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REVIEW

The Design Strategies and Applications of Engineered Nanoparticles for Traumatic Brain Injury

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Abstract: Traumatic brain injury (TBI) is a serious neurological condition. Because of its complex pathophysiological processes, direct treatment options are extremely limited. A key reason for this is the blood-brain barrier (BBB), which makes it difficult for conventional drug molecules to penetrate and maintain effective concentrations in brain tissue. In recent years, nanoparticles have garnered significant attention due to their unique biological properties, enhanced therapeutic effects, and low toxicity. By modifying the surface of nanoparticles with targeting ligands, their penetration capacity can be significantly enhanced, enabling directed delivery to the core injury area and substantially increasing their accumulation at the site of injury. Furthermore, functionally engineered nanoparticles can respond to specific signals in the TBI microenvironment, such as reactive oxygen species (ROS), enzymes, and pH changes, thereby enabling controlled drug release and significantly improving delivery efficiency. This review systematically summarizes the latest advances in engineered nanoparticles for TBI treatment from three perspectives: rational design, therapeutic strategies, and clinical translation.

Keywords: nanomedicine, nanoparticle, neuroprotection, anti-inflammation, anti-oxidative stress, neurogenesis, traumatic brain injury, nanozyme

Introduction

TBI is a complex neurological condition primarily caused by events such as falls, strenuous physical activity, motor vehicle collisions, explosions, or other external forces.[1] TBI represents a major global public health challenge; according to the latest reports, approximately 55 million people are affected annually, resulting in a global economic burden exceeding $400 billion. In Europe, more than 2 million people are hospitalized for TBI each year, and approximately 82,000 of them die.[2,3]

The pathological process of TBI is highly complex: the initial injury triggers a cascade of secondary pathological reactions, including neuroinflammation, oxidative stress, excitotoxicity, and disruption of the BBB. These processes are intertwined and collectively lead to neuronal death and neurological dysfunction.[4] Compounding the challenge is the fact that the adult central nervous system has limited inherent regenerative capacity, making functional recovery after injury extremely difficult.[5]

Currently, drugs used in clinical practice primarily work by inhibiting inflammatory signals in an attempt to create a relatively favorable environment for tissue repair following injury. However, the efficacy of these therapeutic strategies is severely limited by the BBB. The BBB is formed by tight junctions between cerebral capillary endothelial cells, allowing only lipid-soluble small molecules with a molecular weight of less than 400–600 Da to pass through by passive diffusion.[6] Furthermore, conventional drugs often lack selectivity and have short half-lives in vivo, making it difficult to maintain stable therapeutic concentrations at the site of injury.[7] Consequently, the vast majority of conventional drugs fail to achieve satisfactory therapeutic outcomes.[8]

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In recent years, nanoparticles have been increasingly studied in the treatment of TBI. As shown in Figures 1 and 2, nanoparticles play a dual role in TBI treatment: on the one hand, they can act directly as functional therapeutic agents; for example, metal and metal oxide nanoparticles, leveraging their redox activity, can directly scavenge ROS, effectively suppressing neuroinflammation and oxidative stress. On the other hand, they can serve as smart drug carriers, enabling

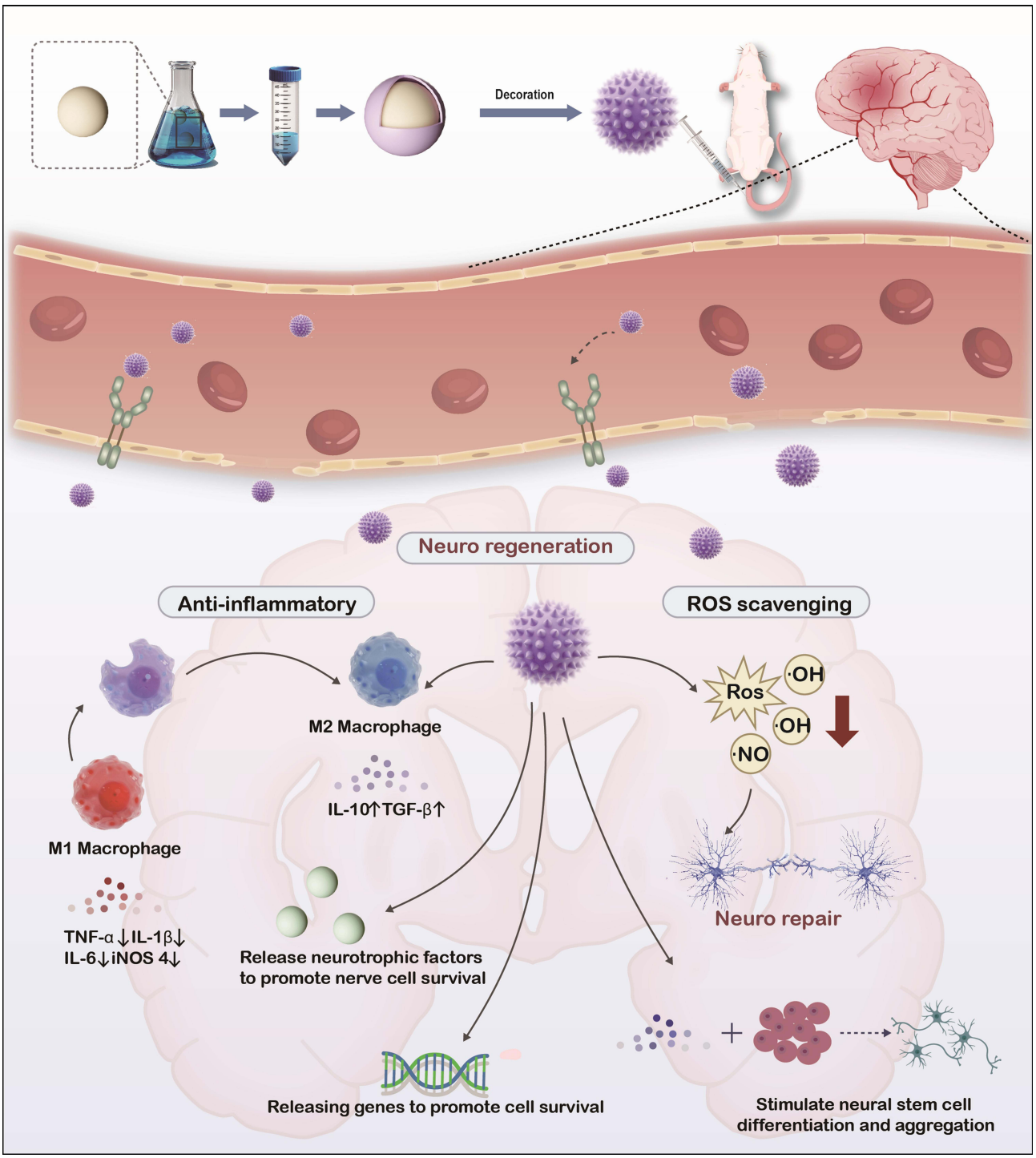

Figure 1 The main mechanism of nanoparticles for TBI. Following systemic administration, rationally designed nanoparticles actively cross the compromised BBB and enrich at injury foci, where they sequentially orchestrate anti-inflammatory macrophage polarization (M1-to-M2 switch), enzymatic ROS/RNS detoxification, and neuroregenerative stimulation via trophic factor release and gene delivery, thereby achieving multimodal TBI therapy. Downward arrows denote downregulation at the molecular level; upward arrows denote upregulation.

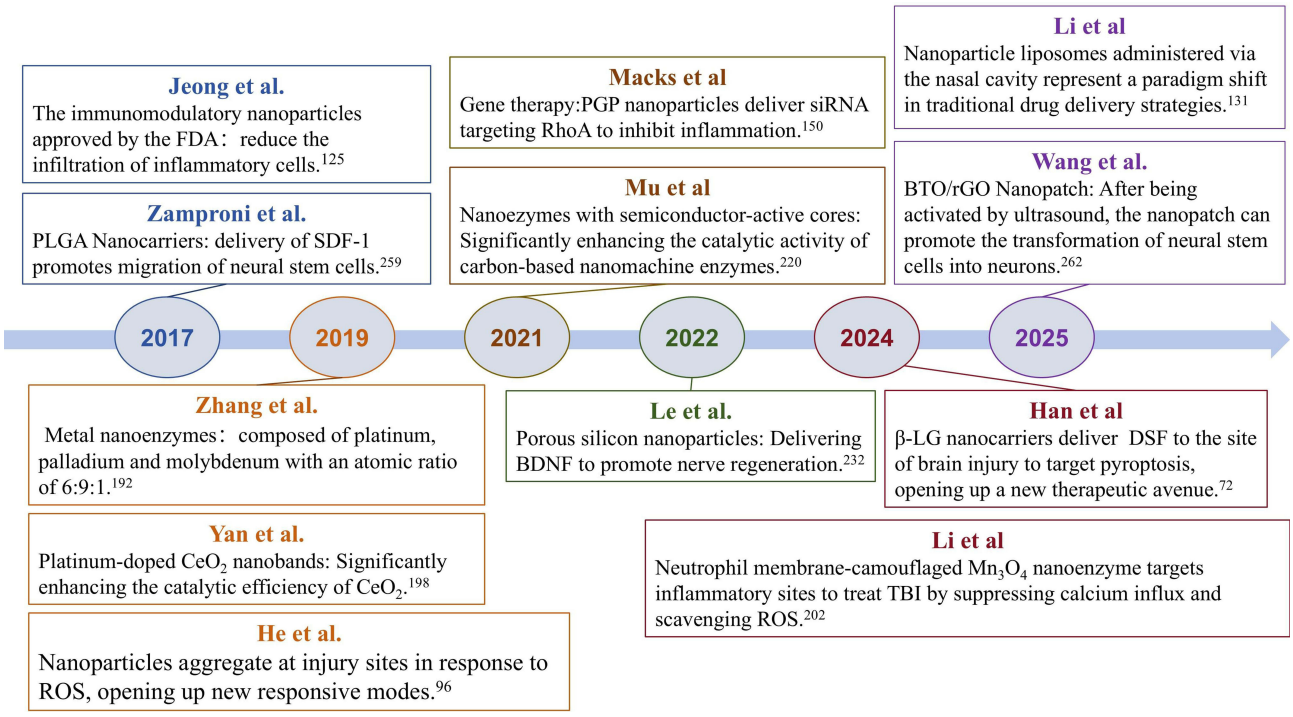

Figure 2 Timeline of the development of nanoparticles with significant surface properties in recent years.

targeted therapy by precisely delivering therapeutic molecules to the site of injury. Based on differences in their constituent materials, nanoparticles are primarily classified into three major categories (Figure 3). Inorganic nanoparticles mainly include metals and metal oxides, which possess both nanoenzyme catalytic activity and therapeutic-diagnostic functions. Organic nanoparticles primarily refer to polymeric materials such as polylactic acid (PLA) and polylactic-co-glycolic acid (PLGA), which mainly serve as controllable drug carriers. Bionic lipid-membrane nanoparticles mimic the bilayer structure of cell membranes, offering excellent biocompatibility and targeting capabilities; additionally, their preparation processes are complex and their stability is relatively low.[9,10] The physicochemical properties of these three types of nanoparticles determine their specific applications in TBI treatment and provide a diverse foundation of material choices for subsequent engineering design.

Although several reviews concerning nanoparticles for TBI currently exist, they predominantly focus on either the design and therapeutic efficacy of specific nanoparticle categories or exclusively on engineering aspects.[11–13] In this review, we systematically summarize the advances and limitations of nanoparticles in TBI treatment across three integrated dimensions: engineering design strategies, therapeutic mechanisms, and clinical translation.

We first comprehensively outline nanoparticle engineering strategies, encompassing surfactant modification, targeting peptide conjugation, and the rational design of stimulus-responsive nanostructures. We then highlight recent progress in nanoparticle-mediated neuroprotection and neural regeneration, with particular emphasis on mechanistic insights into cellular inflammatory modulation. Finally, we delineate the translational predicaments facing nanoparticle-based therapies, contextualized within their intrinsic physicochemical properties and safety profiles. Given the substantial pathophysiological parallels between TBI and other central nervous system disorders, particularly spinal cord injury and stroke, we additionally summarize nanoparticle design strategies developed for these conditions, aiming to provide actionable references for the development of next-generation nanomedicines targeting TBI.

Literature Retrieval Strategy

This article mainly retrieves articles through PubMed and Web of Science. It is mainly divided into two parts. The first part is about the treatment of nanoparticles, with the main search formula being: ("Brain Injuries, Traumatic"[Mesh] OR

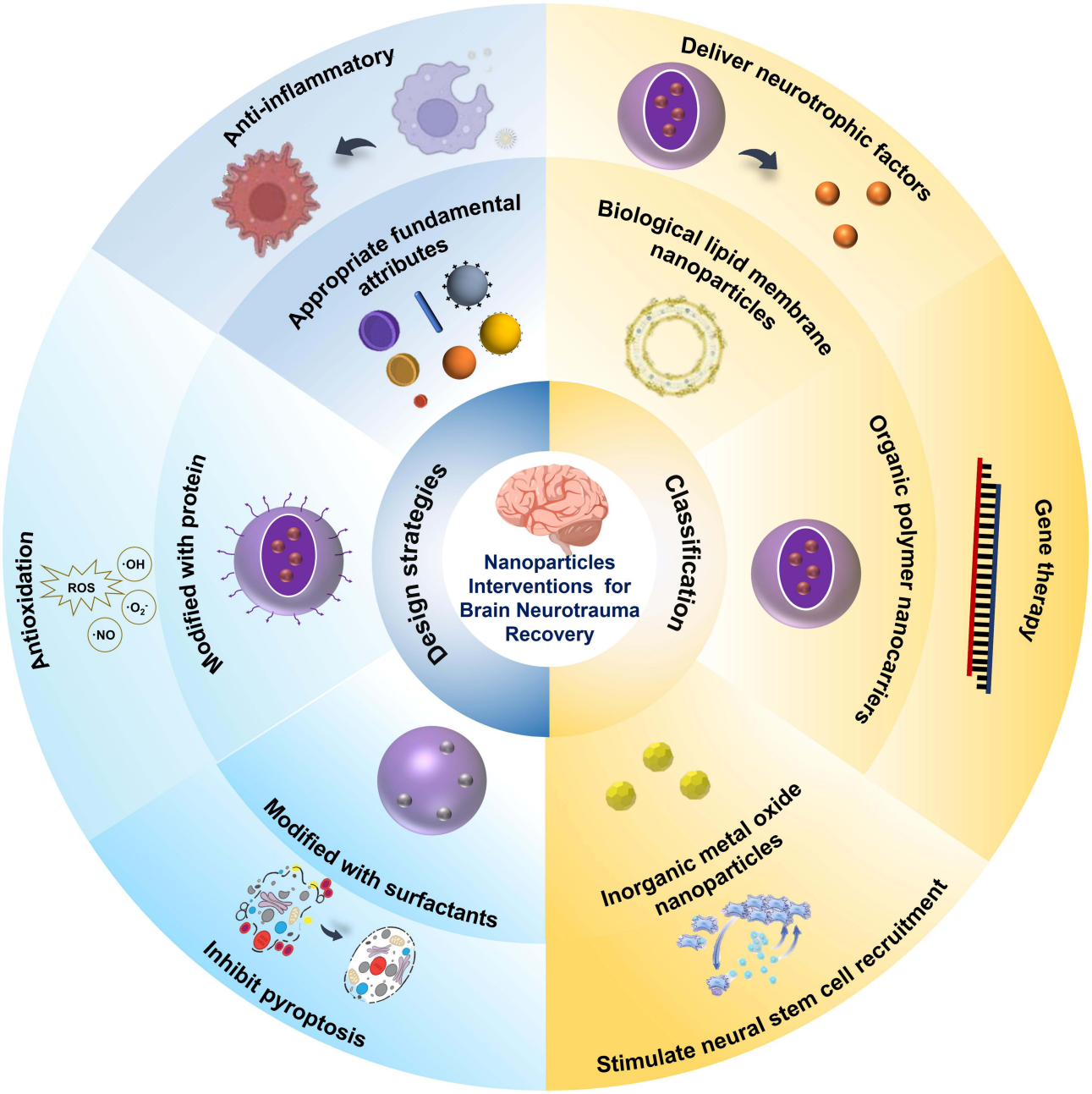

Figure 3 Classification and main functions of nanoparticles.

"traumatic brain injury"[tiab] OR TBI[tiab]) AND ("nanoparticles"[Mesh] OR "nanomedicine"[tiab] OR "engineered nanoparticle*"[tiab] OR nanocarrier*[tiab] OR nanozyme*[tiab]) AND (therapy[tiab] OR treatment[tiab] OR deliver*[tiab] OR repair*[tiab]). The second part focuses on the design of nanoparticles, with the search strategy being: ("Brain Injuries, Traumatic"[Mesh] OR "traumatic brain injury"[tiab] OR TBI[tiab]) AND ("nanoparticles"[Mesh] OR "nanomedicine"[tiab] OR "engineered nanoparticle*"[tiab] OR nanocarrier*[tiab] OR nanozyme*[tiab]) AND (therapy[tiab] OR treatment[tiab] OR deliver*[tiab] OR repair*[tiab]) AND (design [tiab] OR engineering[tiab] OR surface modification[tiab] OR functionalization[tiab] OR construction[tiab] OR synthesis[tiab]). We also attempted to change the term "traumatic brain injury" to "spinal cord injury", "nervous system", "neuron", "brain", and "spinal cord" to obtain more progress on nanoparticles in brain or spinal cord diseases.

The Limitations of the BBB and the Mechanisms of Drug Molecule Entry into the Brain

The BBB is a selective semipermeable membrane located between the bloodstream and brain tissue, composed of cerebral capillary endothelial cells, tight junctions, pericytes, astrocyte processes, and the basement membrane (Figure 4A).[14,15] Endothelial cells form a continuous barrier through tight junction proteins, allowing only lipid-soluble small molecules with a molecular weight of less than 400–600 Da to pass by passive diffusion, while over 98% of small-molecule drugs and all macromolecular therapeutic agents are blocked from entering the brain.[16,17]

To overcome this limitation, four main strategies are currently employed to enable drugs or nanoparticles to cross the BBB (Figure 4B–E): 1) Receptor/transporter-mediated transcellular transport: Proteins or ligands capable of binding to

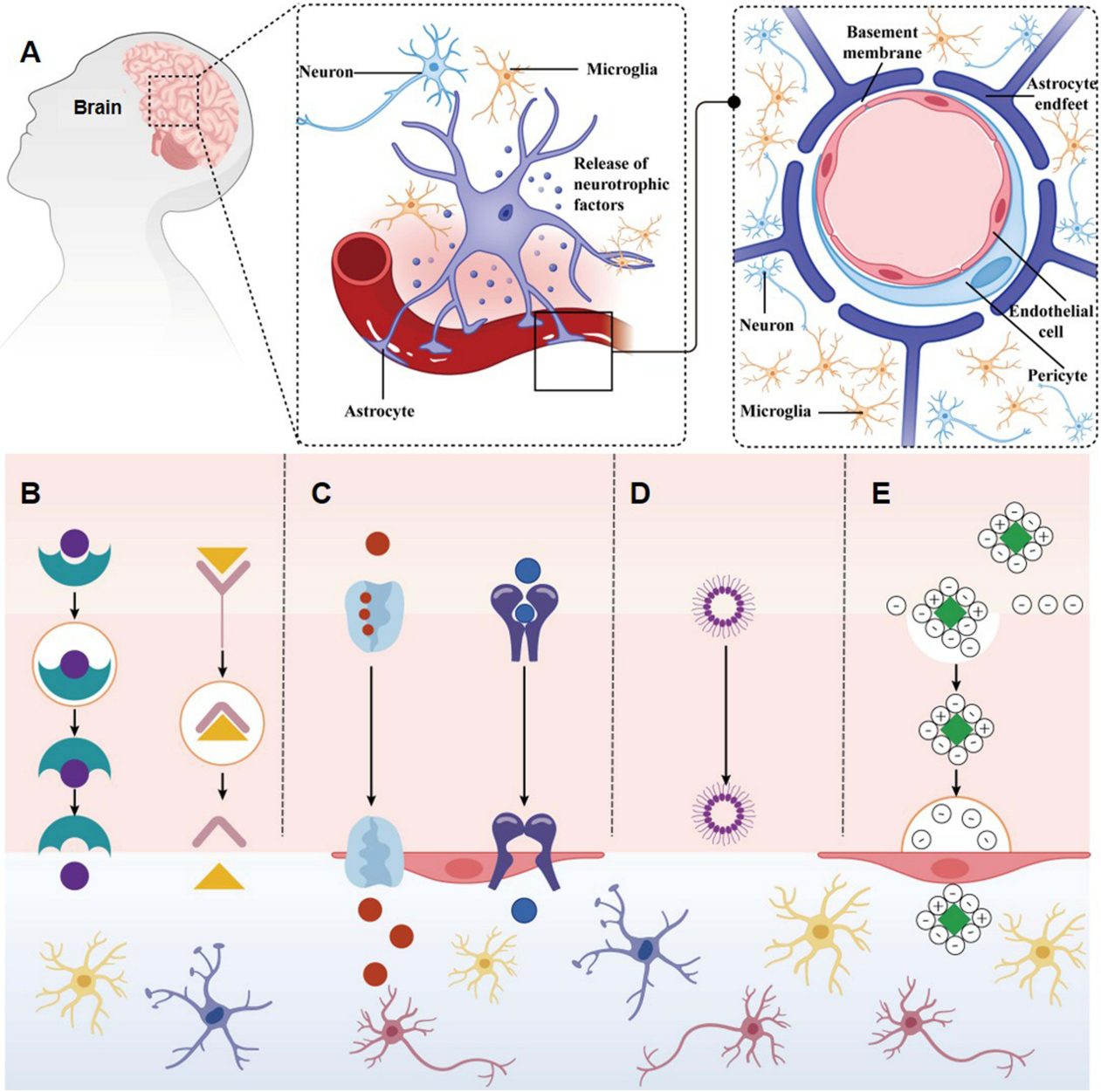

Figure 4 (**A**)The structure of the BBB; (**B**–**E**) The primary way nanoparticles can cross the BBB. (**B**) Receptor mediated endocytosis/exocytosis; (**C**) Transporter mediated active transport; (**D**) Liposomes can pass through the lipid bilayer directly; (**E**) Positively charged nanoparticles interact with the surface charges of endothelial cells for invagination of the membrane and formation of vesicle.

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specific receptors on the BBB are conjugated to the surface of nanoparticles, allowing entry into the brain via receptor-mediated endocytosis or transporter-mediated active transport.[18–27] 2) Passive diffusion: Lipophilic nanoparticles can passively diffuse into the brain directly through the lipid bilayer of the endothelial cell membrane. 3) Adsorption-mediated endocytosis: Positively charged nanoparticles interact electrostatically with the negatively charged endothelial cell membrane, inducing membrane invagination and vesicle formation, thereby enabling transcellular transport.[24] 4) Temporary opening of tight junctions: Following TBI, tight junctions in the BBB undergo temporary disruption, providing a unique window of opportunity for nanoparticles to penetrate the barrier via the bloodstream and accumulate at the site of injury. These strategies provide a crucial basis for the engineering design of nanoparticles.

Engineering Design of Nanoparticles

The engineering design of nanoparticles mainly encompasses three approaches. 1) Achieving improved permeability of nanoparticles across the BBB. 2) Obtaining enhanced targeting specificity to promote accumulation at pathological sites. 3), Designing stimulus-responsive nanoparticle systems for controlled release of active therapeutic agents.

Influence of Nanoparticle Characteristics on BBB Permeability

In the design of nanoparticles, the primary considerations are their physicochemical properties, including chemical composition, size, morphology, and surface charge. These properties significantly influence the interaction between nanoparticles and the BBB; therefore, a thorough understanding of these properties is crucial for the optimized design and surface modification of nanoparticles.

Chemical Composition

The cell membrane of the BBB is primarily composed of a phospholipid bilayer. This structural characteristic allows lipid nanoparticles to interact with the cell membrane and integrate into the bilayer through the membrane's fluidity and phase-transition properties, thereby facilitating their passage across the BBB.[28,29] Additionally, most nanoparticles, particularly inorganic metal oxide nanoparticles, currently lack lipophilicity, which limits their direct application of this mechanism. In the future, strategies such as surface lipid modification or biomimetic membrane coating could be considered to endow non-lipidic materials with similar membrane-affinity properties.

Size

The size of nanoparticles is a key factor influencing their ability to cross the BBB. This size dependence primarily stems from the tight junctions between endothelial cells in the BBB, which restrict the passage of larger particles.[30] Additionally, smaller is not always better. Studies have shown that nanoparticles smaller than 5 nm are rapidly cleared by the kidneys, shortening their circulation time and consequently reducing delivery efficiency to the brain.[31] Research by Ohta et al further confirmed that 15-nm gold nanoparticles penetrate mouse brain tissue more easily than 3-nm and 120-nm particles, while particles larger than 200 nm are largely unable to cross the BBB. This indicates that there is an optimal range for particle size in terms of penetration ability; efficiency actually decreases when the size exceeds this range.[32,33] Nanoparticles ranging in size from 10 to 100 nanometers are considered most suitable for crossing the BBB.[34] Therefore, it is important to ensure that the size of the nanoparticles falls within this range.

Shape

Nanoparticles can be designed in a variety of shapes, such as spherical, rod-shaped, cubic, or disc-shaped.[34] Studies have shown that when nanoparticles are of similar size and have the same surface modifications, their efficiency in crossing the BBB varies significantly depending on their shape. For example, rod-shaped nanoparticles adhere more readily to brain endothelial cells than spherical nanoparticles and achieve higher levels of accumulation in the brain.[35,36] This may be attributed to the fact that the rod-like structure provides a larger surface area, facilitating multivalent interactions with cell surface receptors. A study using a three-dimensional human BBB microfluidic system (μHuB) also confirmed that, under standardized conditions, rod-shaped nanoparticles exhibit significantly superior barrier-crossing capabilities compared to spherical nanoparticles.[37] Although studies have shown that disc-shaped nanoparticles are more readily internalized by cells, there is currently no evidence to suggest that they have an advantage in crossing the BBB.[38] In

conclusion, the shape of nanoparticles has an impact on their ability to cross the BBB. Further investigations and testing are needed in future research to accurately assess the ability of nanoparticles with different shapes to cross the BBB.

Surface Charge

The surface of BBB endothelial cells is rich in negatively charged glycosaminoglycans, allowing positively charged nanoparticles to bind to the cell membrane via electrostatic interactions and facilitate transcellular transport. Experiments have confirmed that positively charged particles cross the BBB more easily than neutral or negatively charged particles.[39,40] Additionally, this strategy has significant limitations: studies by Lockman et al indicate that excessively high positive charges may compromise BBB integrity; furthermore, cationic nanoparticles may induce the production of ROS, leading to cell necrosis or apoptosis.[41] To date, there have been no studies indicating the optimal charge range for nanoparticles. Therefore, when designing nanoparticles, it is essential to carefully balance their charge characteristics to ensure effective penetration of the BBB while minimizing potential damage to brain tissue.

Enhanced Penetration via Modified with Recognition Motifs of Transport

Currently, nanoparticle-based TBI therapy primarily relies on the temporary opening of the BBB following injury. Notably, once this window of opportunity has passed, or when the BBB has partially repaired itself, it once again becomes a major obstacle to TBI treatment. Against this backdrop, receptor-mediated transcellular transport offers a highly promising strategy for facilitating the passage of nanoparticles across the BBB. Table 1 summarizes the relevant targets involved in receptor-mediated transport. This section will focus on several potential protein targets that facilitate nanoparticle transport following TBI, as well as corresponding functional modification strategies.

T7 Peptide

The transferrin receptor (TfR) is highly expressed on the surface of cerebral capillary endothelial cells.[42] During the inflammatory response and tissue repair following brain injury, glial cells and other intrinsic brain cells also upregulate TfR expression. Furthermore, following TBI, various inflammatory cells in brain tissue are activated and secrete

Table 1 Modification Strategies for Receptor-Mediated Transport

Type	Main Expression Distribution	Primary Function	Modification Molecules	Ref
Receptor-mediated endocytosis/exocytosis				
Transferrin receptor 1 (TfR1)	BBB and tumor cells	Mediate iron uptake and regulate intracellular iron levels	T7 peptide and Transferrin	[18]
Lactoferrin Receptor (LfR)	Brain endothelial cells, capillaries and neurons	Mediate iron uptake	Lactoferrin	[19]
Low-density lipoprotein receptor (LDLR)	BBB and the hippocampus of the brain	Regulate the transport and metabolism of cholesterol, Affect the metabolism and clearance of Aβ	Angiopep-2 (Ang-2) and apolipoprotein E (ApoE)	[20,21]
Insulin receptor (IR)	Cerebral microvascular endothelial cells	Regulate the energy metabolism of the body	Insulin	[22]
Folate receptor (FR)	BBB and tumor cells	Mediate the transport and metabolism of folic acid in the brain. Promote the closure of neural tubes	Folic acid	[23]
Nicotinic acetylcholine receptors (nAChRs)	Capillary endothelial cells	Regulate the release and reuptake of neurotransmitters	RVG29 peptide	[24]
Transporter-mediated active transport				
Glucose transporter protein 1 (GLUT1)	Brain endothelial cells	Regulate the transport of glucose in the BBB	D-glucose, D-galactose, and mannose	[25]
L-type amino acid transporters (LAT)	Cerebral microvascular endothelial cells	Transport large neutral amino acids	Amino acid	[26]
Glutathione transporter	Cerebral microvascular endothelial cells	Regulate the transport of glutathione	Glutathione	[27]

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inflammatory mediators, which in turn stimulate the upregulation of transferrin expression in brain cells.[43] The T7 peptide (HAIYPRH) is a short peptide that specifically recognizes TfR.[44] When T7-modified nanoparticles bind to TfR on brain endothelial cells, they can trigger receptor-mediated endocytosis, thereby enabling crossing of the BBB. Notably, TfR is also highly expressed in peripheral organs such as the liver and intestines. This widespread distribution may lead to significant off-target accumulation of T7-peptide-modified nanoparticles in peripheral organs (particularly the liver), where they compete with brain endothelial cells for a limited supply of nanoparticles, thereby reducing brain delivery efficiency.[45,46] Consequently, strategies relying solely on TfR targeting still face challenges in improving brain-targeting specificity and absolute delivery efficiency, and there is an urgent need to develop multi-target synergistic or cascade targeting strategies to overcome this limitation.

Apolipoprotein E

Low-density lipoprotein receptor 1 (LRP1) is a multifunctional cell surface receptor involved in endocytosis and signal transduction. It is widely expressed in cerebral microvascular endothelial cells, neurons, and astrocytes, and is primarily responsible for the clearance of β-amyloid.[47] Following TBI, LRP1 expression is upregulated due to increased demand for Aβ clearance. Nanoparticles modified with apolipoprotein E (ApoE)-derived peptides can specifically bind to LRP1, thereby promoting transcellular transport of the nanoparticles.[48] Additionally, another receptor for ApoE, apolipoprotein E receptor 2 (ApoER2), is also expressed on cerebral microvascular endothelial cells, neurons, and astrocytes.[49] Consequently, ApoE-modified nanoparticles can not only target the BBB but also deliver therapeutic drugs more specifically to neurons and glial cells at the site of injury. ApoE-based targeting offers the dual advantage of targeting both the BBB and parenchymal cells via LRP1 and ApoER2. Given ApoE's natural role in lipid transport and its association with neurodegenerative diseases, this strategy is particularly appealing. Notably, it should be noted that ApoE exists in multiple subtypes (E2, E3, E4), each with varying binding affinities for receptors.[50] In addition, studies have shown that the E4 subtype is associated with reduced cerebral perfusion and oxygen metabolism, leading to a poorer prognosis in the early phases of TBI.[51] Therefore, the selection of ApoE-derived peptide sequences and their potential immunogenicity require careful consideration.

Carbohydrates

Following TBI, the brain enters a state of stress, neuronal activity increases, and energy demands rise significantly. To meet these demands, the brain enhances glucose uptake by upregulating glucose transporters (GLUT).[52] Furthermore, the localized ischemia and hypoxia that occur in brain tissue following TBI activate hypoxia-inducible factor (HIF-1α), which in turn upregulates GLUT expression to adapt to the hypoxic environment.[53] Conjugating specific sugars (such as D-glucose, D-galactose, and mannose) to nanoparticles can facilitate their transport.[25,54] Glucose-mediated targeting exploits the metabolic alterations inherent to TBI pathology, particularly the upregulation of GLUT transporters under hypoxic conditions. This strategy is particularly appealing because it responds to the pathological state of the injured brain. However, glucose transporters are widely expressed in vivo, and physiologically elevated glucose levels create significant competition, which may limit the specificity of this strategy. Although studies have shown that regulating GLUT expression by modulating blood glucose levels can influence the delivery efficiency of nanoparticles, this strategy raises practical concerns regarding clinical translation and patient safety.[55]

Enhanced Penetration via the Regulation of Surfactants

Surfactants are amphiphilic molecules whose molecular structure contains both hydrophilic polar groups (such as carboxylates, sulfonates, and polyethylene oxide chains) and hydrophobic alkyl or aromatic long chains.[56] As a result, they can modulate the surface properties of nanoparticles, enhance their interaction with biological membranes, and facilitate the passage of nanoparticles through cell membranes or their uptake by cells. In addition, surfactants can inhibit the aggregation of nanoparticles in the bloodstream and prolong their circulation time in the body, thereby increasing the opportunities for nanoparticles to interact with the BBB. Next, we will provide a detailed overview of the functions of several common surfactants.

Polysorbate 80

Tween 80 (P80) is a nonionic surfactant with moderate hydrophilicity.[57] It can modulate the charge distribution on the surface of nanoparticles and introduce hydrophilic groups such as hydroxyl groups. These modifications enhance the electrostatic attraction between the nanoparticles and the negatively charged endothelial cells of the BBB, thereby promoting the endocytosis of the nanoparticles by the endothelial cells. Furthermore, the hydrophilicity of P80 ensures good dispersion and stability of the nanoparticles in the bloodstream, reducing their aggregation and precipitation during circulation.[58]

Poloxamer

Poloxamer is a nonionic surfactant with excellent hydrophilicity and biocompatibility.[59,60] Similar to P80, poloxamer modification enhances the stability of nanoparticles in the bloodstream and prolongs their retention time, thereby increasing the opportunity for contact with the BBB.[61] In a study by Khalin et al, poloxamer-modified PLGA nanoparticles were used to deliver neurotrophic factors to rats with TBI. Compared with other groups, poloxamer-modified nanoparticles exhibited significantly higher concentrations in rat brain tissue, markedly improving neurological function and memory deficits.[62]

Sodium Dodecyl Sulfate

Sodium dodecyl sulfate (SDS) is an anionic surfactant that enhances electrostatic interactions between nanoparticles and cells, thereby promoting the endocytosis of nanoparticles.[63] In addition, SDS exhibits some cytotoxicity and can disrupt cell membrane integrity at higher concentrations.[64]

Lecithin

Lecithin is an amphiphilic surfactant that can form cell-membrane-like structures on the surface of nanoparticles, thereby promoting their interaction with cell membranes.[65] Furthermore, because lecithin is a component of cell membranes, it confers excellent biocompatibility to nanoparticles, thereby reducing their clearance by the immune system.[66]

Overall, at present, poloxamer and polysorbate 80 are considered ideal choices for TBI nanotherapy due to their good safety profile, stability, and established application in brain targeting; lecithin is suitable for long-term delivery scenarios requiring immune evasion; whereas SDS should be used with caution due to toxicity concerns. Future research should focus on strengthening the systematic evaluation of surfactant-modified nanoparticles in TBI models and provide more robust evidence to support clinical translation.

Enhance the Targeting Ability

While enhancing the ability of nanoparticles to cross the BBB, promoting their precise targeting to the site of TBI is equally critical. This is because improving the efficiency of nanoparticle accumulation at the injury site can significantly enhance therapeutic efficacy and reduce off-target toxicity. Given that certain proteins are upregulated in the injured region following TBI, short peptides targeting these proteins can be conjugated to the surface of nanoparticles to achieve targeted accumulation at the injury site. This section summarizes several common nanoparticle targeting design strategies.

MAP Peptide

Matrix metalloproteinase-9 (MMP-9) is a zinc-dependent endopeptidase.[67] Following TBI, activated inflammatory cells secrete pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β). These inflammatory molecules upregulate transcription factors such as nuclear factor κB (NF-κB), leading to increased expression of MMP-9. Additionally, ROS and reactive nitrogen species (RNS) generated after TBI damage cell membranes and DNA while activating intracellular signaling cascades, further upregulating MMP expression. Based on this, Chen et al modified nanoparticles using a peptide (MAP) that targets MMP-9. The results showed that, compared to unmodified nanoparticles, MAP-modified nanoparticles accumulated significantly more at the TBI injury site.[68] MMP-9 is a key downstream effector molecule in the inflammatory cascade following TBI. The advantage of this strategy lies in its close association with disease-related inflammation and matrix degradation, resulting in high targeting efficiency during the

peak of inflammation. In addition, a limitation is that MMP-9 expression is time-dependent; it may decline during the late or chronic phases of injury, leading to fluctuations in targeting efficiency over time.[69]

CAQK Peptide

Following TBI, the composition of the extracellular matrix (ECM) in the injured area undergoes changes, with specific protein components such as chondroitin sulfate proteoglycans being overexpressed. The CAQK peptide specifically binds to these overexpressed ECM components, thereby enabling the targeted delivery of nanoparticles to the injury site.[70] Studies have confirmed that the CAQK peptide accumulates exclusively at the site of brain injury, with no significant accumulation observed in normal brain tissue or other major organs. Furthermore, CAQK peptide modification extends the duration of action of the nanoparticles within the brain, thereby reducing systemic drug distribution and associated side effects.[71,72] The advantage of this strategy lies in the relative stability of the target; since ECM remodeling persists for an extended period following injury, it may provide a broader therapeutic window. Furthermore, CAQK exhibits high tissue specificity, which helps minimize off-target effects.

RGD Peptide

Integrins are a class of transmembrane proteins widely distributed on the cell surface. In endothelial cells with an intact BBB, the expression levels of integrin receptors (such as αvβ3 and αvβ5) are low.[73] In addition, when the BBB is compromised, endothelial cells undergo a phenotypic shift, leading to a significant upregulation of integrin receptor expression. Studies have shown that the arginine-glycine-aspartic acid (RGD) peptide sequence can specifically recognize and bind to these integrin receptors. Therefore, RGD-modified nanoparticles can achieve targeted delivery through receptor binding. More importantly, this binding induces endocytosis in endothelial cells, allowing the nanoparticles to enter the cells and thereby achieve efficient brain penetration.[74,75] RGD takes advantage of the upregulation of integrin receptors on endothelial cells following disruption of the BBB to both mediate targeted binding and induce endocytosis, which is crucial for delivering drugs to the brain parenchyma. However, since integrins are expressed in various tissues throughout the body, this may lead to some uptake by non-brain organs. Therefore, RGD-modified nanoparticles require further evaluation of their in vivo distribution and tissue toxicity.[76]

Furthermore, the pathological progression of TBI exhibits significant spatiotemporal heterogeneity: the acute phase (0–72 hours) is dominated by BBB disruption and inflammatory cascades; the subacute phase (3 days–2 weeks) is characterized by glial scarring and vascular remodeling; and the chronic phase (>2 weeks) involves neurodegeneration.[77] The therapeutic windows for different targeting strategies vary. MAP peptides targeting MMPs may be more effective during the acute phase, while the CAQK peptide strategy targeting the ECM may achieve optimal results during the subacute phase.[78] Although synthetic surfactants such as Tween 80 and poloxamer can enhance stability, their non-natural properties may raise long-term safety concerns; natural lipids such as lecithin exhibit excellent biocompatibility but lack sufficient stability.

Stimuli-Responsive Nanoparticles Facilitate the Precise Release of Drug Molecules

Stimulus-responsive nanoparticles are a class of smart nanodelivery systems capable of responding to specific stimuli, leading to reversible or irreversible changes in their physicochemical properties, including particle size, surface charge, morphology, and drug release characteristics.[79,80] By responding to specific stimuli, these nanoparticles can precisely control drug release, thereby reducing side effects and improving safety.[81] Their activation mechanisms can generally be divided into two categories: The first category responds to internal physiological conditions, such as ROS, pH gradients, or specific enzymes; the second category is activated by external stimuli, including light, magnetic fields, or ultrasound.

PH-Responsive Nanoparticles

The pH range of normal brain tissue is 7.33–7.35. Following TBI, the pH of brain tissue temporarily drops to approximately 7.0 and may subsequently recover partially.[82,83] The responsiveness of pH-responsive nanoparticles primarily stems from dynamic covalent bonds (such as amine, acetal, ketone, and ester bonds) or noncovalent intermolecular interactions (such as electrostatic interactions and hydrogen bonds).[84–86] Among these, noncovalent-mediated response release is the most common. pH changes can cause specific chemical groups to undergo protonation or

deprotonation, thereby altering the surface charge of the nanoparticles. These charge changes further affect the hydrophilic-hydrophobic balance of amphiphilic copolymers, leading to a weakening of intermolecular forces, which causes the nanoparticles to disintegrate and release the internal drug molecules.[87] Therefore, nanoparticles designed based on this mechanism are characterized by rapid responsiveness and ease of regulation. Such responsive nanoparticles typically consist of two parts: an outer stabilizing shell and an inner stimulus-responsive core. The outer shell ensures the nanoparticles remain stable within the body, while the core facilitates drug release upon pH changes. Based on this, Takahashi et al developed RNP micelles using polyethylene glycol-polymethylstyrene block copolymers as the matrix to encapsulate the ROS inhibitor, 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO).[88] Under low pH conditions, the amine groups in the core of the RNP micelles undergo protonation, leading to the disintegration of the micelle structure, thereby triggering the selective release of TEMPO and effectively reducing its toxic effects. Fan et al prepared pH-responsive liposomes using a thin-film hydration method, based on soybean phospholipids and cholesterol, with the introduction of the amphiphilic block copolymer DSPE-PEOz.[89] The hydrophobic PEOz segments in these liposomes transition to a hydrophilic state under acidic conditions, causing the liposome structure to disintegrate and thereby enabling controlled drug release.[90]

Conversely, it is worth noting that the in vivo environment is far more complex than the in vitro environment, and pH-responsive systems are also influenced by physiological factors such as blood circulation, metabolism, and organ distribution. Therefore, there is an urgent need for more in-depth evaluation of the in vivo transport mechanisms, controlled-release kinetics, and therapeutic efficacy of these carriers.[81] Furthermore, pH changes at the site of TBI are typically weak and unstable; future research should aim to improve the sensitivity and precision of pH-responsive delivery systems.

ROS-Responsive Nanoparticles

Following TBI, ROS and RNS are generated in the injured area. ROS-responsive nanoparticles rely on redox reactions to achieve functional regulation through the cleavage and recombination of specific chemical bonds. Common ROS-responsive moieties include sulfides, thioketones (TK), selenides, tellurides, and phenylboronates (PBAE), among others. There are three main design strategies for ROS-responsive nanoparticles.[91–93]

1) Main-chain type: Integrate the responsive units into the polymer backbone or use them as core components of nanoparticles. For example, Fu et al synthesized an antioxidant nanocarrier with a polysulfide unit as its core for encapsulating curcumin.[66] These polysulfide units would transform into hydrophilic polyoxosulfide structures in the presence of ROS, eventually leading to the disintegration of the nanoparticles and the release of the encapsulated curcumin, thereby interrupting the self-perpetuating cycle of "ROS- neuroinflammation". (Figure 5A)

2) Side-chain type: Responsive groups are grafted onto the polymer chain as side chains. These nanoparticles are primarily used for dynamic monitoring of the nervous system and the early diagnosis of related diseases by linking fluorescent probes to the responsive units.[94]

3) Prodrug type: Formed through ROS-mediated aggregation of drug molecules. He et al reported a highly ROS-responsive ultra-small nanoenzyme synthesized via the condensation and carbonylation of glutathione and lysine under microwave irradiation. Free sulfhydryl groups are easily oxidized by ROS, promoting the formation of disulfide bonds between particles and triggering particle aggregation (Figure 5B). In vitro experiments indicate that this nanoenzyme can accumulate in the mitochondria of cells damaged by oxidative stress, increasing in volume by 75–100 times while maintaining stable enzymatic activity.[95]

In contrast, the main-chain type is the most common; it is characterized by rapid response, immediate disintegration upon activation, and the ability to deliver a sudden release of the drug for rapid action at the site of the lesion.[96] Conversely, it is prone to premature drug leakage, so the addition of a protective barrier may be considered in the future. The side-chain type is primarily used in imaging applications; in the future, attempts could be made to attach therapeutic small molecules to the side chains to achieve multi-drug synergistic therapy. Prodrug-type systems offer high drug-loading capacity and can self-assemble under ROS conditions to reduce systemic toxicity, presenting significant application potential.[97] However, ensuring effective accumulation of the prodrug at the site of injury remains an area requiring further optimization.

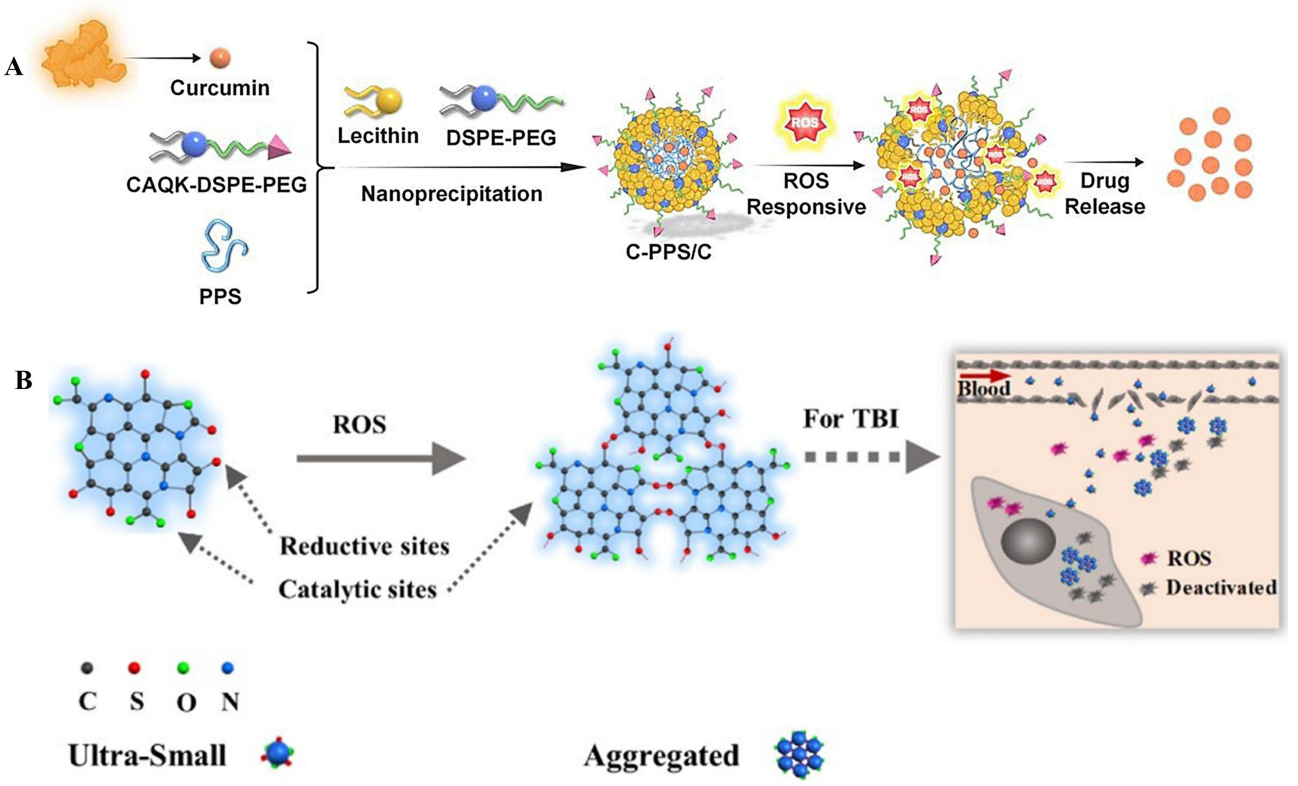

Figure 5 (**A**) ROS-mediated disintegration of nanoparticle structure; Copyright © The Author(s) 2025. (**B**) ROS-mediated nanoparticle aggregation. Copyright © American Chemical Society 2020.

Enzyme-Responsive Nanoparticles

Enzymes play a central role in cellular regulation. When the activity of a specific enzyme is associated with a target tissue, or when the enzyme concentration is high at the target site, nanomaterials can facilitate drug delivery through enzymatic conversion.[98] There are two main strategies for constructing enzyme-responsive nanoparticles: the first involves using enzymatic reactions to cleave specific chemical bonds, thereby releasing the encapsulated drug.[99] The second involves anchoring enzyme-responsive groups to the nanoparticle surface; upon enzyme activation, these groups alter the nanoparticle's physicochemical properties. This strategy is widely applied in the design of enzyme-responsive inorganic nanoparticles and small molecules.[100,101] The enzymes whose activity increases in the injured area following TBI include hexokinase (HK), pyruvate kinase (PK), and NADPH oxidase 2 (NOX2).[102,103] Conversely, to date, no nanoparticles targeting these TBI-associated enzymes have been reported, and further research is needed in the future.

Thermo-Responsive Nanoparticles

Thermosensitive nanoparticles undergo structural changes at specific critical temperatures. They operate in two modes: dissociation above the critical temperature and dissociation below the critical temperature.[104] Given the characteristics of body temperature, the mode involving dissociation above the critical temperature is typically selected. Because the injured site may warm up by 1–2°C due to the inflammatory response following TBI, it is most reasonable to design responsive nanoparticles with a critical temperature between 38–40°C.[105] Conversely, the common thermosensitive units such as poly(N-isopropylacrylamide) (PNIPAM), elastin-like peptides, and polysiloxanes all have critical temperatures that fall either above or below this range.[106–109] Although studies have shown that surface grafting with 4-vinylpyridine can increase the critical temperature of PNIPAM-modified nanoparticles and promote drug release.[110] Nevertheless, the critical temperature of these nanoparticles remains difficult to precisely control. In summary, compared to other approaches, the response conditions for thermosensitive nanoparticles are highly demanding, temperature control is

challenging, and human body temperature is subject to fluctuations. Consequently, the design of temperature-responsive nanoparticles is quite complex and requires further exploration in the future.

Other Exogenous Responsive Nanoparticles

Photoresponsive nanoparticles undergo reversible or irreversible physicochemical changes when exposed to light of specific wavelengths (ultraviolet, visible, or near-infrared), thereby triggering drug release or energy conversion.[111] By introducing photosensitive groups such as coumarin esters, quercetin derivatives, and pyranones into the core of the nanoparticles, light-mediated controlled drug release can be achieved.[112,113] Furthermore, some nanoparticles can convert light energy into thermal energy, which is a unique mode of action for light-responsive nanoparticles.[114] For example, gold nanoparticles generate heat through plasmon resonance when exposed to near-infrared irradiation. Based on this principle, Ko et al embedded gold nanoparticles into a hydrogel, which heated to 40°C under near-infrared, effectively alleviating inflammation caused by nerve damage.[115]

Magnetoresponsive nanoparticles are functional nanomaterials capable of reversible magnetization or permanent magnetism. Their core characteristics include the generation of directed motion, magnetocaloric effects, or magneto-electric effects under the influence of an external magnetic field, therefore they are primarily used in biosensing and medical imaging.[116] Conventional magnetic nanomaterials contain magnetic elements such as iron, cobalt, nickel, and manganese. Among these, iron oxide nanoparticles (IONPs) have become the most common magnetoresponsive materials due to their low toxicity and excellent biocompatibility.[117] In nerve regeneration therapy, the magnetoelectric effect of IONPs imparts electrical conductivity to hydrogels, thereby regulating the fate of neural stem cells.[118]

Under ultrasonic stimulation, certain materials can undergo cavitation and phase transitions, which are the primary mechanisms of action for ultrasonic-responsive nanoparticles.[119,120] These nanoparticles typically consist of a stable shell and an ultrasonic-responsive core. For example, Airan et al used a polyethylene glycol-b-polycaprolactone block copolymer as the matrix to encapsulate a liquid perfluorocarbon core and the target drug. Under ultrasonic irradiation, the perfluorocarbon core undergoes a liquid-to-gas phase transition, thereby enabling drug release.[121]

Overall, endogenous responsive nanoparticles exhibit high targeting efficiency; Conversely, due to significant fluctuations in the molecular composition of the in vivo microenvironment, it is difficult to precisely regulate drug release. Exogenous responsive nanoparticles allow for precise control of drug release via external devices, but they lack sufficient targeting capability. Therefore, future research may consider combining these two strategies to achieve more precise spatiotemporal control of drug delivery.

Nanoparticles for the Treatment of TBI

Secondary injury following TBI involves multiple pathological processes, among which inflammatory response and oxidative stress play particularly significant roles. These pathological physiological processes represent key therapeutic targets for nanoparticle-promoted neuroprotection. Table 2 summarizes the primary roles of various nanoparticles in the treatment of TBI.

Anti-Inflammation

Reduces Inflammatory Cell Infiltration

As a trigger and key determinant of secondary damage, early regulation of the inflammatory response is crucial in the treatment of TBI. Following disruption of the BBB, various immune cells, including monocytes, macrophages, and microglia, migrate to the site of injury.[145,146] Immunomodulatory nanoparticles (IMPs) are carboxylated polylactic-co-glycolic acid particles with a diameter of 500 nm and a highly negatively charged surface; they have been approved by the FDA for use in relevant studies.[147] Research indicates that these nanoparticles can bind to macrophage receptors on the surface of monocytes, redirecting these cells to the spleen and preventing their accumulation at the injury site.[148] Research by Sharma et al confirmed that intravenous administration of immunomodulatory nanoparticles significantly reduces the infiltration of blood-derived monocyte-derived macrophages, thereby alleviating the inflammatory response.[149] Bertossi et al subsequently further clarified the optimal timing for administering immunomodulatory nanoparticles: administration within 6 or even 12 hours after injury still yields significant therapeutic effects, whereas

Table 2 The Design and Main Functions of Nanoparticles

Nanoparticle Type	Targeting Strategy	Targeting Mechanism	Size (nm)	Animal Model	Route of Administration	Main Functions	Ref
Immunomodulatory nanoparticle (IMP)	N/A	Macrophage receptor with collagenous structure on monocytes	500	TBI mice model	Intravenous injection	Reduced the infiltration of monocytes at the site of injury	[122,123]
Gold nanoclusters (AuNCs)	N/A	N/A	1.87 ± 0.14	Ex vivo stroke model	N/A	Inducing microglial M2 polarization	[124]
Engineered extracellular vesicles (EEVs)	Incorporating ultra-small paramagnetic nanoparticles	Guidance by the external magnetic field	118	TBI Rat Model	Continuous intranasal administration	Reduce microglial activation by inhibiting the NF-κB signaling pathway	[125]
PLGA-PEG-COOH based Nanoparticle (T-Hes)	Ligand with two 5-HT ends	Targeting MPO	92	TBI mice model	Intravenous injection	Inducing microglial M2 polarization	[126]
Self-assembled nanoparticles (T-GSK)	Binding cinnamyl-F-(D)L-F-(D) L-F (CFLFLF)	Targeting the formylpeptide receptor (FPR)	73	TBI rat Model	Intravenous injection	Prevent the formation of NETs in brain injury sites	[127]
β-lactoglobulin nanoparticle (C-β-LG/DSF)	Binding CAQK peptide	Targeting ECM	156.54±4.52	TBI mice model	Intravenous injection	Mitigate pyroptosis and reduce inflammation	[72]
Nanoliposome (C-Lips/RV)	Binding CAQK peptide	Targeting ECM	96.35±6.74	TBI rat model	Intravenous injection	Mitigate pyroptosis and reduce inflammation	[128]
Composite PPS_{120} particles (C-PPS/C)	Binding CAQK peptide	Targeting ECM	99.6±2.57	TBI mice model	Intravenous injection	Break the "ROS-Neuroinflammation" vicious cycle	[67]
Ultrasmall organic nanozyme	Free thiols	Response of ROS	Unbound state: 3 Aggregated: 300	TBI mice model	Intravenous injection	Multi-enzymatic antioxidant function	[96]
Trimetallic nanozyme (triM)	N/A	N/A	12.6 ± 0.7	TBI mice model	Intravenous injection	Multi-enzymatic antioxidant function	[129]
CeO_2 nanozymecoated with 6-AHA and PVP (CYX201)	N/A	N/A	3.49±1.11	TBI rat model	Intravenous injection	Multi-enzymatic antioxidant function	[130]
Pt/CeO_2 nanozyme-based bandage	N/A	N/A	N/A	TBI mice model (CCI)	Pasted on the wound	Multi-enzymatic antioxidant function	[131]
Mn_3O_4 nanozyme (NCM@MP)	Coated with neutrophil-like cell membrane	Mimicing the chemotaxis of inflammatory cells	78.8	TBI mice model (CCI)	Intravenous injection	Multi-enzymatic antioxidant function	[132]
PEG modified $Cu_{5.4}$ O nanozyme	N/A	N/A	2.1	TBI mice model	Intravenous injection	Multi-enzymatic antioxidant function	[133]
PEG modified Fe_3O_4 nanozyme	N/A	N/A	N/A	Cerebral ischemic stroke mice model	In situ injection at the injured site	Multi-enzymatic antioxidant function	[134]
ZnO-CuS microsphere (MSs)	N/A	N/A	200-500	In vitro cell model of oxidative stress	N/A	Multi-enzymatic antioxidant function	[135]
2D V_2C MXene nanozyme	N/A	N/A	Thickness:2.7	In vitro cell model of oxidative stress	N/A	Multi-enzymatic antioxidant function	[136]
Poly(ethylene glycol)-functionalized hydrophilic carbon clusters (PEG-HCCs)	Banding anti-P-selectin antibody	Targeting damaged endothelial cells expressing P-selectin	40-60	TBI rat model	Intravenous injection	SOD -enzymatic Antioxidation	[137,138]
Lysine and ascorbic acid-derived carbon dot nanozymes	N/A	N/A	3.1	TBI mice model	Intravenous injection	Multi-enzymatic antioxidant function	[139]

(*Continued*)

Table 2 (Continued).

Nanoparticle Type	Targeting Strategy	Targeting Mechanism	Size (nm)	Animal Model	Route of Administration	Main Functions	Ref
L-lysine and L-cysteine-derived carbon dot nanozymes	N/A	N/A	1.38±0.22	TBI mice model	Not mentioned	SOD-enzymatic Antioxidation	[140]
Oligomeric nanozyme (O-NZ)	N/A	N/A	3.4	TBI mice model	Intravenous injection	Multi-enzymatic antioxidant function	[141]
Porous silicon nanoparticle (pSiNP)	Binding CAQK peptide	Targeting ECM	130	TBI mice model	Intravenous injection	Reduces Lesion Volumes	[142]
Peripheral nerve-derived stem cell spheroids	N/A	N/A	75.1 ± 2.4 μm	TBI rat model	Multiple intrathecal injections	Promote remyelination	[143]
SDF-1 loaded nanoparticles (NP SDF-1)	N/A	N/A	167.9 ± 0.38	TBI mice model	In situ injection at the injured site	No actual functional results have been reported.	[144]
BTO/rGO hybrid piezoelectric nanostickers	N/A	N/A	200	TBI rat model	In situ injection at the injured site	Promoted the differentiation into neurons of NSCs and accelerated the maturation of differentiated neurons	[145]

Abbreviations: 6-AHA, 6-aminocaproic acid; PVP, polyvinylpyrrolidone; 5-HT, 5-hydroxytryptamine; MPO, myeloperoxidase; BTO, barium titanate; rGO, reduced graphene oxide.

delaying administration to 24 hours results in a marked reduction in therapeutic efficacy.[122] This finding suggests that the therapeutic window for immunomodulatory nanoparticles is not limited to the hyperacute phase within 2 hours post-injury but encompasses a broader time window for intervention. In the future, strategies such as surface functionalization, drug-carrying composites, and combination therapy with stem cells are expected to further extend the therapeutic window of immunomodulatory nanoparticles and broaden their range of indications.

Regulate Microglia Polarization

Following TBI, microglia polarize in response to external stimuli and differentiate into the pro-inflammatory M1 phenotype, leading to neuronal damage; simultaneously, there is a tendency for them to differentiate into the anti-inflammatory M2 phenotype, which promotes neural regeneration.[150] Targeting this pathological feature, Lan's team developed dihydrolipoic acid-functionalized gold nanoclusters (DHLA-AuNCs).[123] Results showed that 5 μg/mL of DHLA-AuNCs significantly downregulated the mRNA expression levels of pro-inflammatory M1-like markers (MHC-II, CD86, iNOS) while upregulating the mRNA expression levels of anti-inflammatory M2-like markers (Arg-1, CD206). Further mechanistic studies suggest that DHLA-AuNCs may promote the phenotypic shift of microglia from M1 to M2 by inhibiting the NF-κB pathway. Although promising results were obtained, this study did not include in vivo experiments. Further evaluation is needed to determine whether the in vitro effective concentration of 5 μg/mL is effective in vivo, as well as to assess the in vivo distribution and metabolism of the nanoparticles. In another study, Li et al isolated extracellular vesicle (EV) nanoparticles from human adipose-derived stem cells (hADSCs).[124] These vesicles similarly inhibited microglial activation and M1 phenotypic polarization by suppressing the NF-κB signaling pathway, promoted neuronal branching and dendritic spine formation, and increased total dendritic length (Figure 6). Notably, these vesicles can be administered intranasally rather than intravenously. They fuse directly with the plasma membrane via the transmembrane protein CD9, bypassing endosomal capture, thereby enabling direct delivery to brain cells, which holds great promise for clinical applications.

Both studies identify the NF-κB pathway as a central mechanism regulating microglial polarization. Additionally, the regulation of microglial polarization is a complex, multi-pathway, and multi-level network process; in addition to NF-κB, pathways such as STAT, MAPK, and PI3K/Akt also play critical roles.[146] Therefore, future research should employ multi-omics approaches to systematically analyze the overall impact of nanoparticles on the polarization regulatory network, rather than focusing solely on a single pathway.

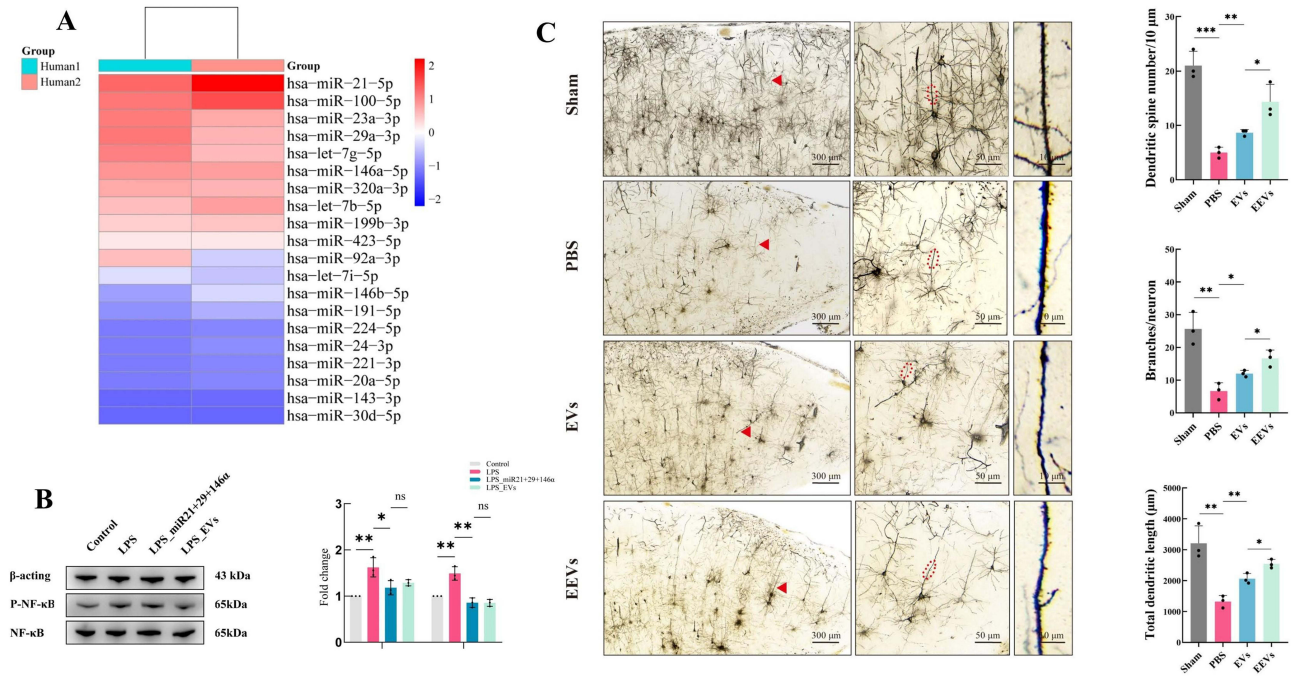

Figure 6 (**A** and **B**) MicroRNAs able to inhibit microglial activation via the NF-kB signaling pathway have been found in extracellular vesicles; (**C**) Nanoparticle treatment leads to enhanced neuronal branching and an increase in dendritic spine density, accompanied by a notable extension of total dendritic length, The image with a 50 μm scale bar is the magnified view of the area indicated by the red arrow in the image with a 300 μm scale bar; the image with a 10 μm scale bar is the magnified view of the area marked by the red circle in the image with a 50 μm scale bar.*P < 0.05, **P < 0.01, ***P < 0.001; "ns": not significant. Copyright © The Author(s) 2025.

Neutralization of Neutrophil-Derived Cytotoxic Products

Neutrophils are the primary mediators of the early inflammatory response following TBI. Studies have shown that within 4 to 8 hours after injury, neutrophils begin to infiltrate and accumulate at the site of injury, thereby causing microcirculatory dysfunction, neuronal death, and cerebral edema.[151] Myeloperoxidase (MPO) is a heme-containing enzyme located in the azurophilic granules of neutrophils; its metabolic products can disrupt tissue barriers and exacerbate local inflammatory responses. Based on this, Yao et al designed and synthesized T-Hes, a hesperidin-based nanodelivery system, to target MPO released by neutrophils. Following intravenous administration, T-Hes sustainably releases hesperidin, inhibiting MPO secretion by neutrophils and thereby significantly reducing the migration and aggregation of neutrophils at the injury site after TBI.[125] Additionally, MPO is a key effector molecule for the bactericidal function of neutrophils, and long-term or excessive inhibition of MPO may increase the risk of infection.[152] Therefore, this nanoparticle is suitable for short-term intervention during the acute phase of TBI, and its long-term safety requires further systematic evaluation.

Neutrophil extracellular traps (NETs) are filamentous structures released by neutrophils in response to specific stimuli, composed of a disassembled chromatin scaffold and granule proteins. Studies have shown that NETs can cause massive host cell death, further exacerbating neurological damage and inflammatory responses.[153] Targeting this mechanism, Mu et al developed a neutrophil-targeted delivery system loaded with the PAD4 inhibitor GSK484, which effectively suppressed NET formation at sites of brain injury, thereby reducing neuroinflammation and improving neurological deficits.[126] In contrast, NETs are a specific product of neutrophil hyperactivation following TBI, and their formation requires PAD4-mediated histone citrullination and chromatin disassembly—a process that rarely occurs under physiological conditions. Therefore, NETs possess high pathological specificity as a therapeutic target, and targeted interventions are unlikely to interfere with the basic defensive functions of neutrophils (such as phagocytosis and chemotaxis), offering a wider safety margin compared to MPO inhibition.

Targeting Pyroptosis

Pyroptosis is a form of programmed cell death typically triggered by pathogen-associated molecular patterns or damage-associated molecular patterns.[154] It is characterized by cell membrane rupture and the release of cellular contents, thereby triggering a robust inflammatory response.[155] Following TBI, the NLRP3 and NLRC4 inflammasome complexes are activated, which in turn activate the Caspase-1 or Caspase-11/4/5 families. Activated caspases cleave Gasdermin-D, causing it to form pores in the cell membrane, leading to the leakage of cellular contents, ultimately triggering a strong inflammatory response and exacerbating brain tissue damage.[156]

Disulfiram (DSF) is an FDA-approved medication for the treatment of alcohol dependence that inhibits pyroptosis by blocking GSDMD-mediated pore formation.[157] Additionally, DSF's rapid metabolism, high hydrophobicity, and poor stability limit its systemic application. Based on this, Zhang et al developed a β-lactoglobulin (β-LG) delivery system loaded with DSF (C-β-LG/DSF) to inhibit pyroptosis (Figure 7).[71] Experimental results showed that C-β-LG/DSF had a half-life of 8.28 hours, significantly prolonging the circulation time of DSF, enhancing accumulation at the site of injury, and remaining present in significant quantities in the circulation even after 24 hours. Resveratrol (RV) is a naturally occurring polyphenol; recent studies have shown that it can also inhibit pyroptosis. Han et al developed C-Lips/RV, a CAQK-peptide-modified nanolipid carrier, for the delivery of resveratrol.[142,143,159] Similar to DSF, C-Lips/RV effectively inhibits pyroptosis by preventing GSDMD-NT pore formation and reducing the release of pro-inflammatory cytokines within cells.

Inhibiting pyroptosis provides a novel therapeutic target for cytoprotection following TBI. Additionally, pyroptosis represents only one of multiple cell death modalities promoted by inflammatory responses, and pyroptosis inhibition alone is insufficient to adequately alleviate inflammation-mediated neuronal injury. Therefore, future research should further explore the mutual regulatory mechanisms between pyroptosis and other forms of cell death, integrating with the progression of inflammatory responses to attenuate inflammatory damage from multiple perspectives.

Gene Therapy

Gene-based nanotherapy represents an innovative and promising approach to disease treatment. RNA interference can effectively silence specific target genes—particularly those for which no corresponding small-molecule antagonists are available—thereby exerting a unique neuroprotective effect.[158,160,161]

Many aspects of secondary injury following TBI are closely associated with the RhoA/ROCK signaling pathway.[162–164] Studies have shown that inhibiting the activation of this pathway can reduce neuroinflammatory responses and promote neurological recovery.[162] Based on this, Christian's team developed a cationic copolymer-based nanocarrier—poly(lactic-co-glycolic acid) grafted with polyethyleneimine—for the targeted delivery of siRNA.[165] In a TBI model, direct injection of the PGP/siRhoA nanocomposite into the parenchyma of the injured area demonstrated significant therapeutic effects: 7 days post-injury, lesion volume was reduced, inflammatory responses were attenuated, cell apoptosis was decreased, and neuronal survival rates were significantly higher compared to the untreated group.

The chemokine CCL20 selectively interacts with its receptor CCR6 and, acting as a chemotactic factor, promotes the migration of various immune cells—including Th17 cells, monocytes, and dendritic cells—to the central nervous system.[166] Cytokines such as IL-17A secreted by these cells further exacerbate neuroinflammatory responses.[167] To address this, Mayilsamy et al utilized branched polyamide-amine to adsorb plasmids encoding shRNA, constructing a nanocomposite named shCombo. The results showed that shCombo effectively delivers shRNA to the brain, silencing the CCL20 and CCR6 genes and thereby suppressing the inflammatory response. Furthermore, shCombo can induce human mesenchymal stem cells to secrete BDNF, further enhancing the therapeutic effect.[168]

Gene-based nanotherapy holds immense potential for TBI treatment, particularly for targets that are refractory to conventional small-molecule drug intervention. Additionally, siRNA/shRNA-mediated gene silencing effects are typically transient. While this reduces the risk of long-term off-target effects, it also necessitates repeated administration to maintain therapeutic efficacy, potentially increasing immunogenicity and cumulative toxicity.[169] Conversely, plasmid-based shRNA expression systems, though capable of prolonging the duration of action, carry concerns regarding genomic integration and long-term uncontrollable expression.[170] Therefore, future efforts may focus on developing intelligent

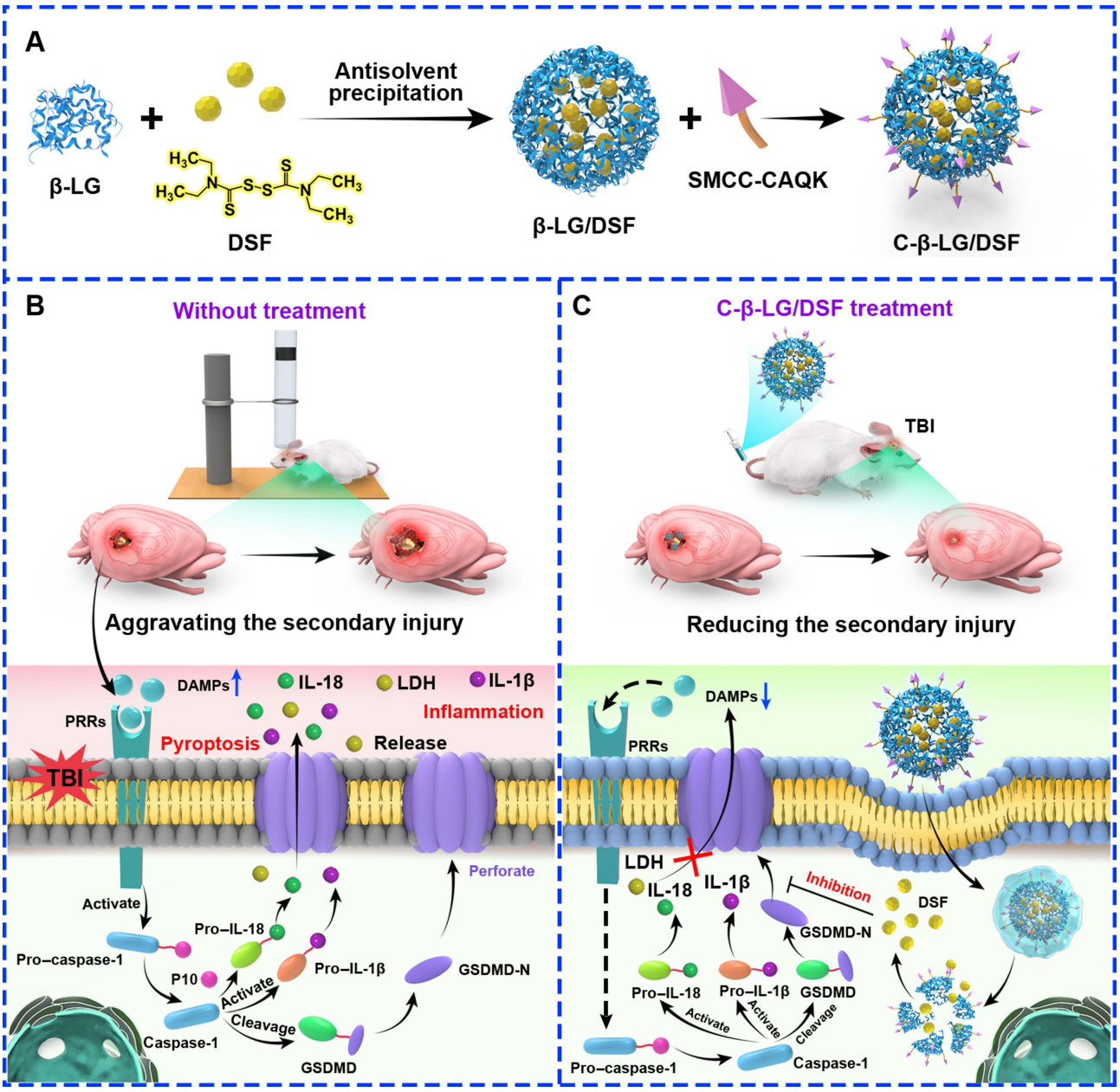

Figure 7 (**A**) Illustration depicting the synthetic procedure for C-β-LG/DSF nanocomposites. (**B**) Following TBI, the absence of C-β-LG/DSF intervention results in elevated damage associated molecular patterns (DAMPs) levels; these endogenous molecules engage pattern recognition receptors (PRRs) to stimulate inflammasome assembly, consequently inducing pyroptotic cell death. The resultant outpouring of pro-inflammatory mediators (eg, IL-18, IL-1β) fuels robust neuroinflammatory responses, aggravating secondary neural damage. (**C**) Administration of C-β-LG/DSF post-TBI attenuates this cascade: DSF prevents GSDMD-N terminal pore assembly on cellular membranes, thereby suppressing pyroptosis and downstream cytokine secretion, ultimately dampening neuroinflammation and ameliorating secondary injury progression. Downward arrows denote downregulation at the molecular level; upward arrows denote upregulation.

carriers capable of releasing nucleic acids in response to the TBI microenvironment, thereby achieving more precise spatiotemporal control.

Other Potentially Beneficial Regulatory Strategies

Astrocytes play a dual regulatory role in central nervous system inflammation, similar to microglia.[171,172] Injury triggers the release of various factors that promote the transformation of astrocytes into A1 or A2 types.[173,174] Among these, A1 astrocytes release pro-inflammatory mediators such as IL-1β, TNF-α, IL-6, C3, MX1, and CCL2, exacerbating the inflammatory response and damaging neurons and synapses.[175] In contrast, A2 astrocytes primarily express and release

anti-inflammatory cytokines and neurotrophic factors, modulating the inflammatory response and promoting neuronal survival, synaptic remodeling, and tissue regeneration.[176] Therefore, regulating the A1/A2 polarization state of astrocytes represents a promising therapeutic strategy for alleviating inflammatory responses.

Regulatory T cells (Tregs) are a distinct subset of $CD4^+$T lymphocytes that exert immunosuppressive functions by secreting inhibitory cytokines such as IL-10 and transforming growth factor-β.[177,178] In healthy brain tissue, Tregs are present in very low numbers and are primarily distributed in the choroid plexus, pia mater, and perivascular spaces of the brain parenchyma.[179] Additionally, under pathological conditions such as TBI, stroke, and neurodegenerative diseases, peripheral Tregs rapidly infiltrate the damaged central nervous system.[180] Upon reaching the site of injury, they modulate the immune response by inhibiting the excessive activation of microglia and astrocytes, reducing the release of pro-inflammatory factors, and blocking the influx of peripheral immune cells.[181]

Although the modulation of astrocytes and Tregs has demonstrated effective anti-inflammatory effects, the use of anti-inflammatory nanoparticles to modulate these cells has not yet been reported in the treatment of TBI. Although certain drug molecules, such as LASSBio-1911 and semaglutide, have been shown to modulate astrocytes or Tregs in stroke or other disease models, there is limited direct evidence regarding their efficacy in the treatment of TBI.[182–184] Therefore, future research could explore loading these drugs onto nanoparticles to evaluate their anti-inflammatory effects in the treatment of TBI. In the future, spatial transcriptomics technology could also be used to map the spatiotemporal distribution of astrocytes and Tregs following TBI, thereby identifying the optimal target regions and timing for nanoparticle delivery.

Anti-Oxidative Stress

Following TBI, mitochondrial dysfunction and the imbalance of endogenous antioxidant mechanisms lead to ROS accumulation at the injured site. These ROS attack unsaturated fatty acids, proteins, DNA, and other cellular components, ultimately resulting in neuronal cell death. Therefore, ROS scavenging represents another important strategy for alleviating secondary damage induced by TBI.[4,185–187]

Scavenge ROS via Nanozyme

Nanozymes can mimic the catalytic activities of natural enzymes, such as catalase (CAT), peroxidase (POD), glutathione peroxidase (GPx), and superoxide dismutase (SOD), among others.[188,189] Based on these catalytic properties, nanozymes have made significant advances in the application of antioxidant stress therapy for diseases.[190,191]

According to their composition and structure, nanozymes can be classified into the following categories: (1) metallic elemental nanozymes, such as gold and platinum nanozymes;[192,193] (2) metal oxide nanozymes, such as cerium oxide (CeO_2), iron oxide (Fe_3O_4), zinc oxide (ZnO), and copper oxide (CuO);[194–197] (3) inorganic non-metallic nanozymes, such as selenium-based compounds, carbon-based materials, carbon nanotubes, and graphene oxide.[198,199] The catalytic efficiency of some nanozymes is comparable to that of natural enzymes. Furthermore, nanozymes typically possess multiple functionalities (eg, magnetic and optical properties), enabling the integration of catalysis with other functions and conferring reusability.[200] Conversely, certain nanozymes still face limitations in biocompatibility, cytotoxicity, production cost, and biodegradability.[201]

Metallic Element Nanozymes

Single-metal nanocatalysts are typically composed of noble metal nanomaterials with good chemical stability. Conversely, bare single-metal nanoparticles (eg, Ag, Pt) tend to aggregate into nanoclusters, leading to decreased catalytic activity.[202] Moreover, most unmodified noble metal nanocatalysts exhibit biological toxicity, limiting their potential applications in clinical medicine.[203,204] Therefore, single-metal nanocatalysts are rarely employed in practical applications. To improve their catalytic performance, they are usually doped with other nanomaterials or adopted in the form of bimetallic or multimetallic alloy structures.[205] Professor Zhang's team synthesized a multimetallic nanozyme (triM) with a Pt:Pd:Mo atomic ratio of 6:9:1.[128] This nanozyme triM exhibits multiple enzyme-mimicking activities, including SOD- and CAT-like activities, which can effectively scavenge ROS and RNS, thereby improving mouse survival. This nanozyme demonstrates a preference for neutral conditions. Conversely, brain tissue pH can drop to

approximately 7.0 following TBI, and the catalytic activity of triM under acidic conditions remains unclear. Future studies should systematically evaluate the catalytic behavior of this nanozyme in the pathological microenvironment of TBI to clarify whether it can maintain high-efficiency activity under pathological conditions.

Metal Oxide Nanozymes

Cerium oxide (CeO_2) is a highly efficient ROS-scavenging enzyme, with Ce^{3+} and Ce^{4+} possessing a self-regenerating recycling mechanism.[206–208] Kang et al synthesized ultra-small polymer-coated cerium oxide nanoparticles (CX201) using 6-aminocaproic acid and polyvinylpyrrolidone as coating materials.[129] The hydrophilic polymer coating enhanced the stability of CeO_2 nanozymes. In a TBI model, the CX201 group demonstrated significantly greater functional recovery compared to the control group.

Studies have shown that certain metals can increase the oxygen vacancy content on cerium oxide nanoparticles to improve catalytic efficiency.[209] For example, Zhang et al incorporated chromium into the cerium oxide nanozyme, resulting in a 3- to 5-fold increase in enzymatic activity.[205] Additionally, Yan et al discovered that platinum single-atom systems exhibit exceptionally high catalytic activity.[130] By integrating Pt into Ce clusters, they prepared a Pt/CeO_2 antioxidant bandage (Figure 8A). More importantly, ultra-small Pt/CeO_2 clusters demonstrate superior ROS-scavenging activity, long-term stability, and enzymatic properties due to their high specific surface area (Figure 8B and C). The lattice expansion induced by platinum atoms on the cerium oxide crystal surface increased nanozyme activity by 3- to 10-fold and ROS clearance capacity by 2-to 10-fold. As a non-invasive therapeutic approach, the Pt/CeO_2 composite enzyme-coated bandage has shown sustained efficacy in reducing oxidative stress following TBI and holds considerable promise for clinical application.

Mn in Mn_3O_4 exhibits multiple valence states ($Mn^{2+,}$ Mn^{3+}, and Mn4+), enabling flexible participation in electron transfer during redox reactions.[210] Mn_3O_4 nanoparticles display SOD- and CAT-like enzymatic activities, attracting considerable interest in the medical field in recent years.[211,212] Li et al engineered a composite Mn_3O_4 nanozyme coated with a neutrophil-mimicking cell membrane (NCM@MP).[131] NCM@MP can respond to inflammatory stimuli to release internal Mn_3O_4 nanozymes, thereby significantly alleviating oxidative stress by inhibiting Ca^{2+} influx and scavenging ROS.

$Cu_{5.4}O$ is a novel copper-based nanozyme with an ultra-small particle size below 10 nm, combining the dual advantages of metallic copper (Cu) and cuprous oxide (Cu_2O) nanocrystals while exhibiting a range of enzyme-mimicking activities.[213,214] In Professor Luo's research, they synthesized an ultra-small $Cu_{5.4}O$ nanozyme with

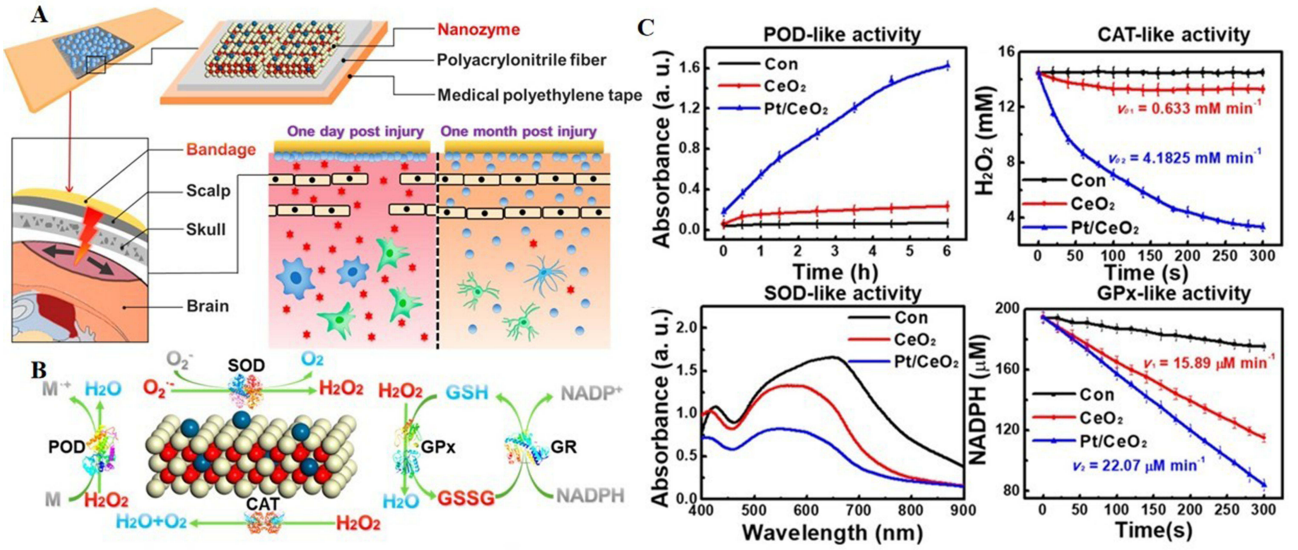

Figure 8 (**A**) Schematic diagram of single-atom catalytic bandage treatment for brain trauma based on nanozyme. (**B**) Enzyme simulation characteristics of single-atom Pt/CeO2. (**C**) The crystal enzyme-like activity of Pt-doped CeO_2 is superior to that of pure CeO_2. Copyright © American Chemical Society 2019.

remarkable ROS-scavenging capacity.[132] Through PEG modification, the biocompatibility of the ultra-small $Cu_{5.4}$ nanozyme was further enhanced. This $Cu_{5.4}$O-PEG nanozyme can regulate oxidative stress and mitigate ferroptosis, thereby effectively protecting neurons following TBI.

Other Potentially Beneficial Metal Oxide Nanozymes

Iron oxide (Fe_3O_4) nanozymes have been demonstrated to possess POD-, CAT-, and SOD-like enzymatic activities,[215] with their catalytic activity primarily derived from the reversible redox reaction between Fe^{3+} and Fe^{2+}. In stroke research, PEG-coated Fe_3O_4 nanozymes have been shown to improve local oxidative stress by reducing ROS levels in ischemic brain regions and enhancing superoxide dismutase activity, thereby protecting BBB integrity.[133,134]

Zinc oxide (ZnO) nanozymes exhibit POD-like catalytic activity and possess numerous advantages including safety, non-toxicity, biocompatibility, and low cost, rendering them widely applicable across various industries.[184] For instance, ZnO nanozymes have achieved favorable outcomes in antitumor and antibacterial therapies through ROS scavenging.[108,216,217]

Vanadium carbide (V_2C) can simulate the enzyme-like behavior of multiple enzymes due to the presence of vanadium in various valence states (V^{2+}, V^{3+}, V^{4+}, and V^{5+}). Chen et al synthesized a two-dimensional V_2C MXene nanozyme (MXenzyme).[135] This MXenzyme can restore endogenous redox balance without interfering with the body's natural antioxidant defense mechanisms, thereby effectively alleviating inflammation and neurodegenerative diseases caused by ROS.

Although these nanozymes have not yet been directly applied to TBI treatment, previous studies have already demonstrated remarkable antioxidant properties. It is noteworthy that zinc is the most abundant trace element in the brain, playing crucial roles in neuronal structure and function, neural signaling, synaptic plasticity, neurogenesis, and neurodevelopment.[218] Additionally, zinc can reduce neuronal cell death by regulating mitochondrial quality control. Conversely, the relatively low catalytic efficiency of ZnO nanozymes limits their application in TBI treatment.[219,220] Therefore, future efforts may attempt to enhance the catalytic activity of ZnO by doping with other elements to modulate its electronic structure and surface properties.

Carbon Nanozymes

Carbon-based nanozymes are a class of nanozymes constructed from carbon nanomaterials, including carbon nanotubes, graphene, and fullerenes, exhibiting exceptional electrical conductivity, significant surface area, and good biocompatibility.[221]

PEG-Hydrophilic Carbon Clusters (PEG-HCC) is a carbon-based nanozyme with excellent biocompatibility that mimics SOD activity, effectively scavenging large amounts of superoxide anion (O_2^-).[136,222] Marcano et al found that PEG-HCC can target damaged endothelial cells expressing P-selectin, effectively alleviating oxidative stress and repairing vascular dysfunction following TBI.[136] Mendoza's team further demonstrated that PEG-HCC can rapidly restore cerebral perfusion after TBI and quickly reestablish oxidative balance in the brain, even under conditions of hemorrhagic hypotension.[137] However, as an SOD mimetic, PEG-HCC primarily scavenges superoxide anions, with relatively limited direct scavenging capacity for hydroxyl radicals and peroxynitrite; therefore, it may be insufficient alone to fully protect neurons from lipid peroxidation and DNA damage. More critically, P-selectin expression after TBI is limited to a narrow time window, typically peaking at 6–24 hours post-injury; missing this window significantly compromises therapeutic efficacy. Therefore, surface modification with neuronal targeting peptides (such as the T7 peptide) can be employed to achieve vascular–neuronal dual-targeting, thereby enhancing the targeting capability of PEG-HCC.[223]

Mu et al synthesized an ultrasmall fluorescent carbon nanocatalyst (CN) using lysine and ascorbic acid as precursors, capable of efficiently scavenging free radicals such as NO and $ONOO^-$.[138] This nanocatalyst demonstrated exceptional antioxidant properties, exhibiting antioxidant capacity 16 times greater than ascorbic acid. Following CN treatment, the TBI lesion area was significantly reduced, accompanied by decreased astrocyte activation. Ouyang et al synthesized another ultrasmall fluorescent carbon dot nanozyme with outstanding antioxidant activity using L-lysine and L-cysteine as raw materials.[139] The core structure of this carbon dot nanozyme

resembles graphene, featuring hydroxyl and sulfhydryl functional groups on its surface that confer excellent hydrophilicity. In vivo experiments confirmed that this carbon dot nanozyme reduces lipid peroxidation levels and ROS content while enhancing endogenous superoxide dismutase activity, thereby inhibiting apoptosis and promoting survival in TBI rats.

The catalytic activity of nanozymes is largely dependent on the core electron transfer process. Increasing the electron transfer rate can shorten the catalytic reaction time, enabling nanozymes to interact with more substrate molecules and thereby significantly enhancing the overall reaction rate.[224] Based on this principle, Mu et al synthesized an oligomeric nanozyme (O-NZ) featuring a semiconductor core active site that facilitates ultrafast electron transfer processes.[140] As shown in Figure 9A and F, the core of O-NZ is a nitrogen-doped graphitic framework exhibiting multi-enzyme-like properties; its surface is rich in functional groups such as amide and hydroxyl groups (Figure 9B-D), enabling efficient scavenging of ROS and RNS. O-NZ demonstrates exceptional electron transfer kinetics: the intracore electron transfer rate is extremely rapid at merely 1.8 nanoseconds, conferring potent SOD- and GPx-like catalytic activities; moreover, the electron transfer speed between the core and surface functional groups reaches an ultrafast level of 1.2 picoseconds. This ultrafast electron transfer allows O-NZ to rapidly and selectively remove O_2•-, •NO, and ONOO- within milliseconds (Figure 9E). This highly efficient and selective nanozyme brings new hope and possibilities for the clinical treatment of TBI and may have profound impacts across multiple medical fields in the future.

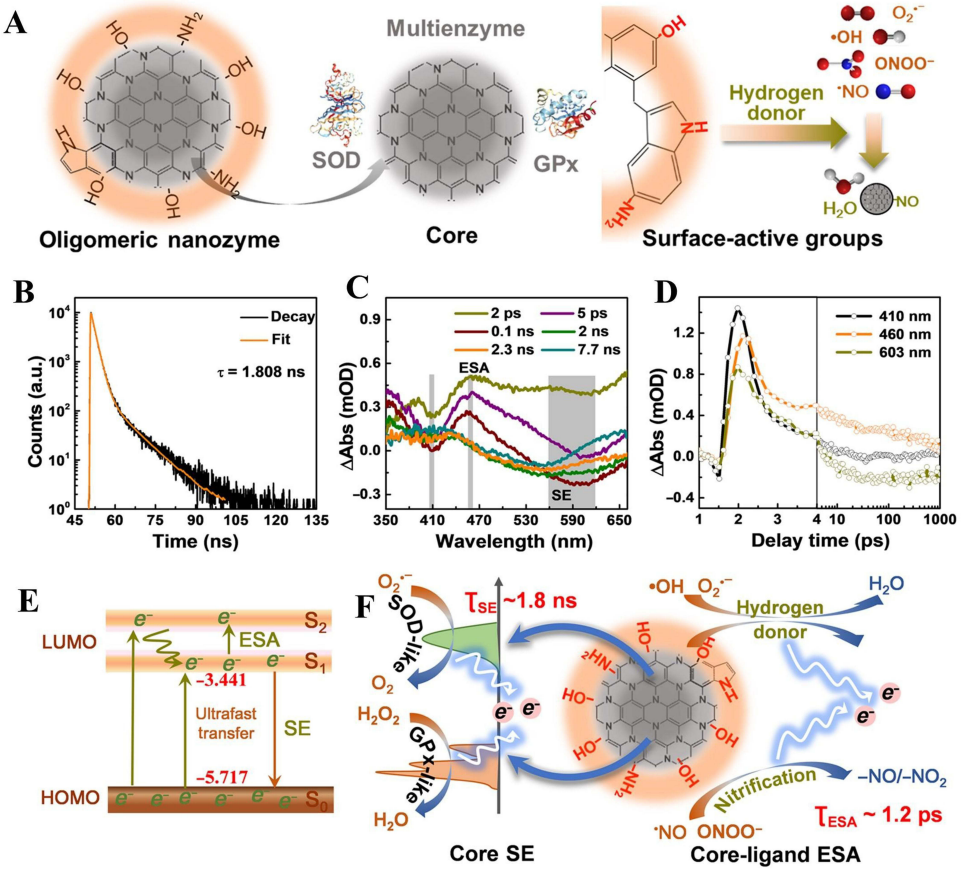

Figure 9 (**A**) Structural illustration of O-NZ, featuring a nitrogen-doped graphite-like core surrounded by surface-active functional groups; (**B**–**D**) Ultrafast electron dynamics of O-NZ; (**E**) Energy level diagram of O-NZ, showing the highest occupied molecular orbital (HOMO) at −5.717 eV and the lowest unoccupied molecular orbital (LUMO) at-3.441 eV; (**F**) Proposed electron transfer mechanism in O-NZ.

Nanoparticles Enhance Neural Regeneration

Following TBI, neural regeneration faces multiple obstacles.[225] First, the deficiency of neurotrophic factors inhibits the proliferation and differentiation/maturation of neural stem cells. Second, the expression and secretion of myelin-associated inhibitory factors, such as Nogo-A, myelin-associated glycoprotein (MAG), and oligodendrocyte myelin glycoprotein (OMgp), are significantly upregulated.[226] These factors bind to specific receptors (eg, NgR1, PirB) on neuronal surfaces, activating the RhoA/ROCK pathway and thereby impeding axonal regeneration.[227] Furthermore, following maturation of the central nervous system, the intrinsic regenerative program of neurons undergoes a transition—genes promoting regeneration (eg, GAP43, Tubb3) are downregulated, while genes inhibiting regeneration (eg, KLF4, PTEN) are upregulated, resulting in a significant decline in the intrinsic regenerative potential of neurons.[228]

Delivering Neurotrophic Factors

Following TBI, the depletion of neurotrophic factors inhibits endogenous neural regeneration. Therefore, supplementation with exogenous neurotrophic factors represents an effective strategy for promoting neural regeneration.

BDNF is one of the most extensively studied neurotrophic factors, promoting neuronal survival, neuroplasticity, and neurogenesis.[229,230] It binds to the high-affinity receptor TrkB and the low-affinity receptor p75, hereby activating the PI3K/Akt and MAPK/ERK pathways to promote neuronal survival and synaptic functional remodeling.[231] However, BDNF has a short half-life and is unstable during blood transport, limiting its direct application. To address this, Wagner et al designed degradable porous silica nanoparticles for encapsulating and precisely delivering BDNF to damaged brain regions.[141] The results showed that this nanodelivery system promoted the growth of slender, highly branched neurites while reducing the extent of brain tissue damage (Figure 10).

NT-3 plays a crucial role in regulating neuronal development and synaptic plasticity, and is predominantly expressed in the hippocampus in the adult central nervous system.[232–235] NT-3 binds to the TrkC receptor, thereby activating key signaling pathways such as PI3K/Akt/mTOR and PI3K/Akt/CREB to enhance neuronal survival, promote axonal elongation, and facilitate myelination.[236] Furthermore, NT-3 promotes the differentiation of neural stem cells into mature neurons while inhibiting their differentiation into glial fibrillary acidic protein (GFAP)-positive glial.[237] Shin et al utilized peripheral neural stem cells to prepare NT-3-secreting nanospheres; following three intrathecal injections, these reduced neuronal loss and promoted axonal regeneration after TBI.[142]

In recent years, in addition to the aforementioned factors, several other neurotrophic factors have been demonstrated to play crucial roles in regulating neurogenesis.[238–247] Though they have not yet been applied to TBI treatment. For example, fibroblast growth factor-2 (FGF-2) is a multifunctional growth factor primarily localized in the subependymal zone of the lateral ventricles and the subgranular zone of the hippocampal dentate gyrus.[248,249] Studies indicate that the high-molecular-weight variant of FGF-2 binds to FGFR1 in the cell nucleus, thereby triggering the expression of neurogenesis-associated genes (such as PROX1 and SEMA5A) and subsequently promoting the survival and differentiation of neural stem cells.[250] Table 3 summarizes the mechanisms of action of these neurotrophic factors. BDNF primarily acts on neuronal survival and synaptic plasticity, whereas its promoting effect on axonal extension is relatively limited. NT-3 plays a crucial role in axonal extension and myelination; however, its capacity to induce neural stem cell proliferation is weaker than that of FGF-2. Conversely, FGF-2 promotes neural stem cell proliferation, but its regulatory effects on neuronal differentiation and synaptic remodeling are inferior to those of BDNF.[251] Single-factor delivery can only intervene in a specific aspect of the regeneration process, making it difficult to address the complexity and dynamic nature of neural regeneration following TBI. Therefore, future strategies may consider the combined administration of multiple neurotrophic factors, with optimization of factor ratios, temporal/phased release control, and other parameters, to provide therapeutic strategies for post-TBI neural regeneration with greater clinical translational potential.[252,253]

Stimulate the Recruitment, Proliferation and Differentiation of Neural Stem Cells

Neural stem cells (NSCs) are considered a promising therapeutic strategy for neurodegenerative diseases due to their ability to generate newborn neurons and replace damaged or lost cells.[254] Furthermore, NSCs secrete growth factors that enhance the brain's intrinsic repair mechanisms. However, the natural process of neurogenesis in the body is often insufficient to fully restore central nervous system function. Despite advances in this field, precisely recruiting newborn

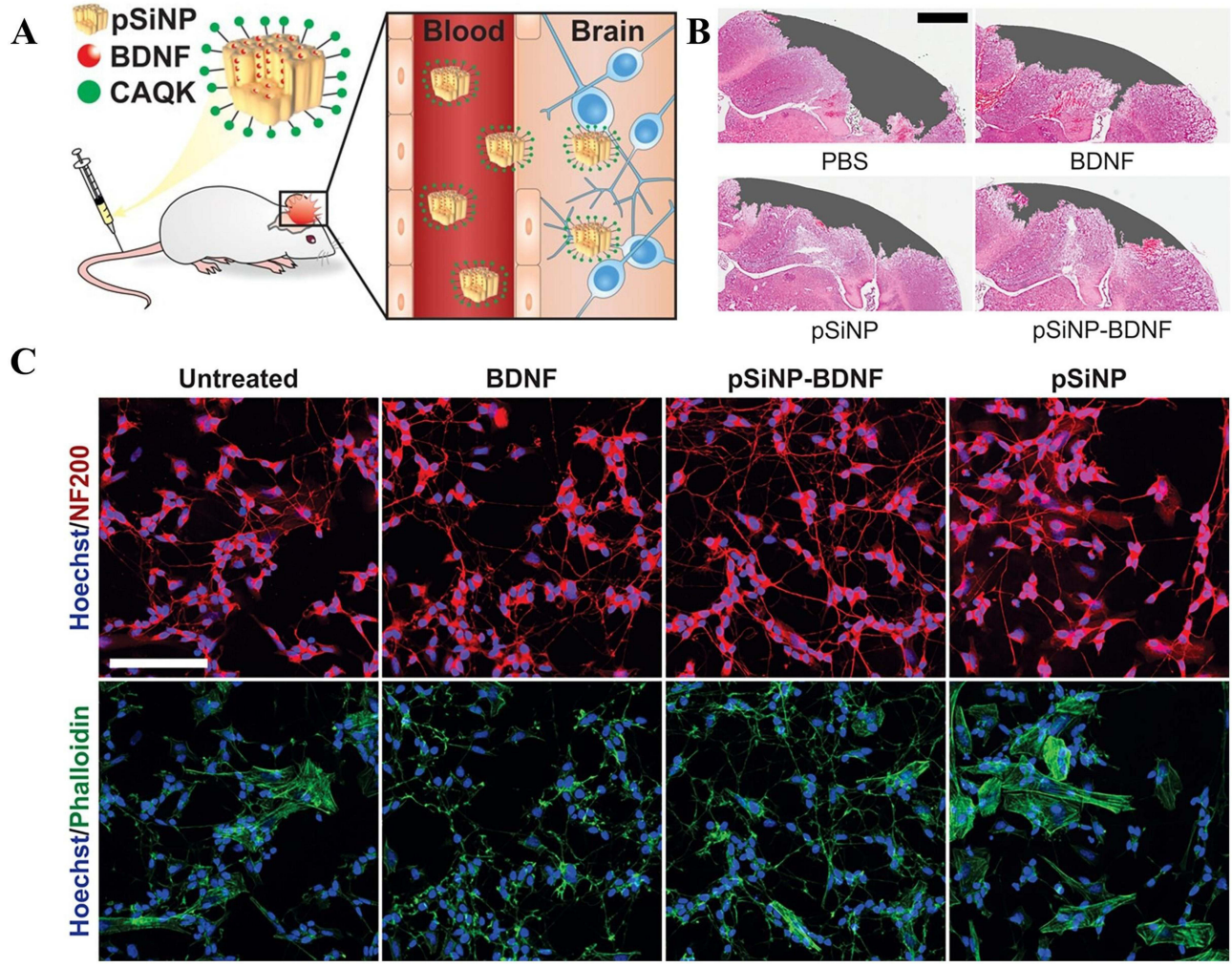

Figure 10 (**A**) Illustration depicting porous silicon nanoparticles loaded with BDNF for application in TBI therapy. (**B**) Following nanoparticle treatment, a decrease in the extent of brain tissue damage was observed. (**C**) Administration of BDNF and pSiNP-BDNF resulted in an increase in the number of intricate and finely branched neurites with multiple junctions, and a reduction in the density of perinuclear cytoskeletal actin. Copyright © American Chemical Society 2022.

neuroblasts and integrating them into damaged tissue remains a significant challenge.[235] Stromal cell-derived factor 1 (SDF-1) is a key protein that regulates stem cell migration and guidance.[255] However, when directly injected into brain tissue, SDF-1 is rapidly degraded by matrix metalloproteinases.[256] To address this, Zamputroni et al developed two types of nano-polymer carriers based on PLGA-nanoparticles (NPs) and microparticles (MPs) for SDF-1 delivery.[144] Although the release profile of MP/SDF-1 resembles the physiological secretion pattern of SDF-1 after brain injury, only NP/SDF-1 promoted the migration of neural stem cells to the injured area, whereas MP/SDF-1 did not. This difference may be attributed to particle size and the sustained release characteristics of NPs.

While promoting neural stem cell recruitment is promising, the low efficiency of NSC proliferation and differentiation limits its clinical application. In recent years, electrical stimulation has attracted considerable attention due to its ability to regulate various stem cell activities, including proliferation, migration, division, differentiation, apoptosis, and necrosis.[257] Studies have shown that electrical signals can stimulate membrane-associated receptors, regulate ion transport and intracellular signaling pathways, and promote the differentiation of NSCs into neurons.[258] Wang et al prepared piezoelectric nanostickers composed of barium titanate (BTO) nanoparticles and reduced graphene oxide (rGO), utilizing the piezoelectric properties of BTO nanoparticles.[145] Under ultrasound stimulation, BTO/rGO nanostickers generate piezoelectric signals that activate voltage-gated calcium channels on the cell membrane, thereby facilitating the transformation of NSCs into neurons, neuronal maturation, and synapse formation. Compared with

Table 3 Summary of Growth Factors and The Mechanisms of Action

Neurotrophic Factors	Receptor	Main Functions	Ref
BDNF	TrkB, p75	Promote neuronal survival	[230,231]
NT-3	TrkC	Promote myelin formation	[234,235,]
FGF-2	FGFR1/2	Promote the extension of damaged axons	[248,249]
NT-4/5	TrkB, p75	Enhance synaptic plasticity and cognitive function	[238,239]
NGF	TrkA, p75	Promote axonal regeneration and myelin formation	[240,241]
EGF	EGFR	Inducing the differentiation of B-type cells in the SVZ into oligodendrocytes	[240]
TGF	TGF-β	Regulation of SVZ cell proliferation	[242]
GDNF	Ret-GFRα1 complex receptor	Directly stimulating neurons to enhance axonal regeneration and promote myelin formation	[243]
CNTF	CNTFRα	Protect glial cells	[254]
VEGF	VEGFR-Neuropilin complex receptor	Regulation of angiogenesis and lymphangiogenesis	[247]

external electrical stimulation, ultrasound-mediated electrical stimulation is safer, more convenient, and avoids the risk of infection.[259]

Challenges in the Clinical Translation of Nanoparticles

Although nanoparticles have demonstrated potential to enhance biochemical functions and improve outcomes in animal models of TBI, our search of North American clinical research centers (clinicaltrials.gov) revealed no registered clinical trials investigating nanoparticles for TBI treatment. This translational gap may be partially attributed to historical setbacks in TBI pharmacotherapy, wherein repeated failures of conventional drug candidates in clinical trials have significantly dampened research progress in this field. For instance, progesterone, a molecule with established neuroprotective and antioxidant properties, demonstrated promising efficacy in Phase II trials by reducing mortality and improving multiple assessment metrics. However, it failed to confer significant improvements in Glasgow Outcome Scale Extended (GOS-E) scores during subsequent Phase III trials.[260,261] Such discrepancies between early-phase promise and late-phase failure have not only eroded investigator confidence but may also have rendered regulatory agencies and funding bodies more risk-averse toward clinical trials of novel TBI therapeutics, including nanoparticle-based delivery systems, thereby indirectly impeding the clinical translation of nanoparticles from bench to bedside. Herein, we analyze the barriers to clinical translation from the perspective of inherent nanoparticle characteristics.

First and foremost, the long-term toxicity of nanoparticles warrants critical attention. Current research predominantly focuses on acute-phase safety observations, while systematic assessments of chronic toxicity (≥90 days) remain extremely scarce. Despite extensive studies, the toxicity mechanisms of metal and metal oxide nanozymes remain poorly elucidated. For metal-based nanozymes capable of persisting in vivo for months to years, such as CeO_2, Pt/CeO_2, and $Cu_{5.4}O$, prolonged accumulation may trigger chronic inflammation, granuloma formation, fibrosis, and even tumorigenesis.[262,263] Furthermore, the metabolic pathways of degradation products (Pt, Pd, and Cr) from multimetallic nanozymes (eg, Pt-Pd-Mo ternary systems, Cr/CeO_2) in vivo remain unclear, and their long-term accumulation risks have yet to be evaluated.[264] More critically, the absence of standardized testing protocols for nanoparticles and the scarcity of multi-omics data severely impede systematic mechanistic understanding. To comprehensively assess these toxicity risks, future research urgently requires unified material characterization, standardized testing conditions, and the adoption of advanced biological technologies to probe mechanistic insights beyond simplistic toxicity screening approaches.[265]

Second, the immunogenicity of nanoparticles warrants particular attention. Studies indicate that approximately 20–40% of the population possesses pre-existing anti-PEG antibodies, which can accelerate the clearance of PEGylated nanoparticles and trigger hypersensitivity reactions.[266] Consequently, PEG-HCC, PEGylated $Cu_{5.4}O$, and PEGylated Fe_3O_4 are all susceptible to this risk. Furthermore, cationic polymers such as PAMAM can activate the complement system, leading to complement activation-related pseudoallergy.[267] Therefore, these PAMAM-assembled nanoparticles require further systematic evaluation of complement activation risks.

Another critical consideration is that nanoparticles become instantaneously enveloped by plasma proteins to form a protein corona within seconds of entering the bloodstream.[268] This phenomenon profoundly alters their biological identity. For instance, following adsorption of apolipoproteins, nanoparticles may be recognized by low-density lipoprotein (LDL) receptors and subsequently sequestered in the liver, fundamentally reshaping their biodistribution.[269] In a similar way, adsorption of immunoglobulins facilitates Fc receptor recognition, triggering immune cell uptake and consequent off-target accumulation.[270] Although pre-adsorbed antibodies can mitigate the impact of protein corona formation while preserving targeting functionality, this strategy is hindered by insufficient in vivo validation, intricate synthesis procedures, and limited drug loading capacity.[271] Consequently, further investigation is warranted to address these limitations.

Summary and Prospect

Nanoparticles hold considerable promise for TBI therapy, attributable to their distinctive physicochemical properties. By modulating particle attributes, such as size, morphology, and surface charge, and employing strategies including receptor-ligand-mediated targeting and surfactant modification, these systems can effectively traverse the BBB and accumulate at lesion sites. Functioning through dual mechanisms, nanoparticles not only mitigate secondary injury via intrinsic antioxidant and anti-inflammatory activities but also serve as efficient vectors for delivering neurotrophic factors and gene therapeutics to promote neural regeneration.

Nevertheless, significant limitations persist in current research designs. Most investigations administer nanoparticles during the acute phase of TBI, assessing efficacy at single time points while neglecting the marked spatiotemporal heterogeneity of disease progression. Pathological targets and microenvironmental signals evolve dynamically across injury phases, from acute neuroinflammation and BBB disruption to subacute glial scarring and chronic neurodegeneration. Consequently, future development should focus on "temporally adaptive" intelligent delivery systems capable of dynamically adjusting targeting strategies and drug release kinetics according to specific pathological phases. Furthermore, although supplementation with neurotrophic factors and modulation of stem cell migration/differentiation facilitate axonal regrowth, axonal regeneration does not equate to functional neural restoration. The reconstruction of neural circuits and synaptic connectivity remains largely uncharacterized, representing a critical knowledge gap requiring mechanistic elucidation. From a translational perspective, nanoparticles face substantial safety hurdles including long-term chronic toxicity, immunogenicity, and protein corona formation that fundamentally alters biodistribution and compromises targeting fidelity.

In summary, current nanoparticle-based interventions primarily function to modulate the pathological microenvironment of secondary injury. Substantial progress remains necessary to achieve true neural regeneration, functional circuit reconstruction, and successful translation from preclinical models to clinical trials.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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