LG, Sosa-Ortiz AL and Torres-Ramos MA: Aryl hydrocarbon receptor in post-mortem hippocampus and in serum from young, elder, and Alzheimer's patients. *Int J Mol Sci* 21: 1983, 2020.
6. Freitas NL, Gomes YCP, Souza FDS, Torres RC, Echevarria-Lima J, Leite ACCB, Lima MASD, Araújo AQC, Silva MTT and Espíndola OM: Lessons from the cerebrospinal fluid analysis of HTLV-1-infected individuals: Biomarkers of inflammation for HAM/TSP development. *Viruses* 14: 2146, 2022.
7. Wang JY, Ren P, Cui LY, Duan JY, Chen HL, Zeng ZR and Li YF: Astrocyte-specific activation of sigma-1 receptors in mPFC mediates the faster onset antidepressant effect by inhibiting NF- κ B-induced neuroinflammation. *Brain Behav Immun* 120: 256-274, 2024.
8. Jernigan JE, Staley HA, Baty Z, Bolen ML, Gomes BN, Holt J, Cole CL, Neighbarger NK, Dheeravath K, Merchak AR, *et al*: RGS10 attenuates systemic immune dysregulation induced by chronic inflammatory stress. *J Neuroinflammation* 22: 49, 2025.
9. Pardridge WM: The blood-brain barrier: Bottleneck in brain drug development. *NeuroRx* 2: 3-14, 2005.
10. Agarwal S, Manchanda P, Vogelbaum MA, Ohlfest JR and Elmquist WF: Function of the blood-brain barrier and restriction of drug delivery to invasive glioma cells: findings in an orthotopic rat xenograft model of glioma. *Drug Metab Dispos* 41: 33-39, 2013.

11. Abbott NJ, Patabendige AAK, Dolman DEM, Yusof SR and Begley DJ: Structure and function of the blood-brain barrier. *Neurobiol Dis* 37: 13-25, 2010.
12. Vieira DB and Gamarra LF: Getting into the brain: Liposome-based strategies for effective drug delivery across the blood-brain barrier. *Int J Nanomedicine* 11: 5381-5414, 2016.
13. Bahlakeh G, Rahbarghazi R, Mohammadnejad D, Abedelahi A and Karimipour M: Current knowledge and challenges associated with targeted delivery of neurotrophic factors into the central nervous system: focus on available approaches. *Cell Biosci* 11: 181, 2021.
14. Betzer O, Shilo M, Opochninsky R, Barnoy E, Motiei M, Okun E, Yadi G and Popovtzer R: The effect of nanoparticle size on the ability to cross the blood-brain barrier: An in vivo study. *Nanomedicine (Lond)* 12: 1533-1546, 2017.
15. Zhang F, He X, Dong K, Yang L, Ma B, Liu Y, Liu Z, Chen B, Zhu R and Cheng L: Combination therapy with ultrasound and 2D nanomaterials promotes recovery after spinal cord injury via Piezo1 downregulation. *J Nanobiotechnology* 21: 91, 2023.
16. Zhang Y, Cai K, Li C, Guo Q, Chen Q, He X, Liu L, Zhang Y, Lu Y, Chen X, *et al*: Macrophage-membrane-coated nanoparticles for tumor-targeted chemotherapy. *Nano Lett* 18: 1908-1915, 2018.
17. Shen K, Li X, Huang G, Yuan Z, Xie B, Chen T and He L: High rapamycin-loaded hollow mesoporous Prussian blue nanozyme targets lesion area of spinal cord injury to recover locomotor function. *Biomaterials* 303: 122358, 2023.
18. Sonali, Singh RP, Singh N, Sharma G, Vijayakumar MR, Koch B, Singh S, Singh U, Dash D, Pandey BL and Muthu MS: Transferrin liposomes of docetaxel for brain-targeted cancer applications: Formulation and brain theranostics. *Drug Deliv* 23: 1261-1271, 2016.
19. Mohapatra P, Gopikrishnan M, Doss CGP and Chandrasekaran N: How precise are nanomedicines in overcoming the blood-brain barrier? A comprehensive review of the literature. *Int J Nanomedicine* 19: 2441-2467, 2024.
20. Murali A, Lokhande G, Deo KA, Brokesh A and Gaharwar AK: Emerging 2D nanomaterials for biomedical applications. *Mater Today (Kidlington)* 50: 276-302, 2021.
21. Cui X, Li X, Xu Z, Guan X, Ma J, Ding D and Zhang W: Fabrication and characterization of chitosan/poly(Lactic-Co-glycolic Acid) core-shell nanoparticles by coaxial electrospray technology for dual delivery of natamycin and clotrimazole. *Front Bioeng Biotechnol* 9: 635485, 2021.
22. Rahimkhoei V, Alzaidy AH, Abed MJ, Rashki S and Salavati-Niasari M: Advances in inorganic nanoparticles-based drug delivery in targeted breast cancer theranostics. *Adv Colloid Interface Sci* 329: 103204, 2024.
23. Dong J, Tao L, Abourehab MAS and Hussain Z: Design and development of novel hyaluronate-modified nanoparticles for combo-delivery of curcumin and alendronate: Fabrication, characterization, and cellular and molecular evidences of enhanced bone regeneration. *Int J Biol Macromol* 116: 1268-1281, 2018.
24. Zhang W, Sigdel G, Mintz KJ, Seven ES, Zhou Y, Wang C and Leblanc RM: Carbon dots: A future blood-brain barrier penetrating nanomedicine and drug nanocarrier. *Int J Nanomedicine* 16: 5003-5016, 2021.
25. You Y, Jiang J, Zheng G, Chen Z, Zhu YX, Ma H, Lin H, Guo X and Shi J: In situ piezoelectric-catalytic anti-inflammation promotes the rehabilitation of acute spinal cord injury in synergy. *Adv Mater* 36: e2311429, 2024.
26. Liu J, Huang Z, Yin S, Jiang Y and Shao L: Protective effect of zinc oxide nanoparticles on spinal cord injury. *Front Pharmacol* 13: 990586, 2022.
27. Fang L, Song Y, Jin H, Liu Y and Gou S: An approach to apply BDNF targeting Fe(3)O(4)-Based nanoparticles as multifunctional anti-alzheimer agents. *Small* 20: e2403625, 2024.
28. Hersh AM, Alomari S and Tyler BM: Crossing the blood-brain barrier: Advances in nanoparticle technology for drug delivery in neuro-oncology. *Int J Mol Sci* 23: 4153, 2022.
29. Sonali, Singh RP, Sharma G, Kumari L, Koch B, Singh S, Bharti S, Rajinikanth PS, Pandey BL and Muthu MS: RGD-TPGS decorated theranostic liposomes for brain targeted delivery. *Colloids Surf B Biointerfaces* 147: 129-141, 2016.
30. Xu HL, Yang JJ, ZhuGe DL, Lin MT, Zhu QY, Jin BH, Tong MQ, Shen BX, Xiao J and Zhao YZ: Glioma-targeted delivery of a theranostic liposome integrated with quantum dots, superparamagnetic iron oxide, and cilengitide for dual-imaging guiding cancer surgery. *Adv Healthc Mater* 7: e1701130, 2018.
31. Li J, Lee WY, Wu T, Xu J, Zhang K, Li G, Xia J and Bian L: Multifunctional quantum dot nanoparticles for effective differentiation and long-term tracking of human mesenchymal stem cells in vitro and in vivo. *Adv Healthc Mater* 5: 1049-1057, 2016.
32. Yin F, Hu K, Chen S, Wang D, Zhang J, Xie M, Yang D, Qiu M, Zhang H and Li ZG: Black phosphorus quantum dot based novel siRNA delivery systems in human pluripotent teratoma PA-I cells. *J Mater Chem B* 5: 5433-5440, 2017.
33. Wu T, Liu K, Chen S, Ye Z, Xia J, He J, Xing P, Yang J, Qian Y and Chen M: Pulmonary microbiota disruption by respiratory exposure to carbon quantum dots induces neuronal damages in mice. *J Hazard Mater* 487: 137255, 2025.
34. Xiang C, Zhang Y, Guo W and Liang XJ: Biomimetic carbon nanotubes for neurological disease therapeutics as inherent medication. *Acta Pharm Sin B* 10: 239-248, 2020.
35. Fabbro A, Prato M and Ballerini L: Carbon nanotubes in neuroregeneration and repair. *Adv Drug Deliv Rev* 65: 2034-2044, 2013.
36. Hirano A, Wada M, Tanaka T and Kataura H: Oxidative stress of carbon nanotubes on proteins is mediated by metals originating from the catalyst remains. *ACS Nano* 13: 1805-1816, 2019.
37. Merugu S, Jagiello K, Gajewicz-Skretna A, Halappanavar S, Williams A, Vogel U and Puzyn T: The impact of carbon nanotube properties on lung pathologies and atherosclerosis through acute inflammation: A new AOP-Anchored in silico NAM. *Small* 21: e2501185, 2025.
38. Kannan RM, Nance E, Kannan S and Tomalia DA: Emerging concepts in dendrimer-based nanomedicine: From design principles to clinical applications. *J Intern Med* 276: 579-617, 2014.
39. Fox LJ, Richardson RM and Briscoe WH: PAMAM dendrimer-cell membrane interactions. *Adv Colloid Interface Sci* 257: 1-18, 2018.
40. Arbez-Gindre C, Steele BR and Micha-Screttas M: Dendrimers in Alzheimer's disease: Recent approaches in multi-targeting strategies. *Pharmaceutics* 15: 898, 2023.
41. Gothwal A, Kumar H, Nakhate KT, Ajazuddin, Dutta A, Borah A and Gupta U: Lactoferrin coupled lower generation PAMAM dendrimers for brain targeted delivery of memantine in aluminum-chloride-induced Alzheimer's disease in mice. *Bioconjug Chem* 30: 2573-2583, 2019.
42. Cui Q, Yang S, Ye P, Tian E, Sun G, Zhou J, Sun G, Liu X, Chen C, Murai K, *et al*: Downregulation of TLX induces TET3 expression and inhibits glioblastoma stem cell self-renewal and tumorigenesis. *Nat Commun* 7: 10637, 2016.
43. Stadler J, Garmo LG, Doyle D, Cheng CI, Richardson G, Waheed Z, Tofan T, Srinageshwar B, Sharma A, Petersen RB, *et al*: Curcumin encapsulated in PAMAM dendrimers for the therapeutic treatment of ischemic stroke in rats. *Front Cell Dev Biol* 12: 1467417, 2025.
44. Ma J, Zhan M, Sun H, He L, Zou Y, Huang T, Karpus A, Majoral JP, Mignani S, Shen M and Shi X: Phosphorus dendrimers co-deliver fibronectin and edaravone for combined ischemic stroke treatment via cooperative modulation of microglia/neurons and vascular regeneration. *Adv Healthc Mater* 13: e2401462, 2024.
45. Morfill C, Pankratova S, Machado P, Fernando NK, Regoutz A, Talamona F, Pinna A, Klosowski M, Wilkinson RJ, Fleck RA, *et al*: Nanostars carrying multifunctional neurotrophic dendrimers protect neurons in preclinical in vitro models of neurodegenerative disorders. *ACS Appl Mater Interfaces* 14: 47445-47460, 2022.
46. Zhao Y, Xiong S, Liu P, Liu W, Wang Q, Liu Y, Tan H, Chen X, Shi X, Wang Q and Chen T: Polymeric nanoparticles-based brain delivery with improved therapeutic efficacy of ginkgolide B in Parkinson's disease. *Int J Nanomedicine* 15: 10453-10467, 2020.
47. Dos Santos Rodrigues B, Banerjee A, Kanekiyo T and Singh J: Functionalized liposomal nanoparticles for efficient gene delivery system to neuronal cell transfection. *Int J Pharm* 566: 717-730, 2019.
48. Kydd J, Jadia R and Rai P: Co-Administered polymeric nano-antidotes for improved photo-triggered response in glioblastoma. *Pharmaceutics* 10: 226, 2018.
49. Kanazawa T, Taki H and Okada H: Nose-to-brain drug delivery system with ligand/cell-penetrating peptide-modified polymeric nano-micelles for intracerebral gliomas. *Eur J Pharm Biopharm* 152: 85-94, 2020.
50. ElMosbah DE, Khattab MS, Ibrahim MA, El-Assal MI and Miniawy HMFE: Preclinical efficacy of oral and nasal rivastigmine-loaded chitosan nano-particles on AICl(3)-induced Alzheimer's-like disease in rats. *Inflammopharmacology* 32: 3943-3952, 2024.

51. Zhang M, Xiang C, Niu R, He X, Luo W, Liu W and Gu R: Liposomes as versatile agents for the management of traumatic and nontraumatic central nervous system disorders: Drug stability, targeting efficiency, and safety. *Neural Regen Res* 20: 1883-1899, 2025.
52. Tang C, Jia F, Wu M, Wang Y, Lu X, Li J, Ding Y, Chen W, Chen X, Han F and Xu H: Elastase-targeting biomimetic nano-platform for neurovascular remodeling by inhibiting NETosis mediated AIM2 inflammasome activation in ischemic stroke. *J Control Release* 375: 404-421, 2024.
53. Fu XX, Qu H, Wang J, Cai HY, Jiang H, Chen HH and Han S: Novel nano-carriers with N-formylmethionyl-leucyl-phenylalanine-modified liposomes improve effects of C16-angiopoietin 1 in acute animal model of multiple sclerosis. *Drug Deliv* 30: 2241664, 2023.
54. Schmitt C, Lechanteur A, Cossais F, Bellefroid C, Arnold P, Lucius R, Held-Feindt J, Piel G and Hattermann K: Liposomal encapsulated curcumin effectively attenuates neuroinflammatory and reactive astrogliosis reactions in glia cells and organotypic brain slices. *Int J Nanomedicine* 15: 3649-3667, 2020.
55. Kurano T, Kanazawa T, Ooba A, Masuyama Y, Maruhana N, Yamada M, Ioka S, Ibaraki H, Kosuge Y, Kondo H and Suzuki T: Nose-to-brain/spinal cord delivery kinetics of liposomes with different surface properties. *J Control Release* 344: 225-234, 2022.
56. Shokr MM: 'Rewiring brain immunity: Targeting microglial metabolism for neuroprotection in neurodegenerative disorders'. *Metab Brain Dis* 40: 326, 2025.
57. Spiteri AG, Wishart CL, Pamphlett R, Locatelli G and King NJC: Microglia and monocytes in inflammatory CNS disease: Integrating phenotype and function. *Acta Neuropathol* 143: 179-224, 2022.
58. Kim DW, Tu KJ, Wei A, Lau AJ, Gonzalez-Gil A, Cao T, Braunstein K, Ling JP, Troncoso JC, Wong PC, *et al*: Amyloid-beta and tau pathologies act synergistically to induce novel disease stage-specific microglia subtypes. *Mol Neurodegener* 17: 83, 2022.
59. Guzman-Ruiz MA, Guerrero-Vargas NN, Lagunes-Cruz A, González-González S, García-Aviles JE, Hurtado-Alvarado G, Méndez-Hernández R, Chavarría-Krauser A, Morin JP, Arriaga-Avila V, *et al*: Circadian modulation of microglial physiological processes and immune responses. *Glia* 71: 155-167, 2023.
60. Goo YT, Grigoriev V, Korzun T, Sharma KS, Singh P, Taratula OR, Marks DL and Taratula O: Blood-brain barrier-penetrating nano-carriers enable microglial-specific drug delivery in hypothalamic neuroinflammation. *Adv Healthc Mater* 14: e2500521, 2025.
61. Wang P, Chen Z, Li P, Al Mamun A, Ning S, Zhang J, Tang C, Sun T, Xiao J, Wei X and Wu F: Multi-targeted nanogel drug delivery system alleviates neuroinflammation and promotes spinal cord injury repair. *Mater Today Bio* 31: 101518, 2025.
62. Feng Q, Zhang X, Zhao X, Liu J, Wang Q, Yao Y, Xiao H, Zhu Y, Zhang W and Wang L: Intranasal delivery of pure nanodrug loaded liposomes for Alzheimer's disease treatment by efficiently regulating microglial polarization. *Small* 20: e2405781, 2024.
63. Nguyen TD, Khanal S, Lee E, Choi J, Bohara G, Rimal N, Choi DY and Park S: Astaxanthin-loaded brain-permeable liposomes for Parkinson's disease treatment via antioxidant and anti-inflammatory responses. *J Nanobiotechnology* 23: 78, 2025.
64. Tredicine M, Ria F, Poerio N, Lucchini M, Bianco A, De Santis F, Valentini M, De Arcangelis V, Rende M, Stabile AM, *et al*: Liposome-based nanoparticles impact on regulatory and effector phenotypes of macrophages and T cells in multiple Sclerosis patients. *Biomaterials* 292: 121930, 2023.
65. Tada R, Nagao K, Tanaka R, Yamada S, Watanabe A and Negishi Y: Involvement of splenic marginal zone macrophages in the recognition of systemically administered phosphatidylserine-coated liposomes in mice. *Int Immunopharmacol* 112: 109209, 2022.
66. DeRidder L, Sharma A, Liaw K, Sharma R, John J, Kannan S and Kannan RM: Dendrimer-tesaglitazar conjugate induces a phenotype shift of microglia and enhances β -amyloid phagocytosis. *Nanoscale* 13: 939-952, 2021.
67. Sharma A, Sharma R, Zhang Z, Liaw K, Kambhampati SP, Porterfield JE, Lin KC, DeRidder LB, Kannan S and Kannan RM: Dense hydroxyl polyethylene glycol dendrimer targets activated glia in multiple CNS disorders. *Sci Adv* 6: eaay8514, 2020.
68. Yin X, Lin S, Xiong Y, Zhang P and Mei X: Biomimetic nano-platform with anti-inflammation and neuroprotective effects for repairing spinal cord injury in mice. *Mater Today Bio* 23: 100836, 2023.
69. Ren C, Li D, Zhou Q and Hu X: Mitochondria-targeted TPP-MoS(2) with dual enzyme activity provides efficient neuroprotection through M1/M2 microglial polarization in an Alzheimer's disease model. *Biomaterials* 232: 119752, 2020.
70. Wang H, Zhang S, Xie L, Zhong Z and Yan F: Neuroinflammation and peripheral immunity: Focus on ischemic stroke. *Int Immunopharmacol* 120: 110332, 2023.
71. Ju H, Park KW, Kim ID, Cave JW and Cho S: Phagocytosis converts infiltrated monocytes to microglia-like phenotype in experimental brain ischemia. *J Neuroinflammation* 19: 190, 2022.
72. Milosevic N, Rutter M and David A: Endothelial cell adhesion molecules- (un)attainable targets for nanomedicines. *Front Med Technol* 4: 846065, 2022.
73. Yuan S, Chai Y, Xu J, Wang Y, Jiang L, Lu N, Jiang H, Wang J, Pan X and Deng J: Engineering efferocytosis-mimicking nanovesicles to regulate joint anti-inflammation and peripheral immunosuppression for rheumatoid arthritis therapy. *Adv Sci (Weinh)* 11: e2404198, 2024.
74. Liu J, Han X, Zhang T, Tian K, Li Z and Luo F: Reactive oxygen species (ROS) scavenging biomaterials for anti-inflammatory diseases: From mechanism to therapy. *J Hematol Oncol* 16: 116, 2023.
75. Xu W, Huang Y and Zhou R: NLRP3 inflammasome in neuroinflammation and central nervous system diseases. *Cell Mol Immunol* 22: 341-355, 2025.
76. Dominic A, Le NT and Takahashi M: Loop Between NLRP3 inflammasome and reactive oxygen species. *Antioxid Redox Signal* 36: 784-796, 2022.
77. Wang W, Wang Y, Yang X, Zhao R, Sandai D, Song Z, Sandai D, Song Z and Zhang H: ATPexGen: ATP-induced cell death database. *Life Conflux* 1: e90, 2024.
78. El Gazzar WB, Farag AA, Samir M, Bayoumi H, Youssef HS, Marei YM, Mohamed SK, Marei AM, Abdelfatah RM, Mahmoud MM, *et al*: Berberine chloride loaded nano-PEGylated liposomes attenuates imidacloprid-induced neurotoxicity by inhibiting NLRP3/Caspase-1/GSDMD-mediated pyroptosis. *Biofactors* 51: e2107, 2025.
79. Song X, Ding Q, Wei W, Zhang J, Sun R, Yin L, Liu S and Pu Y: Peptide-functionalized prussian blue nanomaterial for antioxidant stress and NIR photothermal therapy against Alzheimer's disease. *Small* 19: e2206959, 2023.
80. Gao J, Chen S, Lin S and Mei X: Prussian blue analogues improves the microenvironment after spinal cord injury by regulating Zn. *Int Immunopharmacol* 131: 111868, 2024.
81. Liu L, Liu W, Sun Y and Dong X: Serum albumin-embedding copper nanoclusters inhibit Alzheimer's β -amyloid fibrillogenesis and neuroinflammation. *J Colloid Interface Sci* 672: 53-62, 2024.
82. Zhao L, Ling L, Lu J, Jiang F, Sun J, Zhang Z, Huang Y, Liu X, Zhu Y, Fu X, *et al*: Reactive oxygen species-responsive mitochondria-targeted liposomal quercetin attenuates retinal ischemia-reperfusion injury via regulating SIRT1/FOXO3A and p38 MAPK signaling pathways. *Bioeng Transl Med* 8: e10460, 2022.
83. Zhang F, Zhang Z, Alt J, Kambhampati SP, Sharma A, Singh S, Nance E, Thomas AG, Rojas C, Rais R, *et al*: Dendrimer-enabled targeted delivery attenuates glutamate excitotoxicity and improves motor function in a rabbit model of cerebral palsy. *J Control Release* 358: 27-42, 2023.
84. Alomari OA, Qusti S, Balgoon M, Aljoud F, Alamry KA and Hussein MA: Modified TPP-MoS(2) QD Blend as a bio-functional model for normalizing microglial dysfunction in Alzheimer's disease. *Neurol Int* 15: 954-966, 2023.
85. Onohuean H, Naik Bukke SP, Thalluri C, Abass KS and Choonara YE: Exosome engineering for targeted therapy of brain-infecting pathogens: molecular tools, delivery platforms, and translational advances. *Front Med Technol* 7: 1655471, 2025.
86. Han H, Xing L, Chen BT, Liu Y, Zhou TJ, Wang Y, Zhang LF, Li L, Cho CS, Jiang HL: Progress on the pathological tissue microenvironment barrier-modulated nanomedicine. *Adv Drug Deliv Rev* 200: 115051, 2023.
87. Silva RO, Haddad M, Counil H, Zaouter C, Patten SA, Fulop T and Ramassamy C: Exploring the potential of plasma and adipose mesenchymal stem cell-derived extracellular vesicles as novel platforms for neuroinflammation therapy. *J Control Release* 377: 880-898, 2025.
88. Nance E, Zhang F, Mishra MK, Zhang Z, Kambhampati SP, Kannan RM and Kannan S: Nanoscale effects in dendrimer-mediated targeting of neuroinflammation. *Biomaterials* 101: 96-107, 2016.

89. Gorrie D, Bravo M and Fan L: The yin and yang of the natural product triptolide and its interactions with XPB, an essential protein for gene expression and DNA repair. *Genes (Basel)* 15: 1287, 2024.
90. Siva Sankara C, Shanbhag AR, Rincón Díaz D, Hodges CA, Li C, Harrison JK and Zhang F: Engineering pH-Responsive dendrimer-STAT3 inhibitor conjugates for intracellular delivery. *Biomacromolecules* 27: 459-474, 2026.
91. Sharma R, Kambhampati SP, Zhang Z, Sharma A, Chen S, Duh EI, Kannan S, Tso MOM and Kannan RM: Dendrimer mediated targeted delivery of sinomenine for the treatment of acute neuroinflammation in traumatic brain injury. *J Control Release* 323: 361-375, 2020.
92. Li C, Zhao Z, Luo Y, Ning T, Liu P, Chen Q, Chu Y, Guo Q, Zhang Y, Zhou W, *et al*: Macrophage-disguised manganese dioxide nanoparticles for neuroprotection by reducing oxidative stress and modulating inflammatory microenvironment in acute ischemic stroke. *Adv Sci (Weinh)* 8: e2101526, 2021.
93. Mayilsamy K, Markoutsas E, Das M, Chopade P, Puro D, Kumar A, Gulick D, Willing AE, Mohapatra SS and Mohapatra S: Treatment with shCCL20-CCR6 nanodendriplexes and human mesenchymal stem cell therapy improves pathology in mice with repeated traumatic brain injury. *Nanomedicine* 29: 102247, 2020.
94. Zaleski MH, Omo-Lamai S, Nong J, Chase LS, Myerson JW, Glassman PM, Lee F, Reyes-Esteves S, Wang Z, Patel MN, *et al*: Nanocarriers' repartitioning of drugs between blood subcompartments as a mechanism of improving pharmacokinetics, safety, and efficacy. *J Control Release* 374: 425-440, 2024.
95. Fischer R and Maier O: Interrelation of oxidative stress and inflammation in neurodegenerative disease: Role of TNF. *Oxid Med Cell Longev* 2015: 610813, 2015.
96. Wang YC, Wu PH, Ting WC, Wang YF, Yang MH, Su TH, Su JY, Sun HI, Huang WM, Tsai PL, *et al*: Single-cell signaling network profiling during redox stress reveals dynamic redox regulation in immune cells. *Nat Commun* 16: 5600, 2025.
97. Zeng F, Wu Y, Li X, Ge X, Guo Q, Lou X, Cao Z, Hu B, Long NJ, Mao Y and Li C: Custom-made ceria nanoparticles show a neuroprotective effect by modulating phenotypic polarization of the microglia. *Angew Chem Int Ed Engl* 57: 5808-5812, 2018.
98. He W, Liu M, Zhang T, Sun Y, Wang Y, Wu H, Zheng M, Shi B and Zou Y: Tannic acid-iron complex-based nanozyme ameliorates Parkinson's disease via relieving oxidative stress and neuroinflammation. *ACS Nano* 19: 33212-33229, 2025.
99. Liaw K, Sharma R, Sharma A, Salazar S, Appiani La Rosa S and Kannan RM: Systemic dendrimer delivery of triptolide to tumor-associated macrophages improves anti-tumor efficacy and reduces systemic toxicity in glioblastoma. *J Control Release* 329: 434-444, 2021.
100. Xiong T, Yang K, Zhao T, Zhao H, Gao X, You Z, Fan C, Kang X, Yang W, Zhuang Y, *et al*: Multifunctional integrated nanozymes facilitate spinal cord regeneration by remodeling the extrinsic neural environment. *Adv Sci (Weinh)* 10: e2205997, 2023.
101. Park M, Oh HJ, Han J, Hong SH, Park W and Song H: Liposome-mediated small RNA delivery to convert the macrophage polarity: A novel therapeutic approach to treat inflammatory uterine disease. *Mol Ther Nucleic Acids* 30: 663-676, 2022.
102. Zhang M, Xu X, Su L, Zeng Y, Lin J, Li W, Zou Y, Li S, Lin B, Li Z, *et al*: Oral administration of Sophora Flavescens-derived exosomes-like nanovesicles carrying CX5461 ameliorates DSS-induced colitis in mice. *J Nanobiotechnology* 22: 607, 2024.
103. Shen J, Pan Y, Han L, Luo L, Sun T and Yu Y: Nanozymes as next-generation ROS scavengers: design strategies, catalytic mechanisms, and therapeutic frontiers. *J Mater Chem B* 13: 8286-8297, 2025.
104. Müller J, Bauer KN, Prozeller D, Simon J, Mailänder V, Wurm FR, Winzen S and Landfester K: Coating nanoparticles with tunable surfactants facilitates control over the protein corona. *Biomaterials* 115: 1-8, 2017.
105. Schaeublin NM, Braydich-Stolle LK, Schrand AM, Miller JM, Hutchison J, Schlager JJ and Hussain SM: Surface charge of gold nanoparticles mediates mechanism of toxicity. *Nanoscale* 3: 410-420, 2011.
106. Yücel O, Şengelen A, Emik S, Önay-Uçar E, Arda N and Gürdağ G: Folic acid-modified methotrexate-conjugated gold nanoparticles as nano-sized trojans for drug delivery to folate receptor-positive cancer cells. *Nanotechnology* 31: 355101, 2020.
107. Yu X, Lu Y, Chen J, Deng Y and Liu H: Unlocking ginsenosides' therapeutic power with polymer-based delivery systems: Current applications and future perspectives. *Front Pharmacol* 16: 1629803, 2025.
108. Bartelmess J, Quinn SJ and Giordani S: Carbon nanomaterials: Multi-functional agents for biomedical fluorescence and Raman imaging. *Chem Soc Rev* 44: 4672-4698, 2015.
109. Jitareanu A, Agoroaei L, Caba IC, Cojocaru FD, Vereştiuc L, Vieriu M and Mărţu I: The evolution of in vitro toxicity assessment methods for oral cavity tissues-from 2D cell cultures to organ-on-a-chip. *Toxics* 13: 195, 2025.
110. Ma Y, Liu Y, Chen W, Li F, Guo R, Ji R and Chen J: Carbon quantum dot-induced developmental toxicity in *Daphnia magna* involves disturbance of symbiotic microorganisms. *Sci Total Environ* 904: 166825, 2023.
111. Li X, Sun W and An L: Nano-CuO impairs spatial cognition associated with inhibiting hippocampal long-term potentiation via affecting glutamatergic neurotransmission in rats. *Toxicol Ind Health* 34: 409-421, 2018.
112. Li X, Luo Y, Huang Z, Wang Y, Wu J and Zhou S: Multifunctional liposomes remodeling tumor immune microenvironment for tumor chemioimmunotherapy. *Small Methods* 7: e2201327, 2023.
113. Jiang H, Li J, Tan Z, Guo Y, Liu Y, Hu L, Yin Y, Cai Y and Jiang G: Application of non-stationary phase separation hyphenated with inductively coupled plasma mass spectrometry in the analysis of trace metal-containing nanoparticles in the environment. *Se Pu* 39: 855-869, 2021 (In Chinese).
114. Tian F, Cai L, Liu C and Sun J: Microfluidic technologies for nanoparticle formation. *Lab Chip* 22: 512-529, 2022.
115. Catania G, Guerriero G, Bakrin N, Pourchez J, Kaouane G, Leclerc L, Augeul L, Haegebaert R, Remaut K, Kryza D and Lollo G: Generation of continuous production of polymeric nanoparticles via microfluidics for aerosolised localised drug delivery. *Int J Pharm* 675: 125532, 2025.
116. Yıldırım Ö, Arslan ME, Öner S, Cacciatore I, Di Stefano A, Mardinoglu A and Turkez H: Boron nitride nanoparticles loaded with a boron-based hybrid as a promising drug carrier system for Alzheimer's disease treatment. *Int J Mol Sci* 23: 8249, 2022.



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