Function and application of brain-derived neurotrophic factor precursors (Review)

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Abstract. Brain-derived neurotrophic factor precursor (proBDNF) plays a critical role in the pathogenesis and progression of various human diseases. Through its interaction with p75NTR and sortilin receptors, proBDNF promotes apoptosis, impairs synaptic plasticity, and contributes to the regulation of immune system function, inflammatory responses and cellular metabolic processes. proBDNF is widely distributed throughout the body, and as such, extensive research has demonstrated that proBDNF is significantly associated with the pathophysiological mechanisms underlying several diseases. In the present review, the mechanisms by which proBDNF contributes to different diseases are summarized to highlight its potential therapeutic and diagnostic implications. Specifically, the role of proBDNF in cognitive disorders, focusing on its effects on synaptic function and neural network dynamics, while analyzing the cascade reactions involving proBDNF and downstream effector molecules in inflammatory diseases, to elucidate its bidirectional regulatory effects in tumor initiation and progression. Furthermore, the function of proBDNF in neurogenesis, the mechanism by which it regulates the memory of fear, and enhances individual behavioral flexibility is discussed. Finally, the potential of proBDNF as a biomarker for disease diagnosis and the therapeutic prospects of targeting it using monoclonal antibodies are highlighted while also proposing future research directions. The present review can serve as a reference for translational medical research on proBDNF and its receptors.

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1. Introduction

Brain-derived neurotrophic factor precursor (proBDNF) is a precursor protein of the neurotrophic factor family, which has an essential role in the development and function of the central nervous system (CNS) (1). It is generated through the cleavage of the pro-region signal sequence by the Golgi apparatus from pre-pro-BDNF. proBDNF consists of a 129-amino acid N-terminal pre-structural domain and a 118-amino acid C-terminal mature structural domain (2). Within cells, proBDNF can be processed into mature brain-derived neurotrophic factor (mBDNF) by furin or proprotein convertases, while in the extracellular space, it can be converted to mBDNF by tissue-type plasminogen activator (t-PA) or matrix metalloproteinases (MMPs) (3). The efficiency of cleavage and hence the ratio of pro-BDNF to mature BDNF, is different at different stages of development. proBDNF and mBDNF are detectable in the neonatal and adolescent stages, whereas mBDNF predominates in adulthood (4). proBDNF is predominantly found in CNS structures such as the dorsal horn of the spinal cord, raphe nucleus, trigeminal nucleus of the spinal cord, hypothalamus and amygdala; it also occurs in peripheral tissues including skin, intestine, adrenal gland, pituitary gland, liver and skeletal muscle. Furthermore, it is expressed in immune cells such as monocytes/macrophages and T and B cells (5,6). proBDNF interacts with high-affinity to the p75 neurotrophin receptor (p75NTR), Sortilin, Sortilin-related VPS10 domain-containing receptor 2 (SorCS2), and human follistatin-like 4; by activating signaling pathways such as NF-κB, JNK, or RhoA, it plays crucial roles in neuronal apoptosis, synaptic inhibition, axon

pruning and synapse elimination (7-11). proBDNF contributes to axonal retraction dendritic degeneration, and long-term depression, which is associated with cognitive impairment (CI) (11); abnormalities in proBDNF biosynthesis may correspond to different CIs in several brain diseases (12). For example, elevated proBDNF and p75NTR levels in the aged hippocampus lead to learning and memory deficits (13). There are two common polymorphisms of proBDNF, Val66 and Met66. proBDNF Val66 inhibits long-term potentiation (LTP) and promotes long-term depression (LTD) by activating the glycogen synthase kinase 3β (GSK3β)-pTau signaling pathway, which may facilitate synaptic weakening (14). The present review aims to provide an overview of the function and application of proBDNF and to highlight its role in the progression of various diseases.

2. CI

CI encompasses a spectrum of conditions characterized by persistent and acquired cognitive deficits as the primary clinical manifestation, resulting from abnormalities in higher-level cognitive processing associated with learning and memory in the brain. CI includes mild CI (MCI) and dementia, the latter of which can lead to significant impairments in learning and memory, accompanied by aphasia, agnosia, apraxia, visual-spatial deficits, as well as psychological and behavioral dysfunction (15,16). A 2020 study revealed that among individuals aged ≥60 years old, the prevalence of MCI was 15.54%, whereas the prevalence of dementia was 6.04% (17). The etiology of CI remains unclear but may involve excessive CNS immune-inflammatory responses, neuronal apoptosis, accumulation of amyloid-β (Aβ), microvascular damage, and blood-brain barrier (BBB) dysfunction (18). Cortisol, secreted by the hypothalamus-pituitary-adrenal axis, binds glucocorticoid receptors in the hippocampus, amygdala and prefrontal cortex, influencing neuronal function and cognitive processes alongside neurotransmitters such as glutamate (19). Currently, the diagnosis of CI largely depends on neuropsychological assessments, laboratory biomarkers and relevant neuroimaging examinations. Treatment strategies typically involve a comprehensive approach integrating pharmacological therapy, physical rehabilitation, and psychological and behavioral interventions. However, achieving satisfactory treatment outcomes remains challenging (20). Thus, effective interventions to prevent or slow the course of CI are critically needed.

Neurodegenerative diseases. BDNF plays a role in the development of neurodegenerative diseases, including Parkinson's disease (PD) and Alzheimer's disease (AD). An imbalance in the conversion of proBDNF to mBDNF can significantly affect the progression of these diseases by decreasing synaptic plasticity. The degeneration of neurons in the substantia nigra, striatum and hippocampus can impede the conversion of proBDNF to mBDNF, resulting in higher levels of proBDNF. The concentration of proBDNF is closely associated with the severity of neurodegenerative diseases (3). Prediabetes is associated with an elevated risk of AD and related dementias (ADRD) (21); exercise has been shown to mitigate this risk by modulating brain metabolism and reducing neuroinflammation (22,23). Neuronal extracellular vesicles (nEVs) can carry a variety of biomolecules, including proteins, lipids and RNA. These vesicles facilitate intercellular communication and play a role in various physiological and pathological processes. Furthermore, nEVs can serve as indicators of insulin signaling in the brain (24,25). Insulin regulates a wide array of cellular functions, such as glucose metabolism, mitochondrial activity, oxidative stress response, autophagy, synaptic plasticity and cognitive processes. Alterations in the phosphorylation status of signaling molecules within the insulin pathway contribute to oxidative stress and neuroinflammation. Moreover, insulin signaling is pivotal in maintaining neuronal health and mitigating neurodegenerative processes (26). In a study involving 21 older adults with prediabetes who underwent 12 sessions of 60-min cycling training over a 2-week period, researchers observed enhanced neuronal responsiveness to insulin, as well as increased peripheral insulin sensitivity. The underlying mechanism may involve a significant reduction in fasting levels of proBDNF and increased expression of total protein kinase B (Akt) in nEVs under glucose stimulation following short-term exercise. These changes were closely linked to improvements in peripheral insulin sensitivity, while the decrease in proBDNF suggested that exercise may alleviate neuroinflammation or oxidative stress (27). However, due to limitations such as a small sample size, absence of a control group, and insufficient long-term monitoring of the direct preventative effects of exercise on ADRD, further investigation is warranted to elucidate how alterations in Akt within nEVs influence neuronal function and cognition. Additionally, the precise mechanisms by which proBDNF affects insulin signaling require further exploration to clarify its relationship with brain insulin action following exercise.

AD. AD is a progressive condition that primarily affects memory and cognitive functions. The pathogenesis of AD involves multiple hypotheses, including the Aβ hypothesis (28), molecular mechanisms of tau protein pathology (29), glial cell activation and neuroinflammation (30), insulin resistance and brain energy metabolism (31), gut microbiota dysbiosis (32), pathogenic mechanisms of APOE4 (33), abnormal DNA methylation and histone modifications (34), as well as environmental and lifestyle factors such as sleep disturbances (35) and air pollution (36). Collectively, these factors may contribute to the onset and progression of AD. Microcystin is a potent hepatotoxin produced by certain cyanobacteria. Its relevance to AD stems from its capacity to induce oxidative stress, neuroinflammation and neuronal damage, which are mechanisms central to the pathophysiology of AD. Therefore, microcystin serves as a valuable model toxin for investigating neurodegenerative processes (37). Research has indicated that prolonged exposure to microcystin can markedly decrease the levels of the t-PA enzyme, increase the expression of proBDNF, activate the JNK pathway, and trigger neuronal apoptosis in the hippocampal CA1 and CA2 areas. This exposure also leads to a reduction in spinal cord density, accumulation of Aβ protein plaques, and increased phosphorylated tau. These changes contribute to the development of learning and memory impairments, as well as Alzheimer's-like alterations (38). Similar to microcystin, β-methylamino-L-alanine, a neurotoxin produced by cyanobacteria, has been shown to induce neurotoxicity; Domoic acid, which acts as a glutamate receptor agonist and is produced by algae, triggers excitotoxicity and induces neuronal

damage; heavy metals, such as lead and mercury, have also been demonstrated to promote oxidative stress and cognitive decline, thereby positioning them as significant factors in AD research. Nevertheless, the precise relationship between these toxins and proBDNF requires further investigation (39,40).

The progression of AD is marked by an exceptionally prolonged course, and it remains unclear whether this is due to ongoing neuronal degeneration, dysregulation of associated molecular networks, or a combination of these factors that contribute to the disease's pathogenesis (41-43). As a result, further investigation is necessary to elucidate the complexities of signaling pathways, the synergistic effects between molecules, as well as the presence of positive and negative feedback loops and their spatiotemporal interrelationships. The p75NTR receptor is essential for proBDNF to facilitate the accumulation of Aβ plaques and the phosphorylated tau (44). In Aβ1-40-injected rats and APP/PS1 transgenic mice, the ratio of proBDNF to mBDNF in the CA1 region of the hippocampus was significantly elevated. proBDNF inhibits GABAergic synaptic function via the p75NTR receptor, whereas mBDNF promotes the survival of GABAergic neurons and the expression of KCC2 through the TrkB receptor. Functional abnormalities in the hippocampus are closely associated with cognitive deficits, with the inhibition of GABAergic transmission and the imbalance of the BDNF signaling pathway serving as key pathological mechanisms. The suppression of GABAergic transmission results in reduced synchrony of the hippocampal neural network, thereby impairing memory encoding. Restoring GABAergic inhibitory function can re-establish the excitation-inhibition balance of the hippocampal neural network, rescuing cognitive function (45). Notably, another study demonstrated that in 5xFAD and APP/PS1 transgenic mice, alongside the progression of Aβ deposition and tau pathology in hippocampal neurons, Aβ oligomers reduce the conversion of proBDNF to mBDNF by inhibiting the tPA/plasmin system. Simultaneously, they activate GSK-3β and calpain, promoting the cleavage of the TrkB receptor, which further diminishes the neuroprotective effects of mBDNF. Although soluble amyloid precursor protein α (sAPPα), produced via the non-amyloidogenic pathway, indirectly enhances the mBDNF/TrkB signaling pathway by activating α7-nicotinic acetylcholine receptors and NMDA receptors, Aβ deposition reduces sAPPα, weakening this protective mechanism. Additionally, the decreased expression of sorLA in AD disrupts Aβ clearance, exacerbating the imbalance in the proBDNF/mBDNF ratio (7). The imbalance of proBDNF/mBDNF in the AD hippocampus mediates neurodegeneration via p75NTR and TrkB signaling pathways. The signal transduction mechanisms of proBDNF across AD are illustrated in Fig. 1. Furthermore, the interaction between Aβ and sAPPα exacerbates this pathological process. Future research should concentrate on restoring BDNF homeostasis, inhibiting proBDNF signaling, and targeting critical nodes in sAPPα processing to provide a novel therapeutic strategy for AD treatment.

PD. PD is the second most prevalent neurodegenerative disorder globally, with an incidence rate exceeding 1% among individuals aged ≥65 years old, and it is projected that the incidence rate will double by 2030. In addition to the characteristic motor symptoms of PD, numerous non-motor symptoms are also present, with CI being the most prevalent and occurring at any stage (46). The research data indicates that the average incidence rate of MCI in patients with PD is 25.8%, while the incidence rate of dementia is 26.3%. Additionally, the incidence rate of dementia can escalate to 83% within 20 years following a PD diagnosis (47). Currently, the primary focus lies on early cognitive changes, characterized by impaired executive function and spatial abilities, often accompanied by memory deficits, thereby increasing the risk of early progression to dementia (46). CI represents a prevalent non-motor symptom of PD, spanning from MCI (PD-MCI) to dementia (PDD); the manifestations, severity, and progression of CI exhibit significant heterogeneity and may involve alterations in multiple neurotransmitter systems, including dopamine, acetylcholine, norepinephrine and serotonin, and the neuropathology of CI in PD encompasses a range of pathological changes, such as Lewy bodies, Aβ and neurofibrillary tangles. Additionally, deficiencies in multiple neurotransmitters and genetic risk factors, including α-synuclein mutations and apolipoprotein E variants, contribute to its development (48). A systematic search was conducted in the PsycINFO (https://www.apa.org/pubs/databases/psycinfo/), PubMed (https://pubmed.ncbi.nlm.nih.gov/) and Scopus (https://www.scopus.com/home.uri) databases up to April 2019, yielding 41 eligible studies (involving 7,053 patients with PD); PD-MCI was relatively prevalent among non-demented patients with PD, with an estimated prevalence of ~40%. The multiple-domain subtype represents the predominant manifestation of PD-MCI and is associated with the postural instability and gait difficulty subtype, longer disease duration, higher levodopa equivalent daily dose, and more severe motor symptoms. PD-MCI is further linked to a reduced quality of life, elevated levels of depression and apathy, and serves as a significant predictor of dementia progression (49). Neuropsychological assessment remains the gold standard for diagnosing CI, offering comprehensive evaluations across various cognitive domains; only rivastigmine has been approved by the U.S. Food and Drug Administration for the treatment of PDD, and future treatments for PD will necessitate further research in the standardization of cognitive assessments, early diagnosis and intervention of CIs, as well as the development of effective symptom management and disease-modifying therapies, which represent significant challenges (48). More longitudinal studies are warranted to comprehensively investigate the risk factors and progression of PD-MCI. Additionally, there is a need to develop anxiety assessment tools specifically designed for patients with PD in order to more precisely evaluate the relationship between anxiety and PD-MCI (49).

When neurotrophic factors NT3 and NT4 interact with p75NTR, they activate the PI3K/AKT pathway, upregulate Bcl-2, and confer a protective effect on dopaminergic neurons. Conversely, when proBDNF binds to p75NTR, it triggers apoptosis in dopaminergic neurons, accelerating the progression of PD. The underlying mechanism involves the activation of the JNK, Caspase-3, NF-κB and RhoA pathways (50). The precise mechanism by which proBDNF binds to the p75NTR receptor to mediate the pro-apoptotic pathway leading to CI remains incompletely understood, necessitating further research.

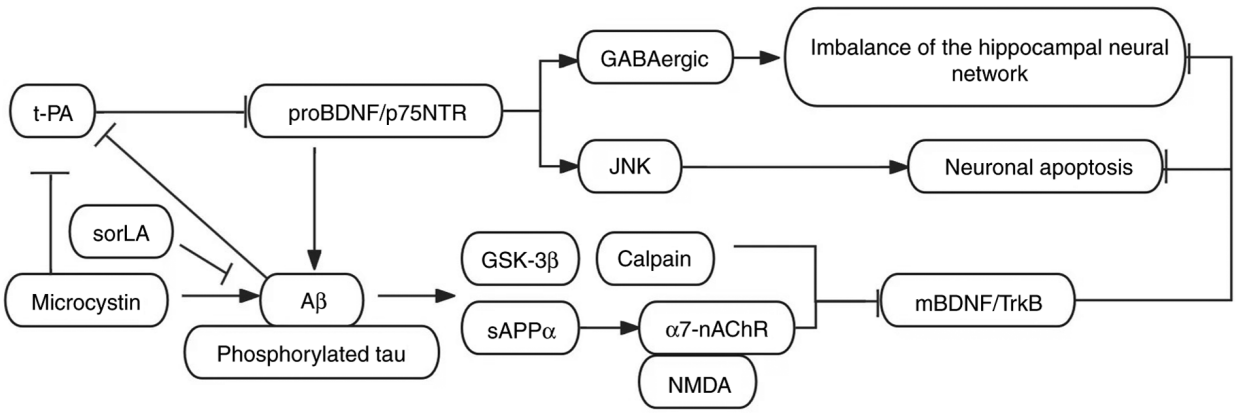

Figure 1. Microcystin can significantly reduce the level of t-PA, increase the expression of proBDNF, activate the JNK pathway, and trigger neuronal apoptosis. Moreover, microcystin can cause the accumulation of Aβ and increase the phosphorylated tau. The p75NTR receptor is crucial for proBDNF promoting the accumulation of Aβ and the phosphorylated tau. ProBDNF/p75NTR can lead to the imbalance of the hippocampal neural network by inhibiting GABAergic transmission. Aβ can inhibit the tPA and reduce the conversion of proBDNF to mBDNF. The reduction of sorLA expression further aggravates the accumulation of Aβ and the imbalance of the proBDNF/mBDNF ratio in Alzheimer's disease. Aβ can inhibit the mBDNF/TrkB pathway by activating GSK-3β and calpain, and reducing the expression of sAPPa, as well as inhibiting a7-nAChR and NMDA receptors. mBDNF can promote GABAergic transmission and plays a crucial role in maintaining the balance of the hippocampal neural network. proBDNF, brain-derived neurotrophic factor precursor.

Multiple sclerosis (MS). MS is a primary inflammatory demyelinating disease of the CNS. CI is a common and debilitating symptom within its broad and unpredictable spectrum of clinical manifestations, significantly impacting the quality of life for patients (51). The prevalence of CI in MS ranges from 20-88%, with the highest occurrence and most severe symptoms observed in primary progressive MS. The underlying mechanism of MS-related CI requires further elucidation (52). Research indicates that the upregulation of proBDNF and its receptor in immune cells in patients with MS and MS model mice is closely associated with demyelination and CNS inflammation. This may occur through the proBDNF/p75NTR/NF-κB pathway, which mediates the release of inflammatory cytokines such as TNF-α, IL-β, IL-6, IL-17 and INF-γ by peripheral immune cells. Furthermore, intraperitoneal (i.p.) injection of an anti-proBDNF antibody has been shown to improve MS by modulating immune system function (53).

The Vps10p-domain receptor family consists of a group of evolutionarily conserved sorting receptors that play essential roles in intracellular protein trafficking and signaling, and the primary members of this family include Sortilin (SORT1), SorLA (LR11/SORL1), SorCS1, SorCS2 and SorCS3, which are implicated in neurodevelopment, synaptic plasticity and metabolic regulation (54). P75NTR, a member of the tumor necrosis factor receptor superfamily, plays a critical role in the survival, apoptosis and synaptic plasticity of neurons (55). The interaction between Sortilin and p75NTR serves as a critical regulatory mechanism for apoptosis, inflammatory responses and metabolic processes (54,56). When proBDNF binds to the p75NTR-Sortilin complex, it activates the downstream JNK pathway, leading to the release of cytochrome C from mitochondria and promoting apoptosis, and this mechanism may exacerbate cell damage in neurodegenerative and inflammatory diseases (57). It is worth noting that the interaction between p75NTR and Sortilin may exhibit distinct functional roles across various cell types and disease contexts (54). The expression of proBDNF is significantly increased in patients with MS and experimental autoimmune encephalomyelitis (EAE) models, thereby promoting neuronal apoptosis and inflammatory responses through the activation of p75NTR-Sortilin receptors. Additionally, the reduced activity of proteases, such as plasmin, may hinder the conversion of proBDNF to mBDNF, thereby exacerbating the pathological progression of MS (58). Although Sortilin is highly expressed in the brain tissue of patients with MS, its deficiency does not appear to significantly influence disease progression in the EAE model and it has been proposed that Sortilin predominantly engages in the innate immune response rather than the adaptive immune response within immune cells, thereby suggesting a limited role of Sortilin in MS (59). A comprehensive understanding of its specific mechanisms across a range of disease contexts, along with the development of highly selective drugs, will continue to be a focal point for future research endeavors.

Depression

Pathogenesis of depression. The pathogenesis of depression includes the neurotransmitter hypothesis, hypothalamic-pituitary-adrenal axis hypothesis, neuroplasticity hypothesis, and immunoinflammatory hypothesis, in which microglia and astrocytes are important (60). It shows neuronal atrophy and synaptic loss in the prefrontal cortex and hippocampus of depressed patients. These changes are associated with deficits in executive function, memory, attention, self-referential processing bias and cognitive rigidity (61). In addition, individuals with major depression often have significant impairments in cognitive function, such as learning, memory, executive function, processing speed, attention and concentration, which are underpinned by multiple interacting neurobiological mechanisms, including neuroinflammation. Moreover, most antidepressants have not been specifically developed or evaluated to improve these cognitive deficits (62). It has been indicated that elevated proBDNF levels may result in CI, leading to behaviors that resemble depression (63).

proBDNF regulates synaptic plasticity. Researchers have discovered that the expression levels of proBDNF and its receptor p75NTR are significantly elevated in patients with

severe depression and in mouse models of depression. When mice were injected with proBDNF into both sides of their hind legs, they displayed depressive-like behaviors within 4 weeks. Furthermore, it was observed that the density and length of synapses in the hippocampal dentate gyrus and amygdala of the mice were diminished, whereas treatment with a proBDNF antibody mitigated depressive symptoms. Thus, proBDNF appears to be a key driver of depression-like behaviors in mice, potentially through reduced synaptic plasticity (64).

proBDNF mediates neuroinflammation and glial cell activation. A recent study comparing the levels of related molecules in the serum and lymphocytes of 32 patients with depression and 20 healthy individuals found that the levels of IL-1β and IL-10 in lymphocytes were positively correlated with the severity of depression, while the levels of TNF-α and IL-6 were negatively correlated. Sortilin levels were positively correlated with IL-1β levels. Furthermore, proBDNF and p75NTR were primarily upregulated in $CD4^+$ and $CD8^+$ T cells in patients with severe depression, and their levels returned to normal following antidepressant treatment. The proBDNF/p75NTR/sortilin pathway may upregulate the expression levels of IL-1β and IL-10 in patients with severe depression, downregulate TNF-α and IL-6, and thus regulate the progression of depression (65). In the mouse depression model associated with periodontitis, researchers observed that microglia and astrocytes in the hippocampus were activated, and the expression of inflammatory factors IL-1β and TNF-α significantly increased. The expression of occludin and claudin5, proteins related to tight junctions, was reduced, and the levels of IL-1β in the serum were elevated; proBDNF was found to be involved in this process (66). Li *et al* (67) found that the deletion of SorCS2 alleviated depressive-like behaviors induced by periodontitis in mice. Thus, it is hypothesized that the deletion of SorCS2 downregulated proBDNF and glutamatergic signal transduction in the hippocampus, restoring neuronal activity.

proBDNF-induced neuronal apoptosis. Post-stroke depression (PSD) is a common complication following a stroke, characterized by persistent depression and diminished interest (68). Yang *et al* (69) established an *in-vitro* model of PSD by depriving neuronal cells of oxygen and glucose and treating them with corticosterone. It was found that proBDNF protein levels in the prefrontal cortex and hippocampal neurons of the PSD model group were significantly elevated compared with the control group. proBDNF binds to the p75NTR receptor, activating the RhoA/JNK signaling pathway, which upregulates the expression of PSD-related proteins such as PSD-95, Syn and P-cofilin. Simultaneously, it downregulates the expression of anti-apoptotic proteins, including RIP2, caspase-3 and Cytochrome C, thereby inducing neuronal apoptosis, reducing the number of mature synapses, and influencing the development of depression. A recent study has shown that the injection of hippocampal exosomes, extracted and purified from a mouse model of stroke, exacerbated depressive-like behaviors in mice. The mechanism is hypothesized to be related to the increased expression of proBDNF and p75NTR, as well as the insufficient expression of synaptophysin and PSD95, caused by hippocampal exosomes from stroke (70).

Based on the aforementioned research findings, it can be inferred that neural-immune mechanisms play a pivotal role in the progression of depression. The proBDNF/p75NTR/sortilin pathway shows considerable promise as a therapeutic target for addressing CIs associated with depression, and future studies should focus on further exploring its clinical translational potential.

HIV-associated neurocognitive disorders (HANDs). HANDs refer to a spectrum of neuro-CIs linked to HIV infection. Despite the substantial reduction in HIV-related mortality achieved through antiretroviral therapy (ART), HANDs continue to be prevalent complications among individuals living with HIV (71,72). HANDs can be categorized into three levels based on severity: Asymptomatic neuro-CI, mild neurocognitive disorder, and HIV-associated dementia (73). The pathophysiological mechanisms underlying the development of HANDs are multifaceted, encompassing direct viral damage to the CNS, immune activation and inflammatory responses, disruption of the BBB, and release of neurotoxic factors such as glutamate, reactive oxygen species (ROS) and nitric oxide (74,75). Treatment strategies for HANDs include the optimization of ART, incorporation of anti-inflammatory therapy, neuroprotective agents and application of immunomodulatory approaches (76-78). The management of HANDs continues to pose significant difficulties. Future research will concentrate on early diagnosis, innovative treatment approaches, and personalized medicine strategies to enhance the quality of life for patients with HANDs (79).

A significant number of individuals infected with HIV-1 develop HANDs, including spatial memory impairment and learning difficulties, even if they are undergoing combination ART (80). Synaptic simplification and loss are prominent features of HANDs. The HIV-1 envelope protein gp120 has been shown to elevate the levels of proBDNF in the body, leading to the binding of proBDNF to p75NTR and a subsequent reduction in synaptic plasticity (81).

Researchers have discovered that gp120 causes intermittent memory impairment and learning deficits by disrupting mitochondrial function and energy production. This disruption may occur through the impairment of the glycolytic pathway at the pyruvate level, leading to the accumulation of glycated end products and inhibiting the cleavage of proBDNF into mBDNF. The accumulation of proBDNF triggers the expression of Inducible cAMP Early Repressor, which occupies cAMP response element binding sites present on the promoter regions II and IV of the BDNF gene, thereby altering normal synaptic plasticity (82). A cross-sectional study revealed that among 157 HIV-infected individuals from sub-Saharan Africa who had not undergone ART, elevated serum mBDNF levels were significantly and positively correlated with the patients' cognitive abilities. By contrast, increased proBDNF levels were negatively correlated with the patients' cognitive abilities, particularly affecting fine motor skills and speed (83). Modulating proBDNF levels could represent a potential therapeutic strategy for ameliorating learning and memory impairments in individuals infected with HIV-1.

Sepsis-associated encephalopathy (SAE). Microglia, as an endogenous immune cell, release both pro-inflammatory and anti-inflammatory cytokines, nitric oxide and neurotrophic factors. The upregulation of intracellular Ca^{2+} concentration in microglia is crucial for its functionality. proBDNF binds to

p75NTR and activates the targeting transient receptor potential melastatin 7 (TRPM7) channel, leading to a sustained elevation of intracellular Ca^{2+} in microglia, thereby enhancing nitric oxide production induced by INF-γ. proBDNF may thus play a significant role in regulating inflammatory responses in the brain (84).

SAE refers to diffuse brain dysfunction caused by sepsis, characterized by decreased attention and disorientation (85). The pathogenesis of SAE primarily involves neuroinflammation, disruption of the BBB, impairment of cerebral vascular function, and alterations in neural metabolism (86). Researchers have discovered that sepsis can increase proBDNF levels, leading to a reduction in the infiltration of cerebral meningeal $CD4^+$T cells. This disrupts the balance of the pro-inflammatory and anti-inflammatory microenvironment in the meninges, including an upregulation of pro-inflammatory factors such as IL-1β and IL-6, as well as a downregulation of anti-inflammatory factors including IL-4 and IL-13. Ultimately, resulting in cognitive dysfunction (87), SAE increases the likelihood of cognitive and memory impairment, with proBDNF potentially playing a significant role in the pathogenesis of SAE.

Cerebral ischemia-reperfusion injury (CIRI). CIRI represents a complex pathological process that ensues when blood flow is reestablished to the brain following a period of ischemia, characterized by an absence of adequate blood supply (88). CIRI involves a variety of complex mechanisms, including oxidative stress and hypoxia, which lead to mitochondrial dysfunction, resulting in the excess release of ROS (89,90); calcium overload activates protease, lipase and endonuclease, leading to cell injury and death (91), mitochondrial dysfunction (89), inflammatory responses mediated by immune cells (92,93), and the breakdown of the BBB. This breakdown of the BBB results in the excessive release of excitatory neurotransmitters, resulting in calcium ion inflow. Reperfusion triggers programmed cell death and necrotic cell death (94,95). CIRI significantly contributes to the morbidity and mortality associated with stroke and other ischemic events. This condition complicates treatment strategies, as while the restoration of blood flow is essential, it may exacerbate outcomes if not carefully managed (96). At present, the primary treatment methods for CIRI include edaravone and N-acetylcysteine, which are used to neutralize ROS and reduce oxidative stress; calcium channel blockers to inhibit calcium overload; anti-inflammatory drugs such as IL-1 receptor antagonists and TNF-α inhibitors; neuroprotective agents to protect neurons from excitotoxicity and apoptosis; and therapeutic hypothermia to reduce metabolic demands and alleviate reperfusion injury (97-99). Emerging therapeutic approaches include targeting the Wnt/β-Catenin signaling pathway for brain ischemia-reperfusion injury (100), and TRPM channels to inhibit oxidative stress, mitochondrial dysfunction, inflammation and calcium overload (101).

CIRI promotes the release of inflammatory factors, resulting in BBB damage (102). This structural and functional impairment of the BBB can further trigger microglial activation, neuronal apoptosis and Aβ deposition, ultimately leading to spatial learning and memory dysfunction (103). In the mouse model of acute ischemic stroke, researchers observed the infiltration of NK cells into the surrounding area of the brain infarction. This subsequently promoted microglial activation, resulting in an inflammatory response and neuronal damage (104). Previous research has shown that microglia can modulate synaptic plasticity; however, the exact mechanism by which they contribute to CIRI is not fully understood. Subsequent studies using a mouse model of middle cerebral artery occlusion (MCAO) have indicated that proBDNF/p75NTR may disrupt glutamatergic synapses within 24 h of MCAO, whereas the mBDNF/TrkB pathway could interfere with GABAergic synapses. This activation subsequently triggers the ERK1/2 and GSK3β pathways, leading to the phosphorylation of the postsynaptic protein Gephyrin at the Ser268 and Ser270 residues, ultimately resulting in excessive synaptic pruning by microglia. By pharmacologically depleting microglia or employing a multi-functional gene editing system known as CRISPR-Cas9 to generate GphnS268A/S270A mutant mice and mice lacking BDNF expression in their microglia, researchers were able to reduce microglial activation within 24 h. This intervention ensured the preservation of both glutamatergic and GABAergic synapses, enhanced synaptic protection, reduced infarct size following ischemia, facilitated tissue repair, and promoted neural network reorganization after CIRI (105). In the rat photochemical occlusion model of ischemic cerebral infarction, researchers observed that administering an anti-proBDNF antibody at a dosage of 5 mg/kg via i.p. injection at 6 h and 3 days post-ischemia exhibited anti-apoptotic and anti-inflammatory effects, demonstrating improved sensory-motor function after CIRI (106); confirming that the proBDNF antibody could reduce neuronal apoptosis and alleviate inflammatory responses in the infarcted area. However, further verification is required to determine whether the proBDNF antibody can improve CI. Additionally, further larger-scale studies are required to investigate the therapeutic effects of different doses of proBDNF antibody to obtain the optimal dose for quicker recovery following CIRI.

Postoperative cognitive dysfunction (POCD). POCD is a prevalent complication among elderly patients undergoing anesthesia and surgery, with studies indicating an incidence ranging from 10-54%. The incidence of POCD in patients undergoing cardiac surgery is notably higher, with up to 80% experiencing postoperative delirium and a subsequent incidence of POCD within 12 months ranging from 10-40% (107,108). POCD primarily presents as anxiety, alterations in personality, psychosis and memory impairment. Its mechanism involves inflammation of the CNS, oxidative stress and apoptosis (109). POCD represents a significant neurological complication following surgery, and there is evidence to suggest that neuroinflammation plays a pivotal role in its pathogenesis. The age-dependent nature of the neuroinflammatory mechanisms underlying POCD underscores the importance of comprehending the involvement of neuroinflammation to elucidate its underlying mechanisms and develop effective strategies for prevention and treatment (110).

Researchers induced POCD in 16-month-old mice through stable femoral fracture surgery under sevoflurane anesthesia, establishing an animal model of POCD. They observed that anesthesia and surgery led to an increase in proBDNF, which negatively regulated synaptic function in the hippocampus and resulted in cognitive dysfunction in aged mice. The administration of P75NTR inhibitors and exogenous BDNF was found

to mitigate the loss of dendritic spines and long-term potentiation in the hippocampus by altering the mBDNF/proBDNF ratio, thereby alleviating postoperative cognitive dysfunction. Modulating the mBDNF/proBDNF ratio may present a promising target for treating POCD (111). Oxidative stress injury is a key pathogenic mechanism of POCD. Studies have revealed a close association between the integrated stress response (ISR) and oxidative stress. In an experiment, researchers induced POCD in male mice by performing tibial surgery at 4 months of age under sevoflurane anesthesia and assessed cognitive function using fear conditioning tests and Y-mazes from postoperative days 3 to 14. The use of ISR inhibitors was found to downregulate the expression of molecules associated with oxidative stress, such as ROS, superoxide dismutase and malondialdehyde in the hippocampus. Additionally, it led to decreased levels of proBDNF and increased levels of mBDNF, thereby mitigating oxidative stress and ameliorating cognitive dysfunction in mice (112). The imbalance between proBDNF and mBDNF holds significant implications for postoperative cognitive dysfunction, yet the associated pathways and mechanisms remain incompletely elucidated. In instances of POCD resulting from anesthesia surgery, aberrant expression levels of proBDNF are associated with neuroimmune inflammatory responses, a relationship requiring further validation in future research. In the present review, the association between proBDNF and cognitive disorders is described and is further summarized in Table I.

3. Inflammatory diseases

Sepsis. Sepsis is a life-threatening condition characterized by organ dysfunction resulting from a dysregulated response to infection (113). Sepsis is primarily associated with excessive inflammation; infection induces the release of a substantial quantity of inflammatory mediators, such as TNF-α, IL-1β and IL-6. Additionally, inflammation-induced increases in microvascular permeability are frequently accompanied by the activation of the coagulation system, resulting in microthrombus formation, tissue edema and subsequent organ dysfunction (114). Sepsis is associated with a high mortality rate, particularly in patients with septic shock. The prognosis is significantly influenced by early diagnosis, timely intervention, and the underlying health condition of the patient (115). Researchers observed that the expression of proBDNF and p75NTR in the cortical area of $CD3^+$ and $CD4^+$T cells in mesenteric lymph nodes of septic mice was upregulated. The upregulation of proBDNF may disrupt the immune-inflammatory microenvironment and significantly contribute to the progression of sepsis (116). Further investigation explored the changes in expression of proBDNF/p75NTR, derived from lymphocytes in the peripheral blood of septic patients, and its impact on lymphocyte differentiation. The expression of proBDNF in the peripheral blood of septic patients was upregulated in $CD19^+$B cells, while the expression of p75NTR was upregulated in $CD19^+$B cells, $CD4^+$T cells and $CD8^+$T cells. The proBDNF/p75NTR signaling pathway may regulate lymphocyte differentiation, decrease the percentage of $CD4^+$ T cells and $CD19^+$B cells, increase the production of inflammatory factors IL-1β and IL-6, and promote the progression of sepsis (117).

Immune-mediated inflammatory diseases (IMIDs). IMIDs encompass a diverse range of conditions characterized by persistent inflammation and immune dysregulation, affecting multiple organ systems. With >100 distinct types identified, the global incidence of IMIDs is increasing. Future treatment strategies for IMIDs should prioritize restoring immune balance and investigating potential interactions between the immune and nervous systems, rather than solely focusing on alleviating inflammation (118). Therefore, it is necessary to understand the pathogenic mechanism of IMIDs and to explore novel therapeutic targets.

Rheumatoid arthritis. In the synovial tissue of the mouse model of arthritis, the levels of proBDNF and p75NTR are elevated in $CD4^+$ and $CD8^+$ T cells, and the levels of inflammatory cytokines TNF-α, IL-1β, IL-6 and IL-10 are also elevated. This elevation can be reversed by treatment with methotrexate (119). The proBDNF/p75NTR pathway is closely associated with the pathogenesis of rheumatoid arthritis, while the expression levels of sortilin are positively correlated with disease severity in patients. Inhibition of the proBDNF/p75NTR pathway may lead to downregulation of the JNK/p38MAPK signaling pathway and a reduction in the release of inflammatory cytokines such as IL-6, IL-8 and MCP-1, thereby alleviating joint pain in individuals with rheumatoid arthritis (120).

Systemic lupus erythematosus (SLE). SLE is a complex autoimmune disease, primarily triggered by a genetic predisposition, exposure to silica and cigarette smoke particles, ultraviolet light, EB virus infection, or environmental factors including the use of medications including procainamide, hydroxychloroquine and contraceptives. These factors interact to activate both innate and specific immunity. T-cell-mediated autoimmune responses stimulate B cells to generate anti-ds-DNA antibodies and other autoantibodies. Hyperactive autoimmune B cells and dysregulation of antibody-secreting cells (ASCs) lead to the production of numerous immune complexes, resulting in widespread tissue and organ damage (121). proBDNF and p75NTR are significantly upregulated in ASCs of patients with SLE. Moreover, there is a positive correlation between proBDNF levels and joint symptoms, erythrocyte sedimentation rate, autoantibody levels, and the degree of SLE activity. In addition, in a mouse model of lupus, it was found that proBDNF and p75NTR were highly expressed in the ASCs of peripheral blood and spleen. The activation of the proBDNF/p75NTR pathway was shown to promote ASC proliferation and differentiation, stimulate the secretion of autoantibodies as well as the deposition of IgG complexes, and exacerbate renal injury, thus confirming the potential pathogenic role of proBDNF in SLE (122).

Immune dysregulation and mitochondrial dysfunction in IMIDs. Chronic inflammation in IMIDs induces aberrant activation of immune cells, including macrophages, T cells, and B cells, leading to a significant increase in their metabolic requirements, such as glycolysis and oxidative phosphorylation. Upon binding to the p75NTR/sortilin complex, proBDNF modulates metabolic enzyme activity, mitochondrial membrane stability, and respiratory chain function, thereby directly or indirectly exacerbating the pathological progression of IMIDs (57). The proBDNF/p75NTR/sortilin complex activates the downstream JNK signaling pathway,

Table I. Cascades between cognitive impairment, proBDNF and downstream effector molecules.

First author, year	Disease	proBDNF and receptor	Downstream molecular	Function	(Refs.)
Eggert *et al*, 2022; Manucat-Tan *et al*, 2019; Bie *et al*, 2022	AD	proBDNF/p75NTR/sortilin↑	JNK↑, KCC2↓	Neuronal apoptosis, tau phosphorylation, Aβ plaques	(7,44,45)
Ali *et al*, 2024	PD	proBDNF/p75NTR↑	JNK, Caspase-3, NF-κB, RhoA↑	Neuronal apoptosis	(50)
Hu *et al*, 2021	MS	proBDNF/p75NTR↑	NF-κB, TNF-α, IL-β, IL-6, IL-17, INF-γ↑	Central nervous system inflammation, demyelination	(53)
Al-Kuraishy *et al*, 2024	MS	proBDNF/Sortilin1↓	mBDNF↓, B cell apoptosis	Weakened autoimmune and inflammatory responses	(58)
Li *et al*, 2024	Depression	proBDNF/SorCS2↓	glutamatergic↑	restore neuronal activities	(67)
Yang *et al*, 2024; Li *et al*, 2023	MDD	proBDNF/p75NTR/sortilin↑	IL-1β, IL-10↑, TNF-α, IL-6↓	Reduce dendritic spine plasticity	(65,66)
Yang *et al*, 2021; Huang *et al*, 2024	PSD	proBDNF/p75NTR↑	RhoA/JNK, PSD-95, Syn, P-cofilin↑, RIP2, caspase-3, Cytochrome C↓	Neuronal apoptosis	(69,70)
Speidell *et al*, 2020; Allen *et al*, 2022; Michael *et al*, 2025	HAND	proBDNF/p75NTR↑	ICER↑	Reduce synaptic plasticity	(81-83)
Mizoguchi *et al*, 2021; Luo *et al*, 2020	SAE	proBDNF↑	IL-1β, IL-6↑, IL-4, IL-13↓	CNS inflammation	(84,87)
Cramer *et al*, 2022	CIRI	proBDNF/p75NTR↑	ERK1/2, GSK3β↑	Downregulate glutamatergic dendritic spines and gephyrin scaffold stability	(105)

AD, Alzheimer's disease; PD, Parkinson's disease; MS, multiple sclerosis; MDD, major depressive disorder; PSD, post-stroke depression; HAND, HIV-associated neurocognitive disorder; SAE, sepsis-associated encephalopathy; CIRI, cerebral ischemia-reperfusion injury; proBDNF, brain-derived neurotrophic factor precursor.

resulting in the activation of pro-apoptotic Bak and Bax proteins within the Bcl-2 family. This leads to the release of cytochrome C from mitochondria and the formation of apoptotic bodies, ultimately culminating in the activation of caspase 3 and caspase 9, thereby inducing apoptosis and synaptic suppression (57,123,124). proBDNF/p75NTR may mediate neuroimmune inflammatory responses, apoptosis and mitochondrial dysfunction, thereby facilitating the progression of MS (58). In individuals with rheumatoid arthritis, proBDNF/p75NTR may regulate mitochondrial glucose metabolism in fibroblast-like synoviocytes and $CD4^+$ T cells, leading to fibroblast-like synoviocyte proliferation, migration, invasion and cytokine secretion that exacerbate joint destruction. Additionally, the proBDNF/p75NTR signal can promote the assembly of mitochondrial respiratory chain complexes in the B cells of patients with SLE, resulting in mitochondrial damage and dysfunction that intensify disease activity. In an animal model of type A acute aortic dissection, upregulation of proBDNF in M2 monocytes may mediate inflammatory responses as well as induce mitochondrial dysfunction and apoptosis within the aortic wall (57).

In conclusion, proBDNF and its receptor p75NTR can trigger tissue and organ damage via an exaggerated inflammatory response. Additionally, proBDNF, p75NTR and the sortilin receptor are capable of regulating mitochondrial function and energy metabolism in cells, inducing apoptosis, and thereby influencing the progression of IMIDs. The role of proBDNF in inflammatory diseases is summarized in Table II. However, the underlying etiology of immune dysregulation in inflammatory diseases remains unclear. Future research should explore proBDNF and its receptors from various angles, focusing particularly on their role in regulating cellular metabolism and mitochondrial function across different immune cell subpopulations, to obtain a deeper understanding of their mechanisms of action.

4. Cancer

Tumor neuralization. The role of the nervous system in regulating tumors is being increasingly recognized, and a recent study by Taylor *et al* (125) published in Nature has revealed that the BDNF-TrkB pathway upregulates AMPA receptors on the membrane of astrocytoma cells. This process increases the fluidity of Ca^{2+}, and enhances the strength and duration of excitatory postsynaptic currents, augmenting synaptic connections between neurons and astrocytoma cells, thereby amplifying the depolarization amplitude of astrocytoma cell membranes, and promoting their proliferation (125). Glioma cells exploit neuroplasticity processes in a sophisticated and dynamic manner, leveraging neural electrical activity to facilitate tumor growth.

The role of neuro-invasion in the tumor microenvironment as a promoter of cancer progression is being increasingly recognized. *In vitro* experiments have shown that cancer cells induce endoplasmic reticulum stress, leading to the synthesis and release of proBDNF through an X-box binding protein 1 (XBP1)-dependent mechanism. proBDNF mediates the transmission of endoplasmic reticulum stress to neurons, thereby promoting the expression of oncogene C-myc-mediated Egl-9 family hypoxia-inducible factor 3 in tumor tissues, which in turn stimulates tumor-associated synapse growth and tumor neurogenesis. In *in vivo* tumor transplant models, endoplasmic reticulum stress induces the expression of XBP1 and proBDNF, as well as tumor neurogenesis. The use of a proBDNF antibody not only inhibits tumor neurogenesis induced by endoplasmic reticulum stress but also impedes cancer progression. Interestingly, it has been observed that the chemotherapeutic drug 5-fluorouracil induces endoplasmic reticulum stress and subsequent tumor neurogenesis; however, this effect can be counteracted by using a proBDNF antibody (126). However, in a prior study, the opposite result was reported. The expression of proBDNF and its receptors, p75NTR and sortilin, were examined in 52 cases of human glioma and 13 control cases using immunohistochemistry, reverse transcription-quantitative PCR and western blot analyses. The expression levels of proBDNF, p75NTR and sortilin were significantly elevated in high-grade gliomas and positively correlated with tumor malignancy. *In vitro*, the proBDNF/p75NTR pathway promoted apoptosis and differentiation of C6 glioma cells while inhibiting their growth and migration (127). The bidirectional effects of proBDNF in glioma may be attributed to the distinct signaling pathways mediated by its precursor form and mature form (mBDNF) through their respective receptors. proBDNF primarily activates JNK and caspase via p75NTR binding, thereby inducing apoptosis, whereas mBDNF activates PI3K/Akt and MAPK pathways via TrkB receptor, promoting cell proliferation. The relative expression levels of proBDNF/p75NTR/sortilin and mBDNF/TrkB may play a critical role in glioma malignancy and prognosis (9,128,129). Changes in the microenvironment of malignant glioma can modulate the signaling of various growth factors. In the tumor microenvironment, the levels of proBDNF-converting enzymes, such as MMPs and tPA, also influence the balance between proBDNF and mBDNF (130-132). Furthermore, the heterogeneity of glioma may result in differential responses of distinct cellular subpopulations to proBDNF. Investigating the precise mechanisms underlying the regulation of proBDNF and mBDNF expression levels in glioma could have significant implications for therapeutic strategies.

Clear cell renal cell carcinoma (ccRCC). ccRCC constitutes 70-80% of all renal cell carcinomas and is characterized by a poor prognosis due to the lack of effective therapeutic targets. Research has demonstrated that p75NTR is significantly overexpressed in tumor tissues and this increased expression is correlated with high Fuhrman nuclear grades. proBDNF is detectable in both tumor and normal tissues, with notably elevated levels observed in tumor samples. proBDNF binds to p75NTR, recruiting TrkB-95 and sortilin to form a functional complex, thereby activating the AKT/ERK signaling pathway; activation of this pathway promotes the proliferation and migration of ccRCC cells, as evidenced in the 786-O and ACHN cell lines. Targeting p75NTR or proBDNF may represent a promising strategy to inhibit ccRCC progression, particularly for patients who exhibit resistance to TrkB inhibitors (133).

Breast cancer. Breast cancer represents a significant healthcare challenge, with limited therapeutic options available for brain metastases (134). Research indicates that migrating

Table II. Cascades between inflammatory disease, proBDNF and downstream effector molecules.

First author, year	Disease	proBDNF and receptor	Downstream molecular	Function	(Refs.)
Wang *et al*, 2019; Wang *et al*, 2023	Sepsis	proBDNF/p75NTR↑	$CD4^+$T, $CD19^+$B↓, IL-1β, IL-6↑	Excessive inflammation	(116,117)
Yang *et al*, 2022; Farina *et al*, 2022	Rheumatoid arthritis	proBDNF/p75NTR/sortilin↑	TNF-α, IL-1β, IL-6, IL-10↑, JNK/p38MAPK↑, MCP1↑	Excessive inflammation	(119,120)
Shen *et al*, 2022	Systemic lupus erythematosus	proBDNF/p75NTR↑	ASCs↑, IgG↑	Excessive inflammation	(122)
Li *et al*, 2023; Al-Kuraishy *et al*, 2024; Putcha *et al*, 2001; Sankorrakul *et al*, 2021	Mitochondrial dysfunction	proBDNF/p75NTR/sortilin↑	JNK↑, Bak, Bax, caspase3, caspase9↑	Synaptic inhibition, neuronal apoptosis, mitochondrial dysfunction	(57,58, 123,124)

proBDNF, brain-derived neurotrophic factor precursor.

cancer cells interact with brain microvascular endothelial cells, thereby facilitating angiogenesis around the metastatic tumor (135). Alhusban *et al* (136) investigated the interaction between proBDNF/mBDNF in brain microvascular endothelial cells and the breast cancer cell line MDA-MB-231. proBDNF suppressed angiogenesis in breast cancer brain metastasis, potentially through inhibition of signal transduction mediated by VEGF. Tamoxifen is commonly used to treat recurrent or metastatic breast cancer and as adjuvant therapy following early breast cancer surgery. Prolonged use of tamoxifen downregulated the mBDNF/ERK/AKT/CREB pathway in the female rat hippocampus, while increasing the levels of proBDNF, leading to reduced neuroplasticity and cognitive dysfunction (137). The primary lesion of breast cancer may predominantly involve TrkB as the receptor (138), leading to the activation of distinct downstream signaling pathways by proBDNF in different tissue locations, and as previously discussed in the context of tumor heterogeneity, glioma and breast cancer cell lines utilized across various studies exhibit distinct receptor expression profiles and differential activation of signaling pathways, thereby contributing to variations in experimental outcomes. In addition, the effects of signaling pathways related to proBDNF on learning and memory function warrant further investigation.

Basal cell carcinoma (BCC). BCC is the most common type of skin cancer. Most cases can be controlled through local treatment, but treatment of advanced BCC remains a challenge. Western blot and reverse transcription-quantitative PCR analysis showed that the protein and mRNA levels of p75NTR/proBDNF in samples from patients with BCC and BCC cell lines (TE354.T and ASZ001) were significantly lower than those in normal skin tissues and immortalized keratinocytes (HaCaT). p75NTR/proBDNF activates the RIPK1/RIPK3/MLKL pathway, significantly inhibiting the proliferation of BCC cells, inducing apoptosis, and reducing tumor-associated macrophages, significantly increasing the infiltration of neutrophils and $CD8^+$T cells, promoting M1-type macrophage polarization, and reshaping the immune microenvironment (139).

The bidirectional effects of proBDNF are likely attributable to its antagonistic receptor signaling pathways, the dynamic regulation of its processing mechanisms, and the heterogeneity inherent in the tumor microenvironment. The emerging field of cancer neuroscience has ushered in a new era in the study of the nervous system and tumors. proBDNF is intricately linked to the malignant biological behaviors exhibited by various tumors necessitating further research into elucidating the mechanisms underlying the actions of proBDNF and its associated signaling molecules in tumorigenesis (Table III). Future research efforts should concentrate on elucidating the regulatory mechanisms underlying the equilibrium between proBDNF and mBDNF while integrating targeted therapeutic strategies against p75NTR or TrkB receptors.

5. Neurogenesis

In the adult hippocampal dentate gyrus and subventricular zone of mature mammalian brains, ongoing neurogenesis occurs. Here, multipotent neural stem cells can differentiate into glial cells and neurons in response to stimuli such as epilepsy, traumatic brain injury and ischemic stroke. These cells develop dendrites and axons, establish synaptic contacts with surrounding neurons, and ultimately integrate into existing neural circuits, facilitating the repair of damaged brain tissue and the restoration of function (140). The activation of astrocytes is characterized by the upregulation of proBDNF and increased metabolic activity within the cell. This modulates neuroplasticity through the release of proBDNF and its impact on synaptic pruning, tissue and histone modification, apoptotic signal transduction, and the expression of genes associated with protein processing. Consequently, this creates an environment in the brain that facilitates neural regeneration (141).

Neural development of the CNS is widely studied and plays a crucial role in maintaining brain function. Notably, neurogenesis also occurs in the peripheral nervous system.

Table III. The function and molecular mechanisms of proBDNF across cancer types.

First author, year	Cancer types	proBDNF and Receptor	Downstream molecular	Function	(Refs.)
Jiang *et al*, 2022	Prostate cancer Pancreatic cancer Colon cancer	ER stress→XBP1/ proBDNF↑	c-myc/EGLN3↑	Neurite outgrowth	(126)
Xiong *et al*, 2013	Glioma	proBDNF/p75NTR↑	GFAP↑	Inhibits proliferation and migration; induce apoptosis and differentiation	(127)
De la Cruz-Morcillo *et al*, 2016	Clear cell renal cell carcinoma	ProBDNF/p75NTR/ TrkB-95/sortilin↑	AKT/ERK↑	Promotes proliferation and migration	(133)
Klann *et al*, 2023	Breast cancer	proBDNF↑	VEGF↓	Suppresses angiogenesis	(137)
Myhre *et al*, 2013	Basal cell carcinoma	proBDNF/p75NTR↑	RIPK1/RIPK3/ MLKL↑	Restore neuronal activities	(37)

proBDNF, brain-derived neurotrophic factor precursor.

Peripheral nerve injury (PNI) represents a relatively prevalent neurological disorder in clinical settings, with etiologies encompassing trauma, compression, metabolic disorders and infections (142). The pathophysiological mechanisms of this condition are intricate, involving axonal damage, demyelination, inflammatory responses and impaired regeneration. Based on the Sunderland classification system, PNI can be categorized into grades I through V. Grade I injury (neuropraxia) is characterized solely by myelin sheath disruption, representing a reversible lesion with recovery typically occurring within several weeks to months. Grade II injury (axonotmesis) involves axonal rupture while maintaining an intact endoneurium, enabling self-regeneration over a period of several months. By contrast, grades III to V injuries (neurotmesis) entail the rupture of the endoneurium, perineurium, or epineurium, necessitating surgical intervention for repair (143). During the acute injury phase, following axonal rupture, distal axons and myelin sheaths undergo degeneration, with macrophages clearing debris. Schwann cells subsequently proliferate to form Bungner bands, facilitating axonal regeneration (144,145). However, the release of pro-inflammatory cytokines such as TNF-α and IL-1β may exacerbate neural damage and hinder the establishment of a regenerative microenvironment (146,147). Additionally, scar tissue formation may impede axonal regeneration. Concurrently, insufficient secretion of neurotrophic factors, including NGF and BDNF, contributes to regeneration failure (148). During chronic injury progression, Schwann cells undergo dedifferentiation, losing their capacity to support nerve regeneration, thereby further compromising repair outcomes (149). A study investigated the impact of proBDNF on peripheral sensory neurons and satellite glial cells (SGCs) through *in vitro* neuron and SGC cultures (150). The proBDNF/p75NTR/sortilin signaling pathway upregulates apoptotic factors such as Bax, caspase-3 and p53 via the mitochondrial pathway while downregulating anti-apoptotic factors such as Bcl-2, leading to neuronal apoptosis following sciatic nerve transection. It also hinders neuronal proliferation and migration. Treatment with a proBDNF antibody inhibited mitochondrial-dependent apoptosis by modulating the mBDNF/TrkB/PI3K/AKT and proBDNF/p75NTR/sortilin/PI3K/AKT signaling pathways, thereby exerting a neuroprotective effect. This presents a novel approach to treating peripheral nerve injury (150).

The binding of mBDNF with the TrkB receptor triggers a signal cascade associated with neuronal survival and plasticity, whereas the interaction between proBDNF and the p75NTR/sortilin receptor complex is involved in the apoptotic process. The relative levels of proBDNF and mBDNF in the cellular microenvironment are likely to play an important role in regulating astrocyte phenotype (150). Ma *et al* (151) further extracted and purified SGCs from the Dorsal root ganglion (DRGs) of rats within 24 h of birth and cultured them *ex vivo*, demonstrating that SGCs are involved in the neural development of the peripheral nervous system. By treating the SGCs extracted from the DRGs with proBDNF antibody, it was shown that SGCs could differentiate into sensory neuron-like phenotypes, whereas proBDNF inhibits their differentiation. The researchers also established a rat sciatic nerve transection model and used proBDNF antibody to promote the differentiation of SGCs into neuron-like phenotypes. Endogenous proBDNF can maintain the SGC phenotype and prevent SGCs from differentiating into neuron-like cells. After treatment with proBDNF antiserum, the mBDNF/TrkB signal transduction may become dominant and promote the differentiation of SGCs into neuron-like phenotypes.

6. Regulation of fear memory

Fear is an emotional response of organisms to potential threats, endowing individual life forms with the ability to adapt to ever-changing and challenging environments. However, it has a dual nature, as severe trauma can etch traumatic memories into the brain, potentially resulting in post-traumatic stress disorder (PTSD) (152). PTSD is an anxiety and/or memory

disorder developed after experiencing disasters, domestic violence, combat-related trauma, or other severely traumatic events (153). PTSD is intricately associated with the excessive consolidation of fear memories and challenges in overcoming them (154), and is mediated by functional disruptions within the prefrontal cortex-amygdala-hippocampus circuit (155), chronic inflammatory states (156) and compromised neuronal plasticity (153). The mBDNF/TrkB signaling pathway in the amygdala plays a crucial role in fear-related learning and memory. Synaptic plasticity is widely considered to be the cellular mechanism underlying fear-related memory formation, but further investigation into the fear extinction mechanism is warranted (157). The regulation of fear memories is crucial during the early stages of establishing the neural circuit for fear. These memories may undergo alterations throughout neural development, and the associated neural circuits also experience dynamic changes (158).

Investigation into the conditioned fear model in rats revealed that elevated levels of proBDNF in the prefrontal cortex of young rats could destabilize retrieval-dependent fear memories that are not strongly consolidated by activating the p75NTR/GluN2B signaling pathway. Researchers examined θ-γ oscillation coupling in the prefrontal cortex using EEG signals from rats and observed an inhibitory effect of proBDNF on memory retrieval in young rats. The experiment confirmed that proBDNF plays a critical role in synaptic function and memory instability, potentially facilitating the extinction of fear memories that are difficult to reconsolidate (159). It has been demonstrated that proBDNF plays a critical role in LTD within the lateral nucleus of the amygdala through its interaction with p75NTR. Suppression of p75NTR signaling leads to a reduction in LTD, and a comparable phenomenon is observed during fear memory extinction in mice. Furthermore, inhibition of proBDNF signaling or administration of anti-proBDNF antibodies attenuates both LTD and fear memory extinction. These findings suggest that the proBDNF/p75NTR signaling pathway is essential for regulating fear extinction and that impaired fear memory removal may be closely associated with the pathophysiological mechanisms underlying PTSD (160).

Phosphodiesterase 4 (PDE4) is an enzyme expressed in the dorsal hippocampus that can hydrolyze cAMP, thereby limiting the phosphorylation of CREB by cAMP-dependent protein kinase (PKA) and the expression of mBDNF, PKA and phosphorylated CREB can mediate memory consolidation or decay. Researchers employed the PDE4 inhibitor roflumilast to upregulate the cAMP/PKA signaling pathway, thereby promoting fear extinction rather than reconsolidation. PDE4 inhibition was found to enhance the expression of proBDNF in the dorsal hippocampus, whereas the expression of mBDNF remained unaffected. This suggests that proBDNF may serve as a critical factor in the long-term modulation of fear memory removal (161). The proBDNF-mediated LTD mechanism via p75NTR plays a critical role in fear extinction. Modulating the levels of proBDNF may offer novel insights into the treatment of PTSD. It is important to highlight that the existing research has primarily been conducted using animal models. Future investigations will need to validate its clinical applicability and refine the targeting strategy. Moreover, the equilibrium between proBDNF and mBDNF within the nervous system may significantly influence the efficacy of PTSD treatment, necessitating careful consideration of potential adverse effects.

proBDNF can facilitate the extinction of fear memories and suppress synaptic transmission, potentially enhancing individual adaptability. Cognitive and behavioral adaptability enable individuals to adjust to changing circumstances involving rewards and objectives. The dorsolateral striatum (DLS) is a component of the cortico-striatal circuitry and plays a role in regulating cognitive adaptability. Researchers observed a significant enhancement in early-stage rat reversal learning correct response rates following the injection of anti-cleaved proBDNF into the DLS of rats, thereby augmenting cognitive adaptability (162). Elevated exogenous proBDNF enhances neural coupling associated with flexibility, leading to the upregulation of endogenous proBDNF in the DLS and infralimbic cortex regions. Conversely, the inhibition of proBDNF in the infralimbic cortex region hampers cognitive flexibility that is mediated by the DLS. These findings suggest the involvement of both the infralimbic cortex and DLS regions in cognitive flexibility, emphasizing the crucial role of proBDNF in this process (163). The precise mechanisms through which proBDNF in the infralimbic cortex and DLS regions modulate cognitive flexibility remain unclear, necessitating further research.

7. Significance of proBDNF in disease diagnosis

Autism spectrum disorders (ASDs). ASDs are neurodevelopmental disorders characterized by impairments in motor function, which are one of their core features. These disorders manifest as persistent deficits in communication and social interaction, along with limited and repetitive behaviors and narrow interests (164). The data indicates a significant increase in the prevalence of ASD, which is hypothesized to be attributed to interactions between the immune system and the nervous system, congenital abnormalities in cell function, neuroinflammation and the activation of microglia (165). ELISA was used to assess the serum levels of mBDNF, proBDNF and insulin-like growth factors (IGF-1) in 22 children aged 5-15 diagnosed with mild to moderate ASD and 29 typically developing controls. No significant differences in mBDNF levels were observed between the ASD and control groups; however, proBDNF levels were notably lower in the ASD group compared with the normal controls, whereas IGF-1 levels were higher. Among the medicated ASD subjects, serum proBDNF levels were also observed to be lower compared with the control group; conversely, there was no difference in IGF-1 and mBDNF levels between those medicated and those who were not (166). These findings appear to corroborate the notion that proBDNF serves as a crucial biomarker for the diagnosis and treatment of ASD. Although the aforementioned study offers valuable insights into the roles of BDNF, proBDNF and IGF-1 in autism, several limitations, including the small sample size, variability in detection methods and the heterogeneity of ASD, constrain the generalizability and reliability of the findings. Future research should enhance the robustness of these conclusions by establishing standardized protocols, conducting multi-center trials, and incorporating additional biomarkers, thereby providing more reliable foundations for the diagnosis and treatment of autism.

Neurological disorders. Due to the absence of early diagnostic techniques in clinical practice, PD, a neurodegenerative condition, cannot be promptly treated, potentially resulting in disability. Therefore, it is crucial to seek biomarkers with high sensitivity and specificity for the early diagnosis of PD (167). A study enrolled 156 participants not receiving medication. The levels of mBDNF and proBDNF in the serum of both the PD and control groups were measured using ELISA. Additionally, a 1-year follow-up was performed, during which the levels of mBDNF and proBDNF in the serum were re-examined. The researchers compared and evaluated the mBDNF/proBDNF ratio and mBDNF levels using ROC curve analysis both cross-sectionally and longitudinally. The findings indicated that the mBDNF/proBDNF ratio can function as an early biomarker for PD, surpassing testing only for mBDNF. proBDNF exhibits superior repeatability and individual discriminability compared with mBDNF (168). Future research involving larger sample sizes is necessary to evaluate the association between proBDNF and the severity of progression, follow-up, and response to treatment of PD. This may contribute to a better understanding of the clinical applicability of proBDNF as a biomarker for PD-related CI.

Researchers have investigated whether mBDNF and proBDNF serum levels may serve as valuable biomarkers for assessing AD. Using ELISA, they measured the levels of mBDNF and proBDNF in the serum of 126 subjects and then assessed their correlation with Mini-Mental State Examination (MMSE) scores. The study revealed significant correlations among MMSE scores, proBDNF levels, and mBDNF/proBDNF ratios. Lower serum levels of proBDNF were associated with higher MMSE scores, suggesting that a combined assessment of both proBDNF and the mBDNF/proBDNF ratio could be an effective diagnostic approach for patients with AD (169).

β-hydroxybutyrate (BHB) is a small molecule produced by the body during fat metabolism. It has various effects, including protecting brain neurons, managing epilepsy, improving cognitive function disorders, preventing or treating diabetes and insulin resistance, aiding in weight loss, exhibiting antitumor properties, delaying aging, and mitigating osteoporosis (170). Interestingly, a study involving healthy older adults aged 65-75 revealed a positive correlation between serum BHB and changes in proBDNF. This correlation was found to be more stable and stronger than that with mBDNF. Consequently, proBDNF may serve as a reliable predictor of brain health (171).

Overactive bladder (OAB). OAB is a syndrome characterized by urgent, frequent and nocturnal urination in the absence of urinary tract infection or other obvious pathological conditions. OAB can be classified into dry OAB and wet OAB based on the presence or absence of urgency incontinence (172). The diagnosis of OAB primarily relies on clinically relevant symptoms combined with self-assessment questionnaires such as the B-SAQ, the Overactive Bladder Symptom Score (OABSS), and the OAB-V8. It is also crucial to exclude factors such as pelvic floor muscle damage, excessive fluid intake and urinary tract infections before making a comprehensive judgment (173,174). The researchers discovered a significant negative correlation between the proBDNF/mBDNF ratio and scores on the OABSS and the Incontinence Impact Questionnaire (IIQ-7), as well as a negative correlation with disease severity. Compared with individual measurements of mBDNF or proBDNF, the proBDNF/mBDNF ratio demonstrated superior diagnostic value. This ratio could serve as an objective and repeatable test for diagnosing and phenotypically classifying OAB (175).

Mental health conditions. Antidepressant medications can achieve their therapeutic effects by reestablishing the equilibrium between mBDNF and proBDNF in the brain. As depressive symptoms are ameliorated by treatment, the levels of proBDNF decrease (176). tPA and plasminogen activator inhibitor-1 (PAI-1) play a significant role in depression by regulating the ratio of mBDNF to proBDNF (177). The combination of tPA, PAI-1, and the mBDNF/proBDNF ratio may provide a useful method for the diagnosis of major depressive disorder, and proBDNF may serve as a more refined biomarker for assessing treatment efficacy. ELISA was used to examine the alterations in plasma and lymphocyte levels of mBDNF and proBDNF in patients with severe depression and bipolar disorder, aimed at evaluating their diagnostic value. The results confirmed that untreated individuals with severe depression and bipolar disorder exhibited significantly lower plasma mBDNF levels. Furthermore, antidepressant medications may influence mBDNF concentrations. Both proBDNF and mBDNF levels were found to be upregulated in lymphocytes. The disparity in mBDNF expression between plasma and lymphocytes may function as a potential biomarker for diagnosing severe depression. Specifically, a plasma mBDNF level <12.4 ng/ml may indicate severe depression or support a diagnosis of bipolar disorder. Additionally, plasma mBDNF levels can act as predictors of the severity of severe depression. However, further research is required to elucidate the implications of elevated proBDNF levels in lymphocytes and whether the combined values of proBDNF alongside mBDNF offer superior diagnostic capabilities compared with mBDNF alone (178). Zwolinska *et al* (179) used ELISA to quantify the levels of mBDNF, proBDNF and calcium-binding protein B (S100B) in the serum of patients diagnosed with severe depression. As treatment progressed, a significant reduction in serum proBDNF levels was observed, while mBDNF and S100B levels remained relatively stable. Consequently, it is hypothesized that decreased human serum proBDNF levels may serve as a potential biomarker for recovery following depression treatment. However, it is important to note that the aforementioned study included only 31 female participants. Therefore, further validation with a larger sample size is necessary. These studies have certain limitations, necessitating future large-scale clinical investigations to evaluate disease progression and severity, follow-up protocols, and treatment responses. Such research will enhance our understanding of the clinical significance of proBDNF and its metabolites as biomarkers for disease progression, diagnosis and early detection.

8. Utilization of proBDNF monoclonal antibody

Researchers have conducted a series of innovative studies focusing on proBDNF and successfully developed a humanized

monoclonal antibody against it, named McAb-proB. This antibody is protected by independent intellectual property rights and patents. It specifically targets peripheral immune cells, effectively neutralizes proBDNF, and importantly, does not interfere with endogenous BDNF in the CNS. Preclinical studies have demonstrated that McAb-proB is efficacious in mitigating the progression of various immune-mediated inflammatory diseases, organ damage and inflammatory pain (180).

Applications in inflammatory pain. In the CFA-induced persistent inflammatory pain mouse model, i.p. administration of 5 mg/kg McAb-proB 2 h post-CFA injection was found to effectively alleviate pain within the 3-72 h timeframe. Furthermore, in the surgical pain model, pretreatment with McAb-proB significantly decreased pain scores. With respect to its ability to penetrate the BBB, researchers conducted an intracerebroventricular injection of McAb-proB. The results indicated that direct central administration had no significant impact on pain relief, suggesting that McAb-proB may primarily inhibit spinal p-ERK activation via peripheral mechanisms rather than through direct penetration of the BBB (181). Regarding pharmacokinetics, comprehensive descriptions of the antibody's half-life, absorption, distribution, metabolism and excretion (ADME) parameters have not been determined to the best of our knowledge. In a separate study, intrathecal administration of 10 μg McAb-proB was shown to mitigate CFA-induced inflammatory pain. Intrathecal injection circumvented the BBB directly, delivering the drug into the vicinity of the spinal cord (182). Unfortunately, the aforementioned study also did not provide a detailed description of the ADME characteristics of McAb-proB. Although no significant acute toxic reactions were reported after a single dose, further repeated-dose and long-term toxicity studies are still needed to evaluate its safety.

Applications for organ damage. In the MRL/lpr lupus mouse model, researchers administered an initial i.p. injection of McAb-proB at a dose of 100 μg, followed by weekly injections of 30 μg for a total duration of 8 weeks. The study demonstrated that McAb-proB could induce apoptosis in $CD3^+B220^+$ cells, reduce proteinuria and lymph node enlargement, and promote body weight gain, while exhibiting no apparent toxicity, although, the long-term risks associated with immunosuppression were not assessed (183). i.p. administration of 100 μg McAb-proB in acute myocardial infarction mouse models may inhibit the activity of MMP-9, which is associated with cardiac repair processes. This inhibition could result in impaired cardiac function, enlarged infarct size, and increased mortality. These findings indicate that McAb-proB may exert pro-inflammatory side effects in the context of cardiovascular diseases (184). The bidirectional effects of McAb-proB in different diseases may indicate variations in the signaling pathways of proBDNF across various disease states. Further investigation into its pro-inflammatory/anti-inflammatory balance mechanism, as well as validation of its safety profile, represent the next critical steps in the study of McAb-proB as a potential therapeutic.

Applications in IMID. In the EAE mouse model, McAb-proB was administered i.p. at a dose of 100 μg per injection, once weekly for 3 months. The treatment was initiated either in the early phase (on days 9, 13, and 17) or the late phase (on days 17, 21, and 25) following EAE induction. The study demonstrated that McAb-proB effectively modulated the immune system by suppressing the expression of inflammatory factors in the spleen and spinal cord, reducing the percentages of $CD19^+$B, $CD4^+$T, and $CD8^+$T cells, alleviating demyelination and inflammatory responses, and significantly ameliorating the clinical symptoms of EAE mice (53). In the lipopolysaccharide-induced mouse model of septic encephalopathy (SAE), two administration methods of McAb-proB were investigated: i.p. injection and intrahippocampal microinjection. i.p. injection was administered 12 post-SAE induction, using 100 μg of McAb-proB dissolved in 0.3 ml physiological saline. Intrahippocampal microinjection involved dissolving McAb-proB to a concentration of 1 μg/μl, followed by stereotactic delivery of 1 μg into the hippocampus. Both administration routes of McAb-proB effectively restored neuronal counts and Nissl body density, enhanced the expression of glutamate receptor 4, N-methyl-D-aspartate receptor subunits NR1, NR2A, NR2B, and postsynaptic density protein PSD95, thereby alleviating cognitive dysfunction associated with SAE. Furthermore, the researchers noted that as a macromolecule, McAb-proB typically exhibited limited permeability across the blood. However, in the SAE model, inflammatory damage may compromise BBB integrity, enabling partial antibody penetration into the brain. Future studies should focus on optimizing McAb-proB BBB penetration, such as through the use of Fc fragment-based BBB transport vectors or the development of small molecule modulators targeting p75NTR (185). Interestingly, in a separate study, pretreatment via i.p. injection of 100 μg McAb-proB was found to improve cognitive dysfunction and modulate the distribution of immune cells in both peripheral tissues and the meninges. By contrast, intraventricular administration of 1 μg McAb-proB did not result in any significant improvement in cognitive function, thereby reinforcing the notion that the peripheral effects of McAb-proB are more critical. Specifically, i.p. injection of McAb-proB significantly ameliorated CIs and restored the proportion of $CD4^+$T cells in the meninges. Conversely, direct central administration exhibited limited efficacy, further corroborating its relatively weak capacity to penetrate the BBB (87).

Thus, McAb-proB may be a safe and promising candidate drug for addressing IMID, inflammatory pain, organ damage and CI. Nevertheless, it is crucial to highlight that varying injection sites in mouse models yield distinct effects. Given that the action of McAb-proB is more likely to manifest within the peripheral immune system, it remains uncertain whether it can effectively penetrate the BBB to target the CNS and exert its therapeutic benefits. The development of more efficient delivery technologies is, therefore, warranted. Additionally, further investigation is required to elucidate the detailed pharmacokinetic parameters (for example half-life, bioavailability, clearance rate) associated with the efficacy and safety of McAb-proB in treating relevant diseases. Moreover, the underlying mechanisms necessitate further exploration.

9. Conclusion

proBDNF, the precursor protein of BDNF, is widely distributed in human tissues and cells. It binds to receptors such as p75NTR, sortilin, or SorCS2 to regulate synaptic activity, pruning, and network reorganization. The binding of proBDNF to p75NTR can promote apoptosis, enhance hippocampal LTD, weaken synaptic transmission, reduce neuronal plasticity, and play a crucial role in the development and progression of depression, cognitive dysfunction, neurogenesis, ischemia-reperfusion injury, and inflammatory diseases. However, proBDNF also has a positive effect on accelerating the removal of fear memories and reducing PTSD, as well as improving cognitive flexibility. Additionally, proBDNF acts as a biomarker, offering a reference for the early diagnosis and prognosis of diseases. McAb-proB, a monoclonal antibody targeting proBDNF, effectively blocks the proBDNF signaling pathway and specifically recognizes proBDNF without cross-reactivity to mBDNF (186). It has demonstrated substantial therapeutic potential in various IMIDs and tissue/organ injuries, particularly in septic-associated encephalopathy (87), inflammatory pain (181), MS (53), SLE (122) and aortic dissection (180); through the neutralization of proBDNF activity, McAb-proB significantly mitigates disease progression, restores immune homeostasis, and suppresses inflammatory responses.

While previous reviews have primarily addressed the potential mechanisms of proBDNF and its influence on the activity of mature neurotrophic factors (1,11), the present review uniquely focuses the relationship between proBDNF and CI, thereby offering a more in-depth perspective on this topic. Additionally, an overview of recent advancements in research on proBDNF in relation to sepsis, tumors, neurogenesis, and regulation of fear memory, was provided. The diagnostic potential of proBDNF and the proBDNF/mBDNF ratio as biomarkers for various diseases was also explored. In contrast to other reviews (57), which emphasize the role of proBDNF in metabolic and mitochondrial regulation, the present review encompasses a wider range of perspectives. Compared with other reviews (3,4), our study offers more actionable insights for clinical translation and application of proBDNF monoclonal antibody.

Despite the confirmed importance of proBDNF in basic physiology, research results remain conflicting and unclear. The varying biological effects of proBDNF across different tumor types are primarily attributed to the expression levels of its receptors (p75NTR and sortilin), the characteristics of the tumor microenvironment, and the heterogeneity of downstream signaling pathways. Future studies should prioritize investigating the binding affinity and signal transduction mechanisms of proBDNF with its receptors in a range of tumor contexts, as well as elucidating how the tumor microenvironment modulates the proBDNF signaling pathway. Cognitive disorder diseases are the result of multiple factors and are among the most critical global health issues. Understanding the mechanism of proBDNF in cognitive disorders remains a research priority for the next stage. Building on the significant breakthroughs achieved in the treatment of IMIDs with McAb-proB, future research will continue to explore its therapeutic targets in cognitive disorder-related diseases and advance clinical preliminary trials to achieve the translation of clinical research findings.

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Authors' contributions

WeiC and RC conceived the topic of study. RC and WeiC performed the literature search and data analysis and drafted the manuscript. DC, PL, YZ, QZ and WenC critically revised the manuscript. Data authentication is not applicable. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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