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REVIEW

The Landscape of Ferritin Nanocages for Neurodegenerative Diseases Treatment

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Abstract: The blood-brain barrier (BBB) is a sophisticated structure composed of brain capillary endothelial cells, basement membrane, and neuroglial membrane, which strictly regulates substance exchange between the blood and brain tissue. While maintaining the homeostasis of the central nervous system, it blocks the entry of over 98% of small-molecule drugs and nearly all macromolecular drugs into the brain parenchyma, posing a significant challenge for the treatment of neurodegenerative diseases (NDs). Owing to their unique hollow architecture, favorable biocompatibility, reversible self-assembly properties, intrinsic targeting capability, and surface modifiability, natural ferritin nanocages have garnered substantial attention in the fields of biomedicine and nanotechnology. This review outlines the pathological mechanisms of NDs, the structure and function of the BBB, as well as its transport mechanisms. It highlights the advantages of ferritin nanocages in crossing the BBB—attributed to their natural nanostructure, brain-targeting potential, and capacity for functionalized surface modification—along with their drug loading capacity, antioxidant activity, and favorable biosafety profile. Recent advances in the application of natural ferritin nanocages for the diagnosis and therapy of NDs are also summarized. However, it is important to note that the evidence supporting their application in NDs remains more limited compared to their extensive research in cancer therapeutics. Finally, current challenges and future prospects of ferritin-based nanoplatforms are discussed, providing valuable insights for developing ferritin nanocage-based strategies in the diagnosis and treatment of NDs.

Keywords: ferritin nanocage, blood-brain barrier, neurodegenerative diseases, receptor-mediated transcytosis

Introduction

NDs represent one of the leading causes of disability worldwide and rank as the fourth most common cause of mortality in developed countries, following heart disease, cancer, and stroke,[1–3] These disorders progressively impair motor function, sensory perception, cognition, and memory in affected individuals. The majority of NDs predominantly affect elderly populations.[4] Globally, the population aged 60 years and older is projected to increase by 1.2 billion between 2013 and 2050.[5] As the proportion of elderly individuals rises, age-related disorders such as NDs are expected to impose a growing economic burden and significantly compromise patients' quality of life. Consequently, the development of effective preventive and therapeutic strategies has become increasingly urgent.[6]

NDs encompass a range of disorders, including increasingly prevalent conditions such as Alzheimer's disease (AD), age-related macular degeneration (AMD), and Parkinson's disease (PD),[7] as well as relatively rare disorders like Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), corticobasal syndrome (CBS), multiple system atrophy (MSA), progressive supranuclear palsy (PSP), and prion diseases. The etiology of NDs is multifactorial and complex, involving genetic predispositions, environmental factors, and other intricate mechanisms.[8] A hallmark of NDs is the progressive and often selective loss of neuronal function.[9] Neuronal atrophy leads to neurodegeneration, resulting in impaired synaptic connectivity, functional deficits, and ultimately neuronal death, which

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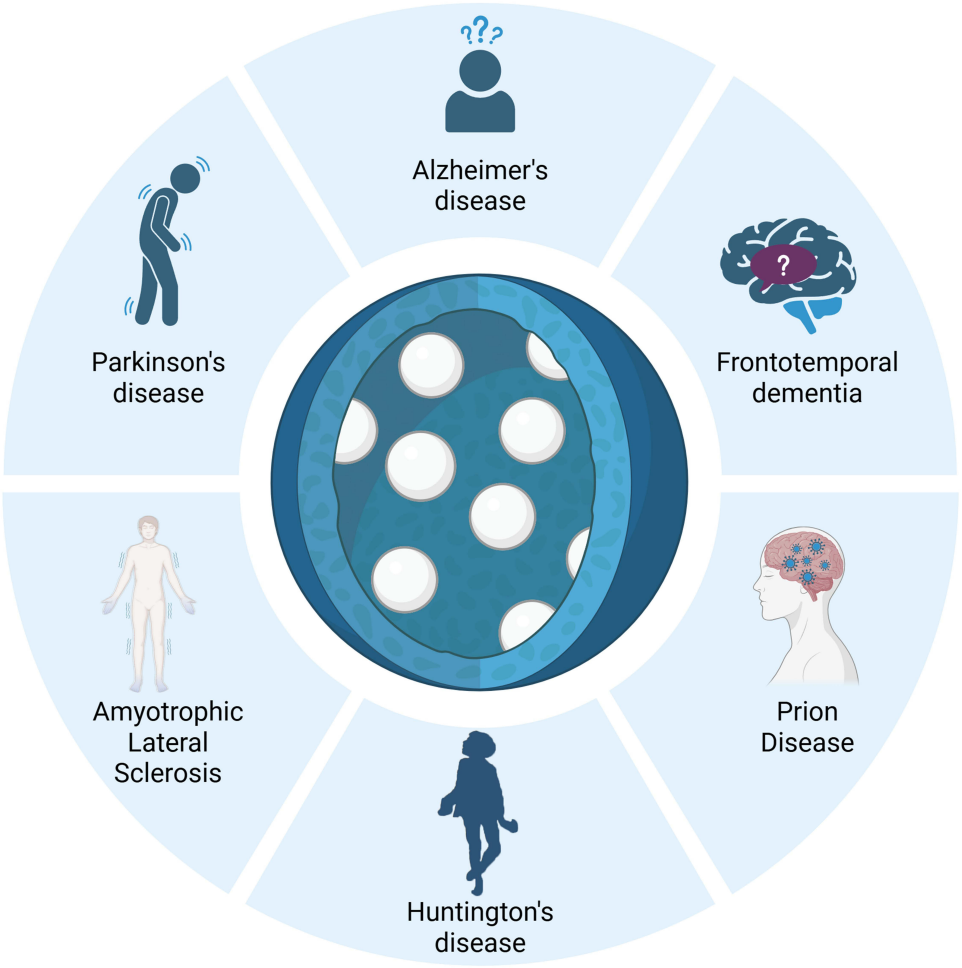
Graphical Abstract



collectively undermine brain function.[10] These diseases are frequently associated with the accumulation of pathological protein aggregates, such as Tau, amyloid-β, α-synuclein, huntingtin, and TDP-43.[11] These aberrant proteins often trigger a cascade of cytotoxic events, including elevated oxidative stress, mitochondrial dysfunction, endoplasmic reticulum stress, synaptic impairment, dysregulated protein degradation, excitotoxicity, DNA damage, neuroinflammation, and aberrant cell cycle re-entry.[12]

Despite significant advances in elucidating the pathological mechanisms of these neurodegenerative diseases, current clinical treatment options remain extremely limited. Existing therapies (eg, cholinesterase inhibitors, NMDA receptor antagonists, dopamine replacement therapies) primarily focus on alleviating certain symptoms or provide only modest disease-modifying effects at intermediate to late stages, none of which can effectively halt or reverse disease progression.[13] Furthermore, these treatments are generally hampered by low bioavailability, poor targeting specificity, limited ability to cross the blood-brain barrier (which prevents approximately 98% of investigational neurotherapeutics from reaching the central nervous system),[14] and significant systemic side effects. Consequently, the development of novel targeted strategies capable of efficiently delivering therapeutic molecules to lesion sites within the central nervous system and enabling precise and safe intervention represents a critical and urgent unmet clinical need in this field. Given that most conventional drugs exhibit poor permeability across the highly restrictive BBB, considerable research efforts have been directed toward the development of novel formulations and delivery strategies to achieve precise brain

targeting. Over the past few decades, a variety of synthetic nanocarriers have been engineered, including solid lipid nanoparticles, liposomes, dendrimers, polymeric nanoparticles, micelles, and stimuli-responsive hydrogels,[15,16] These advanced systems have addressed critical limitations associated with conventional drugs, such as nonspecific biodistribution, rapid metabolism, uncontrolled release kinetics, and low bioavailability, while simultaneously reducing systemic toxicity and adverse effects.[17] However, most existing brain-targeting platforms rely predominantly on synthetic or non-natural materials, which raise concerns over potential chemical solvent residues, inadequate metabolic clearance, and poor biodegradability—factors that limit their applicability in precision medicine. Consequently, the development of novel nanocarriers that combine high biocompatibility with efficient BBB penetration has emerged as a pivotal research direction to overcome the challenges associated with central nervous system drug delivery.[17]

The discovery and purification of natural nanoparticles offer a promising solution to the aforementioned challenges: derived from biological sources such as plants and animals, these nanoparticles not only exhibit high biocompatibility with tissues but also possess a wide range of biological functions, attracting significant research interest.[18] Ferritin, as an endogenous protein nanocage, exhibits distinctive structural and functional characteristics that render it a superior candidate among endogenous protein carriers for brain-targeted delivery. Its spherical architecture, self-assembled from 24 subunits into a structure approximately 12 nm in diameter, confers favorable biocompatibility, structural stability, and intrinsic low immunogenicity.[19] Crucially, its surface naturally presents high-affinity binding domains for transferrin receptor 1 (TfR1), enabling efficient, physiologically relevant traversal across the blood-brain barrier via receptor-mediated transcytosis.[20] The interior cavity, with a diameter of about 8 nm, provides a standardized and controllable space for versatile drug loading, a process further enhanced by pH-dependent reversible assembly/disassembly for controlled release.[21] Conventional protein- and ligand-based systems for targeting the BBB, such as anti-transferrin receptor antibodies, Angiopep-2 peptides, and folate ligands, often face limitations in practical application, including potentially suboptimal biocompatibility, relatively limited transcytosis efficiency, or drug-loading capacities that require further enhancement.[22–24] In contrast, ferritin demonstrates a promising set of advantages as a nanocarrier. Its endogenous origin, inherent brain-targeting capability, appreciable stability, favorable biocompatibility, substantial drug-loading capacity, and flexible surface modifiability establish it as a prospective candidate nanocarrier in the field of therapeutic development for neurodegenerative diseases.

Neurovascular Unit

To overcome the challenge of drug delivery across the BBB, a thorough understanding of its composition and function is essential. The BBB is organized into a neurovascular unit, which comprises four major components: the basement membrane, endothelial cells, pericytes, and astrocytes. In most vertebrates, the BBB represents a highly selective, dynamic, and semi-permeable physiological barrier located in the cerebral microvasculature, effectively separating the bloodstream from the brain's extracellular fluid.[25] It plays a critical role in regulating the transport of substances essential for proper brain function.[26] The BBB is present in the brain and spinal cord of most mammals and other organisms with developed central nervous systems (CNS). It is primarily formed by endothelial cells lining the cerebral microvessels.[26] Within brain capillaries, these endothelial cells are arranged into a continuous tubular structure with tight junctions that confer barrier properties. The luminal surface is enveloped by a basement membrane composed of extracellular matrix. This endothelial tube is further surrounded by pericytes, astrocytic end-feet, and neurons, collectively forming the neurovascular unit.[27]

Basement Membrane

The vascular basement membrane, with a thickness ranging from 20 to 200 nm, is composed of a three-dimensional network of proteins derived from four major glycoprotein families: laminins, type IV collagens, nidogens, and heparan sulfate proteoglycans.[28] Within the CNS, the basement membrane serves to separate endothelial cells, neurons, and glial cells, thereby playing an essential role in the formation and maintenance of the BBB as well as in vascular development.[29] This structure exhibits a high binding affinity for various growth factors, including vascular endothelial growth factor and basic fibroblast growth factor. Furthermore, it constitutes one of the primary pathways that soluble molecules and fluids must traverse to enter or exit the brain, underscoring its critical importance in a wide range of physiological functions.[30–32]

Endothelial Cells

Brain microvascular endothelial cells (BMECs) constitute the structural and functional core of the BBB. They are characterized by complex TJs, primarily composed of endothelial-specific claudins and occludins, which prevent the paracellular passage of ions, molecules, and cells from the blood into the central nervous system (CNS), while also facilitating the efflux of toxic substances.[33] BMECs interact closely with pericytes and astrocytes—pericytes envelop approximately 30% of the endothelial surface, while astrocytic end-feet cover nearly 98%. These interactions not only provide mechanical support to the vasculature but also promote BBB integrity through the secretion of regulatory factors.[34] BMECs perform a wide range of physiological roles: they form a selectively permeable barrier that regulates solute transfer and diffusion; support nutrient delivery and metabolic homeostasis; and modulate vascular permeability, coagulation processes, and leukocyte extravasation. Collectively, these functions contribute to the maintenance of a stable and tightly regulated cerebral microenvironment.[35,36]

Pericytes

Pericytes are vascular mural cells embedded within the basement membrane of microvessels.[37] In the CNS, they play crucial roles in angiogenesis, maintenance of the BBB, regulation of immune cell migration into the CNS, stabilization of microvessels, modulation of capillary diameter, regulation of cerebral blood flow, and clearance of toxic metabolites.[38,39]

Astrocytes

Astrocytic end-feet, extending from the cell body, attach to the basement membrane and endothelial cells. They serve as a critical interface between neuronal signaling and the cerebral vasculature, thereby acting as a bridge within the CNS vascular system.[40,41] Neurovascular coupling in the brain—mediated by astrocytes—links neuronal activity to blood vessel responses and plays a key role in regulating cerebral blood flow in response to neural activation through signal transmission.[42,43] Additionally, astrocytes provide structural, metabolic, and trophic support to neurons.[44]

Cellular Junctions and Transcellular Transport Mechanisms of the BBB

The Connection of BBB

BMECs are interconnected through two primary types of junctions: tight junctions (TJs) and adherens junctions (AJs).[45] TJs are predominantly composed of specialized transmembrane and intracellular proteins within the cerebral microvasculature. Key transmembrane proteins include Junctional Adhesion Molecules (JAMs), Claudins (notably isoforms 1, 3, 5, and 12), and occludin, while a major intracellular scaffold protein is zonula occludens-1 (ZO-1). Adherens junctions are formed by cadherins and catenins, located on the basolateral side of endothelial cell contacts. The cadherin–catenin complex transmits mechanical forces and helps maintain the integrity of the endothelial monolayer.[46] In the brain, the Wnt/β-catenin signaling pathway plays a critical role in inducing the differentiation of cerebrovascular endothelial cells and is one of the key drivers in the formation of the BBB.[47,48] Hussain et al[49] established an endothelial cell-specific β-catenin conditional knockout (ECKO) model in adult mice and observed a significant suppression of endothelial Wnt/β-catenin signaling activity. Their study revealed that β-catenin ECKO mice exhibited substantial leakage of plasma IgG and albumin into the cerebral cortex, indicating that endothelial Wnt/β-catenin signaling is essential for maintaining BBB integrity in adults through coordinated regulation of both paracellular and transcellular transport pathways.

Mechanistic investigations further demonstrated that loss of β-catenin disrupts BBB function through multiple targets: it significantly downregulates the expression of tight junction proteins, directly impairing the physical integrity of inter-endothelial connections; suppresses the expression of Mfsd2a, a key negative regulator of transcytosis, leading to dysregulated transcellular transport; and induces functional abnormalities in Caveolin-1, a protein associated with endocytic vesicles, further exacerbating the loss of endothelial control over molecular flux. These molecular alterations collectively disrupt the coordinated regulatory network between tight and adherens junctions, ultimately compromising the structural stability of the microvascular barrier and impairing the BBB's ability to selectively control molecular trafficking.[50]

The Functions of BBB

First, BMECs are interconnected by specialized tight junctions, which contribute to a high transendothelial electrical resistance (TEER) of approximately 8000 Ω·cm² in an intact BBB.[51] This junctional complexity effectively prevents the paracellular passage of molecules with a molecular weight greater than 180 Da.[52] Second, BMECs express a range of specific transport proteins that actively regulate the influx and efflux of particular substrates, enabling controlled molecular exchange between the blood and the brain. Third, they demonstrate an exceptionally low rate of transcellular vesicular transport, known as transcytosis, which limits nonspecific transcellular trafficking across the vascular endothelium. Finally, CNS endothelial cells exhibit low expression levels of leukocyte adhesion molecules, thereby restricting immune cell infiltration into the brain parenchyma and helping maintain an immunologically privileged environment.[53]

Physiological Transport Mechanisms of the BBB

Under physiological conditions, substances typically traverse the BBB through the following mechanisms: passive diffusion, carrier-mediated transport, adsorptive-mediated transcytosis, receptor-mediated transcytosis, and efflux pump activity.[54]

Passive Diffusion

Passive diffusion is a non-specific, energy-independent, and concentration-dependent transport process limited to small molecules.[55] The presence of tight junctions results in extremely narrow intercellular spaces, thereby physically restricting paracellular movement across the BBB. Molecules capable of crossing the BBB via passive diffusion include gases such as oxygen and carbon dioxide, as well as small lipophilic compounds with a molecular weight below 400 Da or fewer than eight hydrogen bonds—examples include ethanol and certain antidepressants.[45,56]

Adsorption-Mediated Endocytosis

Adsorptive-mediated transcytosis (AMT) utilizes electrostatic interactions between positively charged ligands and negatively charged cell membranes, serving as a mechanism for transporting macromolecules and charged nanoparticles across the BBB.[57] However, AMT is a non-specific delivery approach, which may lead to unintended drug accumulation in peripheral organs. Despite this limitation, AMT exhibits a higher overall transport capacity compared to receptor-mediated mechanisms, as it is not constrained by the limited number of specific receptors expressed on the BBB.[58]

Carrier-Mediated Transportation

Endogenous substances such as glucose, vitamins, amino acids, and neuropeptides are transported into the brain via specific carriers present on the BBB.[59] To facilitate the entry of certain therapeutic agents targeting the brain, these drugs can be chemically modified to structurally mimic endogenous compounds. As a result, they are able to utilize specific carrier systems and successfully cross the BBB through carrier-mediated transport mechanisms.[60] Numerous solute carrier (SLC) transporters, including SLC2, SLC7, and SLC16 families, are expressed on the BBB and play essential roles in this process.[61]

Active External Discharge Transportation

ABC transporters are ATP-driven efflux pumps that are highly expressed on the BBB. They restrict the permeability of a wide range of toxins, including therapeutic agents, and contribute to drug resistance in the central nervous system (CNS).[62] The luminal membrane of endothelial cells contains numerous efflux proteins, such as P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and other drug resistance transporters, which actively remove drugs from the brain.[63]

In the CNS, P-glycoprotein is predominantly localized on the luminal membrane of brain microvascular endothelial cells and the apical plasma membrane of choroid plexus epithelial cells. It helps maintain homeostasis in the neuronal microenvironment by actively extruding neurotoxic xenobiotics, thereby limiting their entry into the brain parenchyma.[64] Studies using mdr1a/mdr1b double-knockout mouse models have provided critical evidence elucidating the neuroprotective role of P-gp. Compared to wild-type controls, these knockout animals exhibited a hundred-fold increase in brain

uptake of ivermectin—a neurotoxic pesticide. This finding not only demonstrates the central role of P-gp in preventing the accumulation of neurotoxic substances in the brain but also highlights the physiological significance of efflux transporters in maintaining the chemical barrier function of the CNS.[65]

Receptor-Mediated Transcytosis

Receptor-mediated transcytosis (RMT) is a process in which ligands bind to specific receptors highly expressed on the BBB, leading to membrane invagination and the formation of intracellular vesicles.[66] The formation of these transport vesicles involves clathrin-coated pits.[67] Clathrin assembly is initiated by adaptor protein AP2, which recruits accessory proteins to form coated vesicles. Dynamin and other adaptor proteins then facilitate vesicle scission from the membrane. The clathrin coat is rapidly removed, and the vesicles are transported to various intracellular destinations. Internalized vesicles fuse with early endosomes and may subsequently be directed to lysosomes for degradation.[68] While some vesicles recycle back to the apical membrane, others are transported to the basolateral membrane for content release. Residual endosomes are degraded via the endosome-lysosome maturation process.[69,70]

In therapeutic strategies for neurodegenerative diseases, RMT represents one of the key mechanisms to overcome BBB delivery limitations,[71] and serves as a major pathway for transporting large molecules across the BBB. It facilitates the homeostatic transport of essential components such as iron, insulin, and leptin.[72]

For small particles under 200 nm, RMT is a primary uptake route.[73] Ferritin, for instance, achieves efficient transport of macromolecules from the blood to the brain parenchyma by binding to receptors on brain microvascular endothelial cells.[74]

Advantages of Ferritin Nanocages in the Diagnosis and Treatment of NDs

BBB Penetration Ability of Ferritin Nanocages

Natural Structure

Discovered in horse spleen in 1937, ferritin is a highly conserved protein found in vertebrates, invertebrates, higher plants, fungi, and bacteria, where it performs diverse and specialized functions across different cell types.[75] Amid growing concerns regarding nanomedicine safety, natural ferritin nanocages have garnered significant interest due to their unique hollow nanostructure, excellent safety profile, and well-defined in vivo behavior, offering distinct advantages over conventional nanodrugs with uncertain biological fate and instability.[76]

Structurally, ferritin is a spherical, hollow cage-like protein with uniform dimensions: an inner cavity diameter of 8 nm, an outer diameter of 12 nm, and a shell thickness of approximately 1 nm. It has a molecular weight of about 450 kDa and can store up to 4, 500 iron atoms within its core (Figure 1).[77]

The ferritin shell is composed of 24 subunits,[79] In vertebrates, ferritin exists in two subunit types: heavy chain (HFt) and light chain (LFt).[80] HFt consists of 178 amino acids with a molecular weight of 21 kDa, whereas LFt contains 174 residues and has a molecular weight of 19 kDa. In contrast, ferritins derived from plants and bacteria consist exclusively of HFt-type subunits.[81] Structural analyses reveal that ferritin adopts a symmetric arrangement of dimers organized with 4-3-2 symmetry. The assembly features eight hydrophilic pores located at the three-subunit interfaces, which serve as the main channels for iron entry and exit. Additionally, six hydrophobic channels are situated at the four-subunit junctions, potentially facilitating oxidation or gas exchange. Each ferritin subunit—whether heavy (H) or light (L)—folds into a characteristic four-helix bundle motif comprising five α-helices (A, B, C, D, E) and a long loop (BC-loop). Helices A through D form a canonical cylindrical four-helix bundle, which stabilizes the 24-mer assembly through hydrophobic interactions and hydrogen bonding with adjacent subunits (Figure 2).[82,83]

Ferritin is a pH-responsive self-assembling protein with remarkable resistance to extreme environmental conditions. The cage-like structure disassembles into monomers under highly acidic (pH 1–2) or alkaline (pH 11–13) conditions. When the pH is restored to neutral, the subunits refold and spontaneously reassemble into the intact nanocage structure.[85] Under physiological conditions, ferritin remains structurally stable, resists metabolic clearance, and can thereby prolong the duration of drug action.

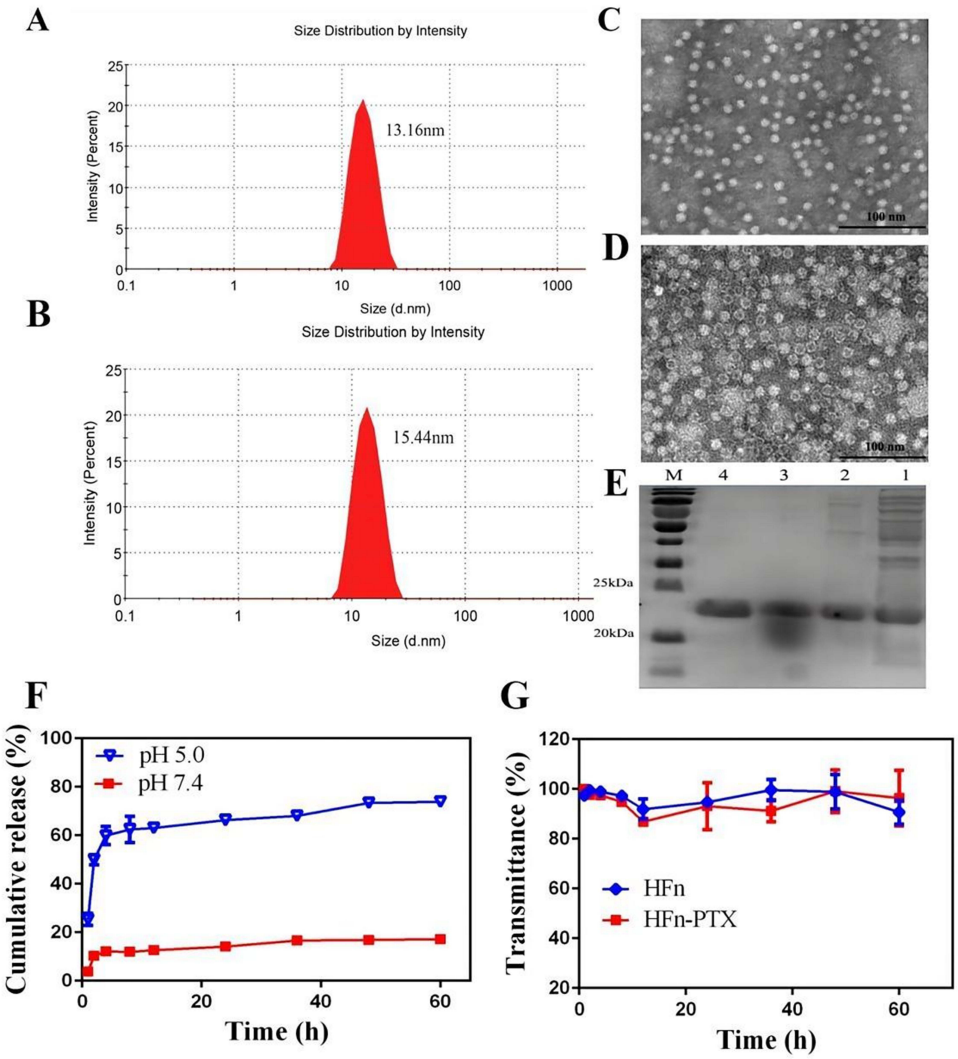


Figure 1 Characterization of HFn. Size distribution graph of HFn (**A**) or after (**B**) loading. The size of HFn shows slight increase after loading. TEM image:Morphological characterization of the HFn before (**C**) and after (**D**) loading. The structure of HFn keeps intact after disassemble and assemble processes. (**E**) The 12% SDS-PAGE gel of HFn after different process of purify. Lane 1, the supernatant of Journal Pre-proof cell lysate. Lane 2, the supernatant of Lane 1 was heat at 70°C for 15 min. Lane 3–4, the eluting protein from DEAE Sepharose anion exchange resin. (**F**) The in vitro release of PTX from HFn-PTX at different conditions (pH 5.0, pH 7.4). (**G**) Stability of HFn-PTX in mouse serum and PBS at 37 °C for over 60 h of incubation. Reproduced with permission.[78] Copyright 2020, Elsevier.

Additionally, ferritin exhibits thermal stability up to 80 °C.[86] Differences in hydrogen bonding and salt bridge interactions between the residue side chains of HFt and LFt contribute to their distinct biophysical properties. HFt possesses approximately 50% more hydrogen bonds than LFt. In HFt, a key iron-binding site located at the junction of the BC-loop and helices B and C, near the inner surface of the four-helix bundle, confers ferroxidase activity, enabling the catalysis of Fe^{2+} to Fe^{3+} and facilitating iron mineralization within the protein cavity. In LFt, a salt bridge between Lys62 and Glu107 occupies the spatial position corresponding to the iron-binding site in HFt, which enhances resistance to conformational changes and contributes to the high stability of ferritin under elevated temperatures and in the presence of chemical denaturants.[81,87]

Targeting Ability

TfR1 is a type II transmembrane glycoprotein, and transferrin (Tf) is an iron-binding protein present in the bloodstream. Both are central regulators of iron metabolism, coordinating the uptake, transport, and metabolic processing of iron.[88,89] In TfR1-targeted delivery systems, the most extensively studied biological molecular carriers include transferrin, heavy chain ferritin (HFn), anti-TfR1 antibodies/peptides, and nucleic acid aptamers. These molecules leverage their inherent

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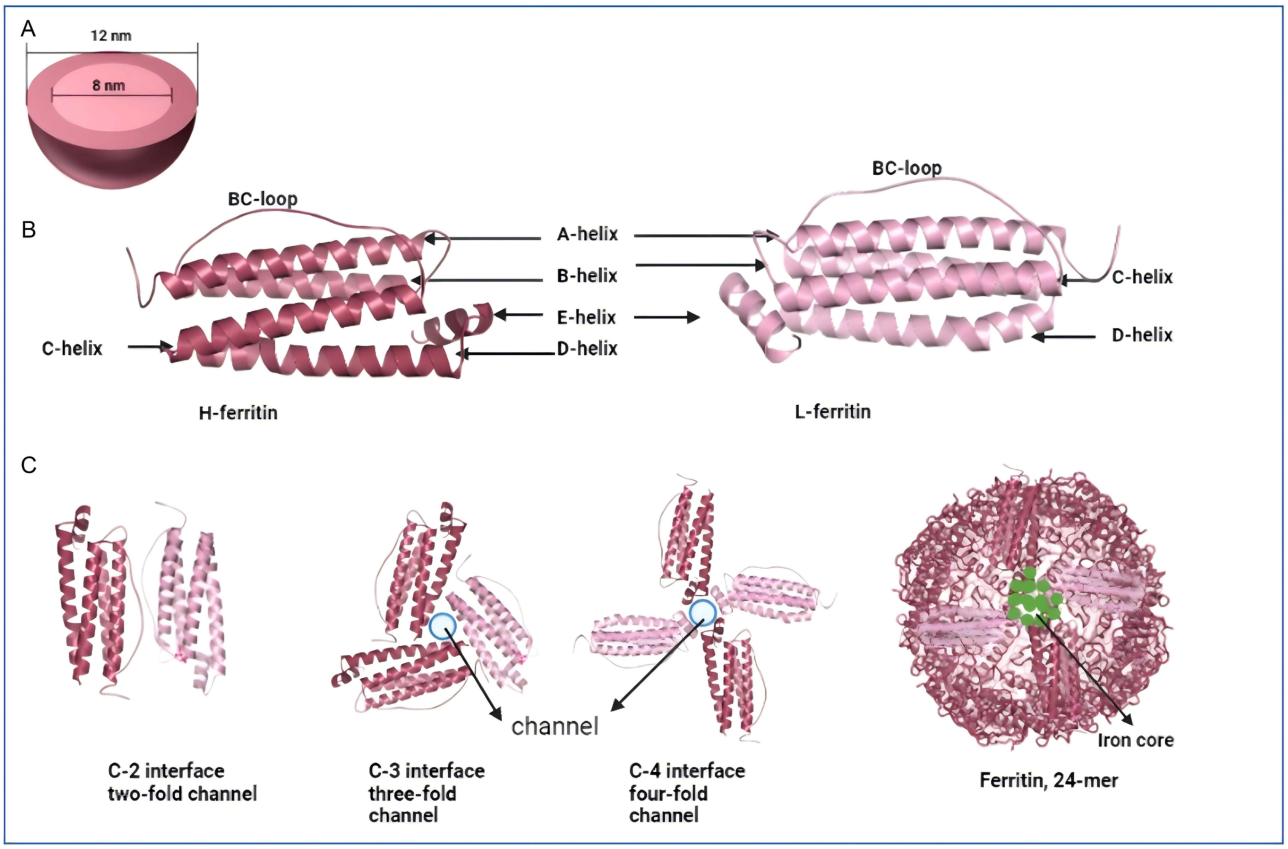

Figure 2 Structure of ferritin. (**A**) A representation of ferritin as a sphere showing the inner core and outer core diameter. (**B**) Graphical representation of the identical ferritin H- and L- peptides. (**C**) The various interfaces of the heavy and light chain ferritin. The three- and four-fold channels represent the open channels through which iron atoms can flow in and out of the structure. Finally, a 24-mer representation of the ferritin structure containing iron atoms is also presented. Reproduced with permission.[84] Copyright 2023, Elsevier.

biological properties to ensure biosafety, maintain high affinity for the target, and achieve precise and specific binding, as demonstrated in experimental studies.[90] HFn enters cells primarily through recycling and lysosomal degradation pathways. Upon binding to TfR1, HFn is internalized via clathrin-coated pit formation, resulting in transport vesicles that traverse endothelial cells and release their cargo into the brain parenchyma (Figure 3). The endolysosomal pathway triggers the disassembly of ferritin, facilitating drug release, followed by degradation of the protein shell via lysosomal and proteasomal mechanisms.[91,92] It is noteworthy that ferritins from different species may engage distinct receptors,[93] For instance, human heavy chain ferritin specifically binds to TfR1, while horse spleen ferritin interacts primarily with Scara5.[94] This diversity enables the exploitation of species-specific ferritin-receptor pairs for different targeting applications.

Recent studies have revealed that TfR1 is overexpressed on brain endothelial cells and tumor cells. In vivo distribution experiments in mice demonstrated that, compared to free Cy5, a significant amount of Cy5-labeled ferritin heavy chain 1 (Cy5-FTH1) crossed the BBB and accumulated in brain tissue, with fluorescence intensity peaking at 24 hours (Figure 4). This indicates that FTH1 possesses a remarkable ability to traverse the BBB.[95] Furthermore, human HFn has been shown to successfully cross the BBB via TfR1-mediated transcytosis and exert cytotoxic effects on glioma cells, highlighting its potential for actively targeted tumor therapy and brain-specific drug delivery.[96] Huang et al developed a dual-targeting drug delivery system by functionalizing the surface of HFn with an integrin α2β1-targeting ligand, enabling enhanced BBB penetration and glioma targeting. Using bio-layer interferometry, the team dynamically monitored and validated the targeting specificity toward α2β1 integrin. Subsequent in vitro transcytosis assays and in situ glioma animal models confirmed that this system efficiently crosses the BBB and exhibits significantly improved tumor targeting compared to conventional strategies.[97] In recent years, efforts have been made to develop gene delivery vectors

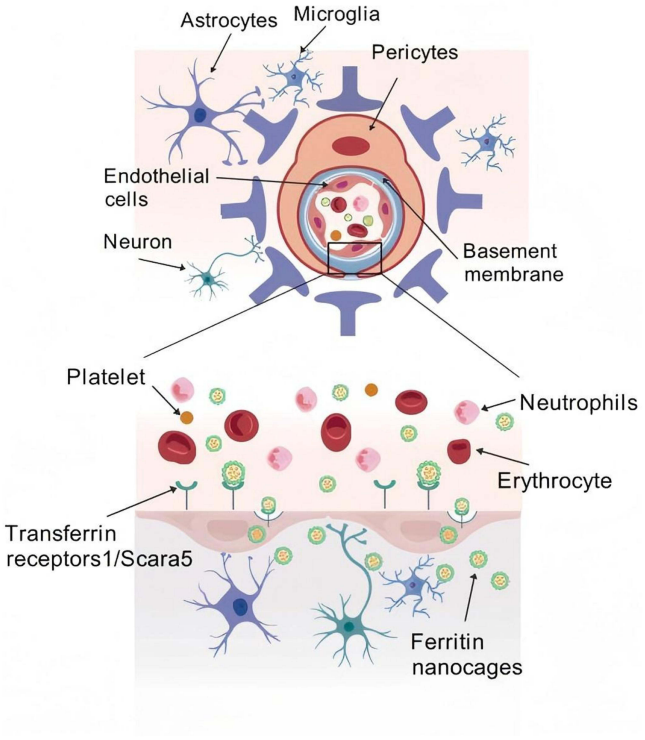

Figure 3 The neurovascular unit and receptor-mediated endocytosis. Created with https://biogdp.com/.

for treating brain-related disorders. One such approach involves self-assembling HFn nanoparticles (NPs). By introducing arginine mutations on the HFn surface, a series of cationic HFn variants (HFn+ NPs) were engineered. These NPs encapsulate siRNA through pH-dependent assembly, leveraging strong electrostatic interactions within the cavity to achieve high siRNA loading efficiency. The HFn+ NPs effectively delivered siRNA across the BBB into glioma cells.[20] Similarly, Wang's team employed a genetic engineering strategy to fuse a glioma-targeting peptide (RGE) with self-assembling ferritin nanoparticles, constructing a biomimetic delivery system termed RGE-HFn. This system maintained structural integrity and targeting specificity after loading the STING pathway agonist SR717, enabling efficient CNS delivery. Animal studies demonstrated that SR717@RGE-HFn NPs successfully penetrated the BBB and released the payload specifically within the glioma microenvironment, activating a potent local immune response. This biomimetic platform offers a promising strategy for overcoming the challenges of BBB traversal.[98] Yan et al developed a novel ferritin carrier, tHFn(+). tHFn(+) crosses the blood-brain barrier by binding to transferrin receptor 1 and targets glioma in vivo. The siRNA delivered by tHFn(+) demonstrates excellent therapeutic efficacy against glioma in vivo. In a brain glioma model, it successfully achieves lysosomal escape and efficient gene knockdown of siRNA, showing significant therapeutic effects.[99] They also constructed a novel supramolecular delivery system using HFn, which successfully addresses the in vivo toxicity and targeting challenges of a cationic fullerene derivative (TAPC) and endows it with the ability to cross the blood-brain barrier. In a glioma mouse model, H@T@H exhibited higher accumulation in the brain and stronger tumor suppression compared to ordinary PEG-coated TAPC.[100] Hayat et al developed rosuvastatin-loaded human H-ferritin nanoparticles (Rsv@HFn) as a brain-targeted nanoplatform. This platform enhances the drug's ability to cross the blood-brain barrier, increases its accumulation at the injury site, and improves its therapeutic efficacy. It improved blood-brain barrier integrity, reduced brain edema, and alleviated neuropathological damage in intracerebral hemorrhage mice.[101] The core pathological processes of neurodegenerative diseases—including dysregulation of brain iron homeostasis, accompanying oxidative stress, chronic neuroinflammation, and impaired blood-brain barrier function—are closely linked pathophysiologically to the expression and functional regulation of TfR1 in brain microvascular endothelial cells.[102,103] For instance, pathological iron deposition can activate cellular iron-homeostatic regulatory pathways, often leading to upregulation of TfR1 expression to maintain intracellular iron balance.[104] Meanwhile, the

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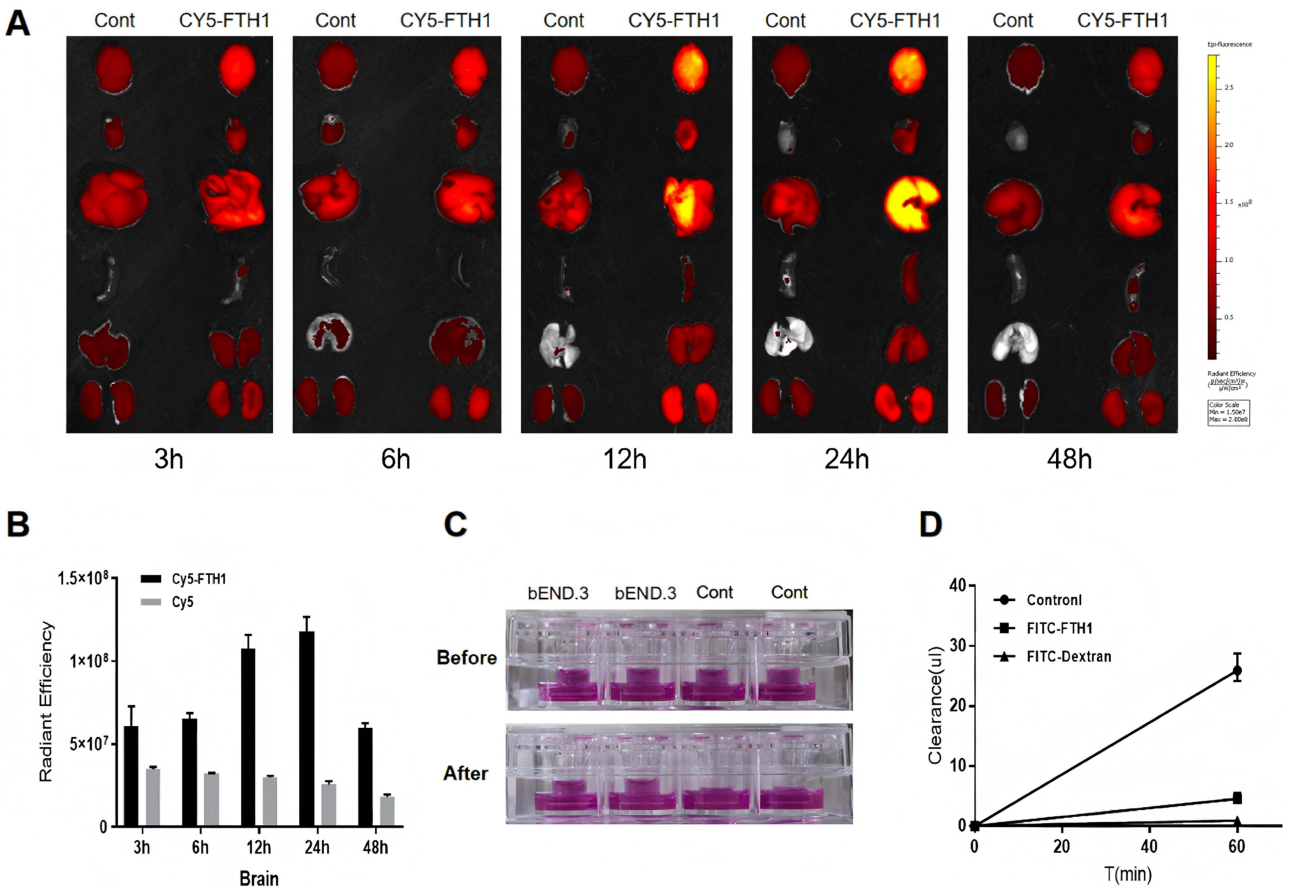

Figure 4 Distribution of FTH1 in C57BL/6J Mouse Brain Tissue. (**A**) In vivo brain imaging of mice following intravenous injection. (**B**) Quantitative analysis of fluorescence intensity in the brain. (**C**) Transport of FTH1 in the in vitro BBB model. (**D**) Each value is presented as the mean ± SD (N = 3). Reproduced with permission.[95] Copyright 2024, Academic Press Inc.

inflammatory microenvironment has also been shown to significantly influence TfR1 expression levels.[105] Therefore, TfR1 should not be regarded merely as a passive drug delivery target; rather, its altered expression and activity under disease conditions themselves constitute an integral part of the neurodegenerative pathological process. However, current research on the specific mechanisms linking neurodegenerative diseases to the regulation of TfR1 expression remains relatively limited, and further exploration in this field is of significant importance for the future development of TfR1-based targeted therapeutic strategies.

Functionalized Surface Modification

Each of the 24 subunits of ferritin contains amino, carboxyl, thiol, and other reactive groups that can be chemically modified, while the amino acid sequence itself can be precisely engineered using biological methods.[106] Leveraging this versatility, Zhai et al[107] encapsulated vincristine sulfate (VCR) into apoferritin nanocages and functionalized the surface with GKRK peptide ligands, constructing a dual-targeting nanodrug delivery system termed GKRK-APO-VCR. This system demonstrated enhanced glioma targeting and exhibited potent anti-glioma efficacy.

Drug Loading Capacity of Ferritin Nanocages

The unique hollow cavity structure of ferritin provides a foundation for its application as a drug delivery vehicle, with its potential lying in a range of efficient and controllable drug loading strategies. The classical drug delivery methods based on the reversible self-assembly characteristics of ferritin mainly include the following three approaches: pH-dependent behavior, Heat-driven loading, and Ion concentration (Figure 5).[17] These methods enable the efficient encapsulation of a

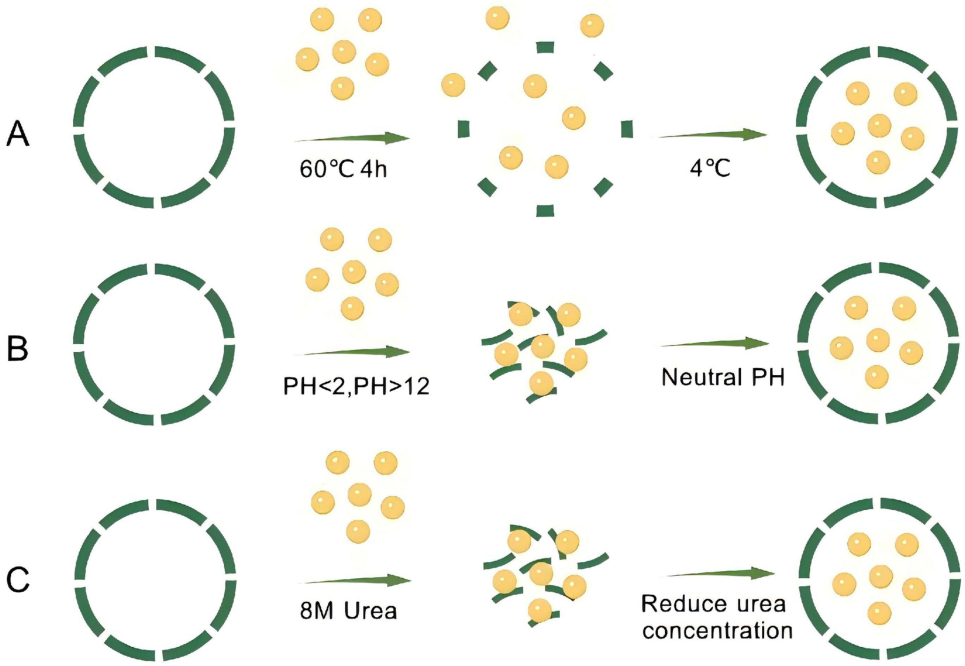

Figure 5 Ferritin-based cargo loading methods: (**A**) Heat-driven loading; (**B**) pH-dependent behavior; (**C**) Ion concentration. Created with https://biogdp.com/.

wide variety of therapeutic agents into the inner cavity without compromising the structural integrity of the native nanocage.

pH-Dependent Behavior

Studies have revealed that pH-induced dissociation of ferritin is triggered by a slight expansion caused by the rotation of monomers within the dimeric units, ultimately leading to the loss of salt bridges and hydrogen bonds, which results in the disassembly of the ferritin cage.[108] At pH 2.0 or 12.0, ferritin dissociates into individual subunits. When the pH is readjusted to neutral conditions, the subunits spontaneously reassemble into the intact cage-like structure.[109] Utilizing this mechanism, researchers have successfully encapsulated quercetin and curcumin into ferritin by modulating the solution pH for the treatment of triple-negative breast cancer. The results demonstrated that when ferritin was used as the drug carrier, a lower drug dosage was sufficient to achieve significant therapeutic efficacy.[110] Zhang et al[111] employed pH-mediated self-assembly to encapsulate a Au agent (C6) within ferritin. After crossing the BBB and entering the brain parenchyma, the ferritin released the gold species in the acidic microenvironment, inducing lethal autophagy and apoptosis to eliminate glioma cells. These studies collectively confirm the feasibility of ferritin as a drug carrier for treating parenchymal brain diseases and nervous system tumors.

Heat-Driven Loading

Studies have shown that when native ferritin is subjected to temperatures near 80 °C, significant alterations occur in its secondary structure, primarily characterized by the disruption of α-helical conformations. This results in the enlargement of pores in the protein nanocage.[112] Such thermally induced structural modifications can effectively facilitate the release of encapsulated drugs. Notably, upon returning to physiological temperatures, ferritin spontaneously refolds and restores its original architecture Such thermally induced structural modifications can effectively facilitate the release of encapsulated drugs. Notably, upon returning to physiological temperatures, ferritin spontaneously refolds and restores its original architecture.[113]

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Ion Concentration

Numerous studies have demonstrated that urea treatment can effectively enlarge the channel pores of ferritin, thereby facilitating the entry of macromolecules into its inner cavity while preserving the structural integrity of the protein.[114,115] Dong et al[116] observed that low concentrations of urea induced a fourfold expansion of the ferritin channels. Upon removal of urea via dialysis, the channels returned to their original dimensions. The researchers successfully utilized 20 mM urea to promote the co-assembly of ferritin with epigallocatechin gallate (EGCG), enabling efficient EGCG penetration into apo-red bean ferritin without disrupting the nanocage structure. This method shows promising applications for the encapsulation of drugs and functional food components.

Biocompatibility and Metabolic Safety of Ferritin Nanocages

Ferritin is an endogenous natural protein widely present in nearly all forms of life, where it functions as an iron storage molecule. Due to its intrinsic origin, it exhibits high biocompatibility and low immunogenicity, with a strong tolerance by the immune system that helps avoid antibody neutralization or inflammatory responses, underscoring its favorable biosafety profile.[117,118] Hemolytic assay demonstrated that ferritin exhibited a low hemolysis rate.[119] Complete blood count analysis showed that parameters including red blood cells, white blood cells, and platelets remained within normal ranges.[120] Furthermore, H&E staining of major organs from mice administered with ferritin revealed no obvious signs of histopathological toxicity.[121] These results collectively confirm the favorable biocompatibility of ferritin as a drug delivery platform.

Within the cellular environment, ferritin subunits can be degraded by esterases or proteases. The resulting metabolites—including amino acids and iron ions—are efficiently recycled through biological pathways and reused by the organism to support normal physiological functions. No long-term toxic effects have been observed associated with ferritin or its breakdown products.[122]

Antioxidant Properties of Ferritin Nanocages

Ferritin, as an ancient superfamily of protein nanocages, plays a central role in cellular iron metabolism through dynamic regulation of its synthesis: 1) It acts as a multifunctional metabolic hub, participating in iron ion concentration, heme biosynthesis, Fe-S cluster assembly, and the production of iron-containing proteins; 2) Under oxidative stress, it contributes to the cellular antioxidant defense system by catalyzing the coupled reaction of hydrogen peroxide with ferrous ions (Fe^{2+}).[112] Different tissues exhibit functional specificity in their preference for ferritin subunit types: In organs such as the liver and spleen, where iron storage is a primary function, L-type ferritin predominates (accounting for up to 90% of ferritin content). This subtype is characterized by high structural stability and superior iron storage capacity. In contrast, tissues such as the heart and brain, which rely on efficient antioxidant mechanisms, preferentially express H-type ferritin. This subtype demonstrates exceptional peroxide scavenging efficiency due to its unique surface charge distribution and pore properties.[123,124] All ferritin subtypes efficiently interact with Fe^{2+}, catalyzing its oxidation via a conserved ferroxidase active site and facilitating the formation of nanoscale mineralized iron deposits within the cavity. This ferrous oxidation process is coupled with peroxide reduction, effectively quenching toxic intermediates such as hydroxyl radicals generated during metabolism, thereby providing a dual mechanism of antioxidant protection.[125] H-type ferritin exhibits diverse functions: it can enter the nucleus to protect against iron-mediated DNA oxidative damage and is also actively secreted extracellularly to participate in various physiological processes.[126] Mitochondrial ferritin, expressed in specific mammalian tissues, safeguards mitochondrial integrity against oxidative damage by regulating iron ion homeostasis.[127,128]

Application of Ferritin Nanocages in the Treatment of NDs

Alzheimer's Disease

Clinically, patients with AD exhibit memory decline accompanied by varying degrees of cognitive dysfunction, which may also include aphasia, agnosia, impaired visuospatial abilities, difficulties in abstract thinking and problem-solving, as well as personality and behavioral changes.[129] The deposition of β-amyloid and hyperphosphorylation of Tau protein are

hallmark pathological features of AD.[129] Other contributing factors include synaptic loss in the neocortex and hippocampus, mitochondrial dysfunction, oxidative stress, and neuroinflammation.[130,131]

In a pioneering study, the Gagliardi team developed an innovative nanotherapeutic approach using HFn to encapsulate bisdemethoxycurcumin (BDC-HFn), offering a novel direction for AD treatment. This system utilized HFn as the core carrier and employed a mild preparation process that avoided organic solvents or surfactants, significantly enhancing the biocompatibility and safety of the drug delivery system. The unique spatial confinement effect within HFn improved the stability of BDC. In an in vitro BBB model, the HFn carrier increased the delivery efficiency of BDC into the brain. Furthermore, the BDC-HFn formulation significantly reversed the expression patterns of 17 differentially expressed inflammatory genes between AD and control groups, demonstrating potent neuroanti-inflammatory activity.[132] Subsequent research explored HFn as a nanocarrier for curcumin (Cur) to enhance its bioavailability and therapeutic potential in AD. Studies in 5XFAD mice showed that HFn-Cur slightly improved cognitive performance. Additionally, HFn-Cur specifically bound to inflammatory cells in the brain, reducing the number of activated microglia while significantly suppressing astrocyte proliferation, thereby effectively mitigating neuroinflammatory cascades (Figure 6).[133] Researchers also constructed a recombinant human H-ferritin nanocage (rHuHF) loaded with the natural antioxidant lycopene (LYC), opening new multi-target intervention strategies for AD treatment. This nanodrug achieved systemic amelioration of neurodegeneration through a triple mechanism: First, it reversed core cognitive impairments associated with AD. Second, it maintained neuronal Nissl body integrity and regulated lipid metabolism, establishing a dual protective mechanism. It also strongly inhibited microglial activation and prevented abnormal deposition of neurotoxic proteins in the hippocampus. Finally, it restored damaged neuronal communication networks by activating synaptic plasticity-related signaling pathways, leading to the recovery of postsynaptic density protein 95 (PSD-95) expression and increased levels of the synaptic connection protein synaptophysin.[134] Furthermore, when chicoric acid (CA), which inhibits β-amyloid peptide formation, was encapsulated in ferritin (Ft-CA), cellular experiments demonstrated that CA also suppressed tau phosphorylation. In SH-SY5Y cells, both CA and Ft-CA treatments inhibited tau hyperphosphorylation, with Ft-CA showing more significant effects than free CA, validating the beneficial role of ferritin encapsulation and highlighting its potential in preventing neurodegenerative diseases.[135] Additionally, a dual-delivery nanoparticle system was developed using lipophilic triphenylphosphonium (TPP)-conjugated LYC encapsulated in ferritin (TPP-rHuHF-LYC). These nanoparticles maintained endogenous BBB transcytosis capability and exhibited mitochondrial targeting within neurons. Significant neuroprotective effects were observed, including reduced intracellular oxidative stress, alleviated mitochondrial dysfunction, and enhanced neuronal survival.[136]

Parkinson's Disease

The primary clinical features of PD include bradykinesia (slowness of movement), rigidity (increased muscle tone), tremor, and alterations in gait and postural reflexes.[137] Its key pathological hallmarks are the loss of dopaminergic neurons and the formation of Lewy bodies containing α-synuclein in the substantia nigra.[138] α-Synuclein is considered the principal pathogenic protein in PD.[139]

Kaili Hu et al constructed lactoferrin (Lf)-conjugated poly(ethylene glycol)-poly(lactide-co-glycolide) (PEG-PLGA) nanoparticles (Lf-NPs) to evaluate the in vitro and in vivo delivery properties of a novel biodegradable brain drug delivery system. Both in vitro and in vivo experiments demonstrated that Lf-NPs exhibited significantly greater BBB penetration compared to unconjugated nanoparticles. Animal studies showed that intravenous administration of urocortin (UCN)-loaded Lf-NPs effectively attenuated 6-hydroxydopamine-induced striatal lesions in rats. This study provided the first evidence that non-invasive delivery of UCN to the brain is feasible and that the Lf-NP delivery system holds promise for non-invasive treatment of PD.[140]

In another study, the natural antioxidant lycopene was loaded into the cavity of rHuHF, and the outer surface was modified with lipophilic TPP. This nanoformulation enabled neuronal enrichment and mitochondrial targeting of lycopene through BBB transcytosis and mitochondrial localization capabilities. It promoted the extracellular clearance of pathogenic α-synuclein and enhanced the survival of dopaminergic neurons. Furthermore, these nanoparticles restored Parkinsonian-like motor symptoms in a PD mouse model. This integrated therapeutic strategy, spanning mitochondrial protection to neuronal survival, offers a transformative innovative solution for complex brain disorders such as PD.[141]

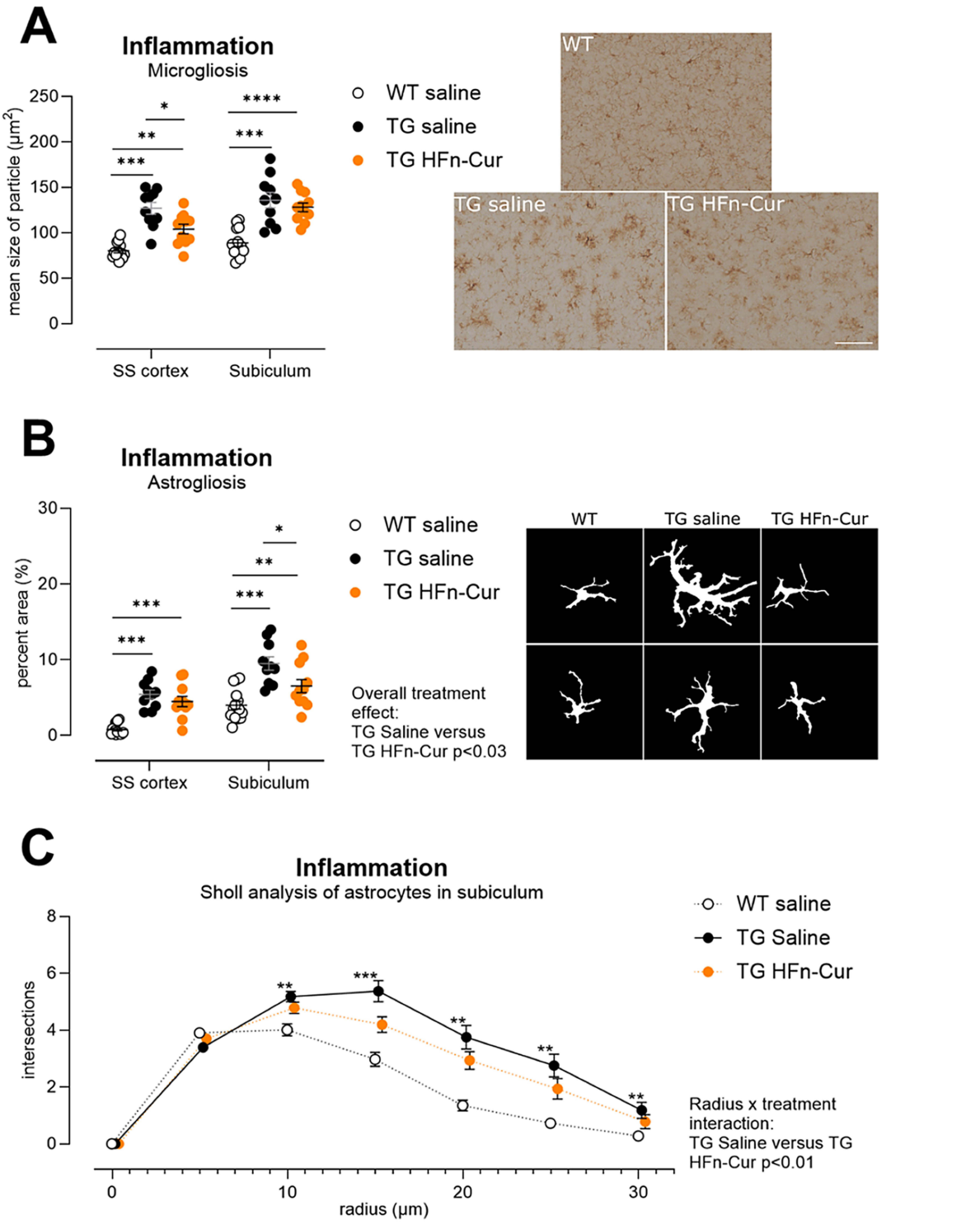

Figure 6 Therapeutic Efficacy of Ferritin-based Nanodrug Delivery Systems In Vivo.Microgliosis (**A**): Treatment with HFn-CUR reduced microglial size in frontal somatosensory cortex but not in subiculum. Photomicrographs depict somatosensory cortex of a saline-treated WT (top), saline-treated TG (lower left) and HFn-CUR-treated TG (lower right) mouse. Scale bar = 100 μm. Frontal cortex: TG saline 95% CI: 112–142, TG HFn-Cur 95% CI: 93–116. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$. Astrocytosis (**B**): HFn-CUR treatment resulted in an overall reduction in GFAP-positive astrocytes compared with saline-treated TG mice, with post-hoc testing revealing a specific effect in subiculum (**B**). Black and white images show representative astrocytes used for morphological analysis (saline-treated WT: left column, saline-treated TG: middle column; HFn-CUR-treated TG: right column). Each image is 80 μm x 80 μm. Saline-treated TG 95% CI 7.5–11.5, HFn-CUR-treated TG 95% CI 4.6–8.5. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.0001$.Morphological analysis of astrocytes in subiculum revealed a partial normalisation of astrocyte morphology in HFn-CUR-treated TG mice (**C**). ** $p < 0.01$, *** $p < 0.001$ compared with WT saline. Symbols in graphs are of individual mice together with group mean ± sem (**A** and **B**) or of group mean ± sem (C, in instances where there are no error bars, they are obscured behind symbols). Reproduced with permission.[133] Copyright 2024, BioMed Central.

Table 1 Applications of the Cargo-Loaded Ferritin Formulations

Ferritin Type	Loaded cargo	Loading Method	Application	Drug Efficacy	References
Recombinant human HFn	BDC	pH-dependent behavior	AD	Improve the stability of BDC Anti-neuroinflammatory.	[132]
Recombinant human HFn	Curcumin	pH-dependent behavior	AD	Reduce microgliosis and astrogliosis Neuroprotective effect.	[133]
Recombinant human HFn	LYC	pH-dependent behavior	AD	Attenuate neuronal damage, increase the level of unsaturated fat, inhibit the activation of glial cells, and activate synaptic plasticity.	[134]
Recombinant human HFn	Chicoric acid	pH-dependent behavior	AD	Regulate glucose metabolism and inhibit tau phosphorylation.	[135]
TPP-Recombinant human HFn	LYC	pH-dependent behavior	AD	Regulate mitochondrial function, protect synaptic mitochondria, and enhance synaptic plasticity in hippocampal neurons.	[136]
TPP-Recombinant human HFn	LYC	pH-dependent behavior	PD	Promote neuronal enrichment and mitochondrial regulation, reduce oxidative stress, and facilitate the survival of pathogenic α-synuclein and dopaminergic neurons.	[141]

In summary, ferritin nanocages demonstrate significant potential for the treatment of currently incurable NDs, including AD and PD. We have summarized the applications of cargo-loaded ferritin in neurodegenerative diseases (Table 1).

Others

ALS is a neurodegenerative disease characterized by progressive, painless muscle weakness due to the death of motor neurons in the brain, brainstem, and spinal cord. Muscle weakness begins in the facial, tongue, and pharyngeal muscles in bulbar-onset ALS, leading to dysarthria followed by dysphagia, or in the distal upper or lower limb muscles in spinal-onset ALS.[142] HD is an autosomal dominant disorder characterized by motor dysfunction, cognitive decline, and psychiatric symptoms. HD features widespread brain atrophy and degeneration of the striatum (caudate nucleus and putamen), with specific loss of efferent medium spiny neurons.[143] Prion diseases are fatal neurodegenerative disorders in humans and animals. Clinical manifestations include behavioral abnormalities, motor dysfunction, cognitive impairment, and ataxia.[144] Currently, there is no effective treatment for human prion diseases.[145] FTD is an insidious neurodegenerative clinical syndrome characterized by progressive deficits in behavior, executive function, and language.[146] It is primarily associated with the aggregation of Tau protein or another protein named TDP-43 in the frontal and temporal lobes of the brain.[147] ALS, HD, prion diseases, and FTD are all refractory neurodegenerative diseases for which effective treatment options are currently lacking. Although studies have explored the application of nanomaterials such as solid lipid nanoparticles, mesoporous silica nanoparticles, graphene quantum dots, and selenium nanoparticles in their treatment, related investigations remain relatively limited.[148–151] Notably, no reports have been published on the use of ferritin as a nanocarrier for the treatment of the aforementioned diseases.

Ferritin demonstrates significant potential in the field of neurodegenerative disease therapy due to its unique natural cage-like structure, excellent biocompatibility, potential for crossing the blood-brain barrier, precise targeting capability, inherent antioxidant properties, and flexible drug loading and functionalization capacity. These characteristics position it as a highly promising nanodelivery platform, offering new possibilities for innovative treatment strategies for ALS, HD, prion diseases, and FTD.

Application of Ferritin Nanocages in the Diagnosis of NDs

Strategies integrating diverse imaging probes into a single ferritin nanocage enable researchers to simultaneously employ multiple imaging modalities, thereby obtaining more comprehensive and accurate diagnostic information.[152,153]

The conjugation of fluorescent dyes or quantum dots to ferritin nanocages has been successfully utilized for high-contrast imaging in CNS diseases.[154,155] In AD mouse models, fluorescently labeled ferritin nanocarriers achieved

precise targeting of pathological regions, demonstrating not only efficient BBB penetration but also high-contrast fluorescence imaging, providing a powerful tool for pathological visualization.[96] Researchers have combined MRI and fluorescent imaging probes within ferritin nanocages to demonstrate that multimodal imaging offers high contrast in MRI and high resolution in fluorescence imaging, significantly enhancing the detection capability for NDs.[156] A groundbreaking ferritin-based magnetic probe enabled dual-modality imaging in live mice with a single injection. This technology utilized radiolabeled iodine-125 (^{125}I) tagged human H-ferritin nanocages (^{125}I-M-HFn). By leveraging the TfR1-mediated endocytosis-recycling pathway, it ingeniously overcame the challenge of signal blockage in traditional MRI nanoprobes caused by high-dose injections. A single intravenous administration allowed simultaneous acquisition of integrated functional imaging via single-photon emission computed tomography (SPECT) and anatomical details via MRI. Notably, this probe system exhibited unique capabilities for precise localization of brain lesions, offering an innovative solution for theranostics in NDs.[157] Furthermore, recent advances in NDS research have shown that by modulating the expression of TfR on neuronal surfaces, HFn not only ameliorates dysregulated iron metabolism—a core pathological feature of NDs—but also enables breakthroughs in multimodal neuroimaging in vivo. Specifically, HFn enhances cellular contrast in magnetic resonance imaging (MRI) by optimizing TfR-mediated iron transport, providing novel tools for tracking early neuroinflammation, visualizing synaptic damage, and monitoring pathological protein aggregation in diseases such as AD and PD. Importantly, this smart responsive mechanism allows HFn to function dually as both a disease reporter and a targeted therapeutic vehicle, opening new avenues for precision medicine in NDs.[158–161]

Through structural optimization, ferritin nanocages can be engineered to detect and monitor NDs, paving new pathways for early diagnosis and treatment. The Barolo team innovatively developed a humanized ferritin nano-delivery system for the precise encapsulation and targeted delivery of BT1, a tau protein-specific fluorescent probe. By mimicking the natural structure of ferritin, this nano-platform successfully crossed the retinal cellular barrier and delivered BT1 into retinal cells differentiated from human induced pluripotent stem cells, achieving for the first time the in vivo detection of neurofibrillary tangles—a core pathological hallmark of tauopathies. This groundbreaking technology not only validates the efficient delivery capability of nanocages in complex biological systems but also establishes a new paradigm for non-invasive monitoring of neurodegenerative pathologies through the retinal window, offering a revolutionary tool for early screening and disease progression monitoring in AD and other tauopathies.[162]

Leveraging its unique structure, endogenous targeting capability, and multimodal compatibility, ferritin has significantly advanced diagnostic paradigms for neurodegenerative diseases. Through integration with MRI, PET, and fluorescence imaging technologies, it has successfully extended diagnostic dimensions from macroscopic morphology to molecular metabolism, establishing a solid foundation for early diagnosis, disease subtyping, and dynamic monitoring of treatment response. This progress drives the field of neurodegenerative disease diagnostics and therapeutics toward a new era of precision and visualization.

Summary and Prospects

This review has summarized the pathological mechanisms of NDs, the structure and function of the BBB along with its transport mechanisms, and the advantages of ferritin in the treatment of NDs—including its natural nanostructure, brain-targeting capability, functional modifiability, well-defined biosafety profile, drug-loading capacity, and antioxidant properties. Finally, we highlighted the applications of natural ferritin nanocages in both the treatment and diagnosis of NDs.

Owing to its unique hollow structure, excellent biocompatibility, outstanding brain-targeting ability, reversible self-assembly behavior, surface modifiability, and antioxidant activity, ferritin demonstrates broad application potential in biomedicine and nanotechnology. Currently, ferritin nanocages have been successfully employed in various fields such as drug delivery (eg, chemotherapeutic agents and nucleic acids), molecular imaging (MRI/fluorescence imaging), nanozyme catalysis (peroxidase mimicry), and vaccine development (antigen display platforms). While their primary application has been in oncology, their use in NDs remains relatively limited. Notably, ferritin-based strategies have not yet been explored for intractable NDs such as ALS, HD, FTD, or prion diseases. Nevertheless, their unique biological properties offer promising therapeutic solutions for these challenging neurodegenerative disorders.

Transitioning ferritin nanocages from current experimental research to practical clinical application faces a series of critical scientific, technological, and translational medicine hurdles. The following three challenges represent core issues urgently requiring resolution in this field:

1. Challenge of Large-Scale Good Manufacturing Practice (GMP)-Compliant Production: Currently, the preparation of ferritin-based nanocarriers remains primarily at the laboratory scale, with an unclear industrial-scale pathway. As a recombinant protein, its large-scale fermentation and purification processes are complex, characterized by low production yields and high costs, making it difficult to meet the economic viability and stable supply requirements for clinical-grade pharmaceuticals. Furthermore, achieving precise control over the uniformity of drug loading processes and nanocage self-assembly, as well as batch-to-batch consistency—a core requirement of GMP—is challenging. Therefore, developing a robust, scalable production process that ensures structural integrity and loading stability is a primary prerequisite for its translation.
2. Insufficient Systematic Assessment of Long-Term In Vivo Safety and Biotoxicity: While the endogenous nature of ferritin confers a favorable baseline biocompatibility, its long-term in vivo behavior and safety profile after chemical modification, loading with exogenous therapeutic molecules, or conjugation with targeting ligands require systematic evaluation. This includes: the potential for long-term accumulation of nanoparticles in organs such as the liver and spleen; unintended immunogenicity that may be introduced by engineering modifications; and the long-term retention within the brain microenvironment, along with the potential neurotoxicity of its degradation products. Presently, there is a widespread lack of long-term, systematic toxicological, pharmacokinetic, and immunogenicity data that meet the requirements for new drug applications. This represents a critical gap that must be addressed before clinical trials can proceed.
3. Issues of Standardization and Stability in Surface Modification and Functionalization Technologies: Engineering modifications made to the ferritin surface to enhance targeting and therapeutic capabilities often introduce new uncertainties. For instance, the chemical conjugation of targeting molecules (eg, antibodies, peptides) may interfere with inter-subunit interactions, leading to nanostructure disassembly or decreased physicochemical stability. Non-standardized modification strategies readily result in product heterogeneity, severely affecting performance reproducibility and reliability. More critically, these modifications may suffer from functional loss or accelerated clearance within the complex physiological milieu (eg, due to protein corona formation or enzymatic degradation). Consequently, developing stable, controllable, and standardized functionalization techniques is a current key requirement.

Looking forward, overcoming the aforementioned obstacles is fundamental to advancing related research towards application. Promising research directions include:

Comparative Preclinical Studies: Systematic evaluation of ferritin nanocarriers alongside other clinically established nanoplatforms (eg, lipid-based or polymeric systems) in terms of targeting efficiency, safety, and therapeutic outcomes in disease-relevant models.

Advanced Preclinical Validation: Currently, there is a lack of reliable advanced preclinical validation (eg, long-term efficacy and safety assessments in large animal models) for ND-specific ferritin nanoformulations, and no studies have yet entered the clinical stage.[163] Progression to non-human primate studies to better approximate human pharmacokinetics, biodistribution, and safety profiles prior to early-phase clinical trials.

Disease-Adaptive and Responsive System Design: Development of ferritin-based systems capable of stage-specific drug release or biomarker-responsive behavior, enabling personalized therapeutic strategies for progressive neurodegenerative diseases.

Expansion to Understudied Neurodegenerative Disorders: Exploration of ferritin nanocarriers in conditions such as ALS, Huntington's disease, and prion diseases, where therapeutic options remain critically limited.

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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