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Review

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Potential role of FNDC5 in exercise-induced improvement of cognitive function

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Abstract: Cognitive dysfunction often occurs in Alzheimer's disease, Parkinson's disease, cerebrovascular disease, or other neurodegenerative diseases, and can significantly impact the quality of life of patients and create serious social, psychological, and economic burdens for individuals and their families. Numerous studies have confirmed that exercise can slow down the decline in cognitive function through multiple pathways, in which FNDC5 plays an important role. However, the current research on the modulation of FNDC5 by exercise and its improvement of hippocampal cognitive function lacks a systematic and comprehensive understanding. Therefore, this article focuses on the latest research progress regarding the role of exercise-induced FNDC5 in cognitive function, systematically reviews the positive effects of FNDC5 on cognitive function impairment caused by various factors, and clarifies the specific mechanisms by which exercise-induced FNDC5 improves cognitive function by inhibiting neuroinflammation and improving hippocampal neurogenesis and hippocampal synaptic plasticity. Based on the existing literature, we also identify the areas that require further research in this field. Overall, this article provides a theoretical basis for the exercise-based prevention and improvement of cognitive function impairment.

Key words: Exercise; FNDC5; Irisin; Cognitive function; Hippocampus

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1 Introduction

Cognition refers to the process by which the human brain receives external information and processes, transforms, and converts it into internal mental activities in order to acquire or apply knowledge; this encompasses various aspects such as memory, language, visual-spatial skills, executive functions, calculation, comprehension, and judgment. Cognition serves as the foundation for human thinking and behavior and plays a crucial role in learning, memory, and creativity (Posner and Petersen, 1990; Birle et al., 2021). Cognitive dysfunction is defined as the impairment of one or more of the cognitive functions mentioned above, and can manifest as memory deficits, orientation difficulties, language impairments, decreased computational abilities, decreased judgment, impaired problem-solving abilities, and so on (Yang et al., 2022). Cognitive impairment occurs in a variety of diseases, including diabetes mellitus (DM), Alzheimer's disease (AD), Parkinson's disease (PD), cerebrovascular disease, and psychiatric disorders (Zilliox et al., 2016; Bondi et al., 2017; Aarsland et al., 2021; Huang et al., 2022; Knight and Baune, 2018), affecting patients' thinking, communication, comprehension, and memory processes, and placing a serious social, psychological, and economic burden on patients and their families. Early diagnosis and timely intervention are important for improving cognitive dysfunction, as the progression of cognitive impairment to a certain stage is often irreversible. Currently,

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research on cognitive impairment has shifted towards a focus on the stage of mild cognitive impairment (MCI) or even subjective cognitive impairment (SCI). Multiple studies have shown that pharmacological treatments have limited and costly effects on improving cognitive impairment, while non-pharmacological interventions, such as cognitive training, exercise interventions, dietary interventions, music therapy, and non-invasive brain stimulation techniques, have gradually become research hotspots. Among them, exercise interventions have received considerable attention (Colcombe and Kramer, 2003; Chang et al., 2012; Verburgh et al., 2014).

Exercise interventions can prevent or delay the decline in cognitive function by modulating synaptic plasticity, increasing the volume of cognition-related brain regions, improving cerebral blood flow, and controlling vascular risk factors. Numerous studies have indicated that exercise can enhance the bioavailability of neurotrophic factors such as brain-derived neurotrophic factor (BDNF), insulin-like growth factor-1 (IGF-1), and vascular endothelial growth factor (VEGF), which in turn regulate synaptic plasticity and improve cognitive function (Bettio et al., 2019; Erickson et al., 2012; Boyne et al., 2020; Vital et al., 2014; Rojas Vega et al., 2010). In addition, aerobic exercise has been shown to increase hippocampal volume in older women with MCI (Ten Brinke et al., 2015), and high-intensity resistance training can slow down the atrophy of hippocampal CA1 and DG regions in patients with MCI and improve their cognitive ability (Broadhouse et al., 2020). These findings provide evidence for the close relationship between the beneficial effects of exercise on cognitive function and its impact on hippocampal volume and structure. Guiney et al. (Guiney et al., 2015) assessed habitual physical activity estimates, cognitive function, and cerebrovascular function in 55 healthy young adults, confirming that physical exercise can improve cognitive function by regulating cerebral blood flow. In addition, vascular risk factors such as hypertension, diabetes, and hyperlipidemia can negatively affect the cerebrovascular system, leading to insufficient cerebral blood flow, cerebral ischemia, and neurodegenerative changes, which can impact cognitive function (Van Der Flier et al., 2018). Exercise can effectively reduce vascular risk factors by lowering participants' blood pressure and controlling their blood glucose and lipid levels, thereby indirectly preventing or delaying the occurrence and development of cognitive impairment (Phillips et al., 2015; Gerage et al., 2020; Balducci et al., 2014; Clifton, 2019). Indeed, there is no doubt about the positive effects of exercise intervention on the improvement of cognitive function, and exploring its underlying molecular mechanisms is crucial for its application in clinical practice. Previous studies on the mechanisms by which exercise improves cognitive function have mostly focused on BDNF, a protein widely found in the central nervous system, which is a key factor in regulating neuronal development, plasticity, and energy homeostasis (Lapchak and Hefti, 1992). It has been shown that fibronectin type III domain-containing protein 5 (FNDC5), the precursor protein of Irisin, can protect neuronal cells from damage by increasing BDNF secretion. The FNDC5/BDNF pathway can regulate exercise and affect the microstructure and function of the brain, participating in the neuroprotective regulation of diseases such as AD and PD (Lang et al., 2020; Jodeiri Farshbaf et al., 2016). Meanwhile, exercise has been proven to be an important regulator of FNDC5 expression in skeletal muscle and brain tissue. Therefore, FNDC5 plays a crucial role in maintaining the normal function of the nervous system and is an area worth exploring in the process of improving cognitive function through exercise. However, existing studies have not comprehensively elucidated the systemic effects of FNDC5 in mediating the impact of exercise on cognitive function. Thus, by analyzing the relevant literature on exercise, FNDC5, and cognitive function, this study explores the relevant mechanisms by which exercise regulates FNDC5 to improve cognitive function, clarifies the role of FNDC5 in the process of improving cognitive function through exercise, and provides a systematic theoretical basis for the treatment of cognitive impairment in patients with neurological disorders.

2 Overview of FNDC5

FNDC5 is a transmembrane protein that contains two fibronectin type III domains, one signal peptide, and one C-terminal hydrophobic domain. Its expression can be detected in mammals such as humans, mice, and rabbits (Hofmann et al., 2014). It has been found that the start codon of the FNDC5 gene in humans, unlike in most mammals, mutates from ATG to ATA, which may prevent ribosomes from recognizing the sequence,

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leading to abnormal translation initiation or extremely low translation efficiency (Ivanov et al., 2011). However, it has been confirmed that Irisin exists in human blood, indicating that the start codon of the human Irisin precursor FNDC5 is ATA (Jedrychowski et al., 2015; Raschke et al., 2013). Further research shows that, among all reported species, human FNDC5 is the only protein that initiates translation with a non-ATG start codon, and the G-A mutation at the start codon position of the human FNDC5 gene relative to other organisms may be necessary for adaptation to the environment or evolution (Xu et al., 2017; Touriol et al., 2003). FNDC5 was initially reported to be expressed in skeletal muscle, and its expression is regulated by peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α) (Schumacher et al., 2013; Roberts et al., 2013). It has been found that exercise initially induces the upregulation of PGC-1α expression in skeletal muscle, which in turn increases the expression of FNDC5 on the cell membrane, and the extracellular portion of FNDC5 is then proteolytically sheared to generate a new form, Irisin, which is subsequently secreted into the bloodstream (Boström et al., 2012). Since FNDC5 is the precursor of Irisin, it is commonly used as a representative marker for Irisin in studies (Ge et al., 2017). Due to the fact that FNDC5 is primarily synthesized and secreted in response to muscle contraction during physical exercise, it is considered to be a myokine, and its expression is influenced by exercise frequency, mode, and intensity (Bao et al., 2022; Sousa et al., 2021; Colpitts et al., 2022). As a newly discovered exercise-induced myokine, FNDC5 is most abundantly expressed in muscle-rich tissues such as skeletal muscle and cardiac muscle, followed by brain tissue, liver, lung, and adipose tissue, where its expression can also be detected (Teufel et al., 2002; Huh et al., 2012; Kim et al., 2017; Grygiel-Górniak and Puszczewicz, 2017). In adipose tissue, FNDC5 converts white adipocytes to brown adipocytes by increasing the level of uncoupled protein-1 (UCP1), which enhances energy expenditure (Boström et al., 2012). Adipose browning can decrease fasting insulin levels, increase glucose tolerance, and promote weight loss (Christodoulatos et al., 2019; Huh et al., 2014a). Furthermore, in bone tissue, the muscle factor FNDC5 influences the physiological function of bone cells by targeting signaling pathways such as mitogen-activated protein kinases (MAPK), the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), and Wnt/β-catenin, and enhances bone metabolism, thus delaying the onset and progression of bone-related diseases (Qiao et al., 2016; Jia et al., 2022; Chen et al., 2020). FNDC5 levels also undergo changes in various inflammatory diseases such as inflammatory bowel disease, sepsis-induced myocardial injury, acute pancreatitis, non-alcoholic fatty liver disease, and malignant tumors (Zhang et al., 2023; Korta et al., 2019). Specifically, FDNC5 can exert anti-inflammatory effects by inhibiting the elevation of inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), antagonizing cell apoptosis and the activation of NF-κB, and improving tissue damage (Mazur-Bialy, 2017; Tan et al., 2019; Ren et al., 2019; Park et al., 2015; Gaggini et al., 2017). Therefore, FNDC5 holds promise as a biomarker for the diagnosis of inflammatory diseases and as a therapeutic target for their treatment. As a regulator of organismal biochemical metabolism, FNDC5 not only plays a role in the aforementioned disease but also influences neural tissues. In recent years, the relationship between exercise-induced secretion of FNDC5 and cognitive dysfunction has gained increasing attention from researchers, and several studies have shown that FNDC5 can indirectly elevate the level of BDNF in the brain through the blood–brain barrier, thereby enhancing brain function, and it may be a potential molecule mediating the improvement of cognitive dysfunction through exercise (Wrann et al., 2013; Forouzanfar et al., 2015; Hashemi et al., 2013) (Fig. 1, Table 1).

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3 Role of FNDC5 in cognitive function

FNDC5 is expressed in various regions of the brain, including the Purkinje cells of the cerebellum (Dun et al., 2013), the hypothalamus (Varela-Rodríguez et al., 2016), and the hippocampus (Wrann et al., 2013). Research has shown that the overexpression of FNDC5 in mouse embryonic stem cells (mESCs) during neurogenesis leads to an increase in markers of neuronal maturation, including BDNF, glial fibrillary acidic protein (GFAP), microtubule-associated protein 2 (MAP2), beta-tubulin III, and neurocan (Forouzanfar et al., 2015). Knocking down FNDC5 in neural precursor cells significantly reduces the neuronal differentiation rate

of mESCs, and this effect may be attributed to the reduction in the levels of NGF and BDNF proteins (Hashemi et al., 2013). The above studies indicate that FNDC5 plays an important role in the differentiation and maturation processes of neurons, laying the foundation for studying its role in neurological function. There have been several reports on the relationship between exercise-induced myokine FNDC5 and cognitive function; Belviranli et al. (Belviranli et al., 2016) found that serum levels of IGF-1, BDNF, and Irisin in endurance athletes were higher than those in sedentary individuals, and the scores on the Mini-Mental State Examination (MMSE), a simple mental status evaluation scale, were also higher in endurance athletes. Furthermore, the correlation analysis showed a positive association between Irisin and BDNF levels and cognitive function. Further research found that 30 days of endurance exercise induced the expression of FNDC5 in the hippocampus of mice, thereby increasing the expression of BDNF to achieve neuroprotection and improve cognition, whereas knockout or an increase in the expression of the FNDC5 gene in brain tissue results in a decrease or an increase in BDNF expression, respectively (Wrann et al., 2013). In summary, FNDC5 is closely related to the nervous system and has the potential to not only influence the neurologic functions of organisms, but also mediate the improvement of cognitive impairment caused by various diseases through exercise (Fig. 2).

3.1 FNDC5 and cognitive impairment caused by AD

AD is a neurodegenerative disease that predominantly affects the elderly population, and the main pathological changes in AD include the deposition of amyloid beta protein (Aβ) and the formation of neurofibrillary tangles in the brain. Patients with AD typically experience progressive memory decline and cognitive impairment (Ossenkoppele et al., 2022; Villain et al., 2022). Lourenco et al. (Lourenco et al., 2019) conducted a study investigating the potential relationship between the exercise-induced factor FNDC5 and AD. They found that, in late-stage AD patients, there was a significant reduction in Irisin levels in the hippocampus and cerebrospinal fluid compared to age-matched early AD patients or cognitively normal subjects, suggesting that the decrease in Irisin may be associated with the development of AD and cognitive decline. In animal models, knocking down brain FNDC5 impaired synaptic plasticity and memory in mice, while increasing the central or peripheral expression levels of this gene protected mice from memory deficits induced by beta-amyloid peptide oligomers (AβOs), suggesting that FNDC5 may be a novel potential drug target for combating synaptic failure and memory impairment in AD (Lourenco et al., 2019). Researchers investigating FNDC5 as a potential therapeutic agent for AD found that FNDC5 can directly bind to the amyloid precursor protein (APP) and influence its β-cleavage, reducing the production of different forms of Aβ and alleviating the aggregation of the protein, thus improving cognitive decline in mice (Noda et al., 2018; Xia et al., 2017). In addition, a recent study indicated that the myokine FNDC5 could increase the secretion of neprilysin (NEP) in astrocytes by down-regulating the IL-6/extracellular signal-regulated kinase (ERK) and signal transduction and activator of transcription 3 (STAT3) signaling pathways, thereby reducing the accumulation of Aβ in astrocytes for the prevention and treatment of AD (Kim et al., 2023). In addition to reducing the deposition of Aβ in the brain, FNDC5 also has the ability to improve learning and memory by attenuating the inflammatory response mediated by IL-1β and IL-6 in astrocytes, stimulating the transient phosphorylation of extracellular ERK and up-regulating the expression of BDNF, which in turn weakens the Aβ-induced cytotoxic response and influences neuronal plasticity and memory formation in the brain (Wang et al., 2018; Lourenco et al., 2022).

In summary, the low expression levels of the exercise factor FNDC5 in AD patients are closely associated with cognitive impairments, and FNDC5 has been shown to play a neuroprotective role by reducing Aβ deposition in the brain and attenuating Aβ-induced cytotoxic responses, thereby improving memory and cognitive impairments in AD patients, providing a new potential avenue and preventive strategy for the treatment of AD. However, the current research has mainly been conducted in cell and animal models; further clinical trials are needed to validate the potential efficacy and safety of exercise-induced FNDC5 as a therapeutic intervention for AD.

3.2 FNDC5 and cognitive impairment caused by DM

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DM is a chronic metabolic disorder induced by various factors, generally classified into type 1 and type 2, with type 2 diabetes mellitus (T2DM) being the predominant type, accounting for over 90% of all cases. With the development of society and population aging, the incidence of T2DM is increasing year by year, seriously affecting the quality of life of patients and their families, increasing the economic burden on society, and posing challenges to clinical doctors and researchers (Saeedi et al., 2019; Berezin, 2016). The main characteristic of T2DM is abnormally high blood glucose levels, and its hyperglycemic toxicity can damage neurons in the brain, affecting the function of the central nervous system and resulting in varying degrees of cognitive dysfunction in patients, with a series of symptoms such as memory decline, reduced attention and executive function, decreased learning ability, and impaired motor coordination, which can lead to dementia in severe cases (Liu et al., 2018). The possibility of T2DM patients developing cognitive impairment or dementia is 1.5-2.0 times higher than that of non-T2DM patients, and the discovery of FNDC5/Irisin opens up a new field for the prevention and treatment of cognitive impairment due to T2DM. Studies have shown that circulating FNDC5 levels in patients with T2DM are lower than those in healthy control groups with normal glucose tolerance, suggesting that the exercise factor FNDC5 may play an important role in the pathology of insulin resistance-related disorders, such as T2DM (Choi et al., 2013). Lin et al. (Lin et al., 2019) evaluated plasma Irisin levels in 133 Chinese patients with T2DM, and their findings showed that T2DM patients with MCI had significantly higher plasma Irisin levels compared to cognitively normal T2DM patients. Moreover, elevated plasma Irisin levels were associated with overall cognitive impairment, particularly in terms of executive function. The results of this study contradict previous reports of lower Irisin levels being associated with cognitive impairment, and the reason for this difference lies in the different study populations. Patients with T2DM often suffer from metabolic dysfunction and, similar to the increase in insulin levels in insulin resistance, the bodies of T2DM patients with MCI have decreased sensitivity to Irisin, leading to increased secretion of Irisin in the body and resulting in higher levels of Irisin in the patients' plasma (Doumatey et al., 2010; Shoukry et al., 2016). Therefore, increased plasma Irisin levels may serve as a predictive factor for the occurrence of T2DM-related cognitive impairment. Further research has revealed that FNDC5/Irisin can increase the levels of BDNF in the hippocampal tissue of rats, enhancing the vitality of primary hippocampal neurons and indirectly preventing cognitive dysfunction caused by T2DM (Huang et al., 2019). In addition, FNDC5/Irisin can also improve cognitive impairment caused by DM through the regulation of astrocyte activity. Astrocytes are a type of essential glial cells in the central nervous system that maintain the survival and normal physiological functioning of neurons, and repairing damaged astrocytes can improve cognitive deficits in DM mice (Coleman et al., 2004; Shen et al., 2023). Wang et al. (Wang et al., 2019) randomized male C57BL/6J mice at 8 weeks of age into control, Irisin (0.5 mg/kg/day), streptozotocin (STZ) (150 mg/kg), and STZ plus Irisin (0.5 mg/kg/day) groups. After 3 weeks of injection, GFAP, a marker of astrocyte activation, was used to assess the regulation of astrocytes. The results of the study showed that Irisin inhibited the upregulation of GFAP protein induced by STZ, thereby alleviating neural damage caused by DM. Furthermore, the study also discovered that Irisin could mitigate inflammation in the mouse brain by inhibiting signaling pathways associated with neuroinflammation, such as p38MAPK, STAT3, and NF-κB, thus improving cognitive dysfunction and memory decline in mice with DM.

In summary, the exercise-induced protein FNDC5 is associated with cognitive impairment caused by DM and can improve cognitive function by increasing the levels of BDNF in brain tissue, regulating astrocyte activity, and modulating neuroinflammatory responses. The development of FNDC5/Irisin-targeted drugs and therapies may therefore help prevent cognitive dysfunction in patients with DM. It is worth noting that, due to the relatively recent discovery of Irisin, research on its relevance to cognitive impairment in diabetes is still in the early stages of exploration. It is not yet clear which intervention targeting FNDC5 would be most effective in improving cognitive function, and further investigation is warranted in the future.

3.3 FNDC5 and cognitive impairment caused by other neurological diseases

Recent studies have found that FNDC5 not only has the potential to improve cognitive function in patients

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with AD and DM, but also exhibits a beneficial effect on other neurological diseases such as depression, PD, and stroke. Clinical studies have shown that reduced levels of FNDC5/Irisin in serum are associated with an increased risk of depression in patients with stroke, coronary heart disease, and chronic obstructive pulmonary disease, suggesting a correlation between FNDC5/Irisin and depressive mood (Tu et al., 2018; Han et al., 2019; Papp et al., 2017). In animal experiments, central administration of Irisin reduces the immobility time of wild-type mice in the tail suspension test (TST) and the forced swim test (FST), indicating an improvement in depressive-like behavior (Siteneski et al., 2018). Hu et al. (Hu et al., 2022) investigated the potential effects of Apelin-13 on cognitive impairment and depressive-like behavior in a chronic unpredictable mild stress (CUMS) model. The results revealed that Apelin-13 may protect neurons by increasing the expression of FNDC5 in the hippocampus of mice, thereby improving cognitive dysfunction and depressive-like behavior. In addition, the exercise-induced factor FNDC5 also plays a protective role in PD. It has been demonstrated to promote the secretion of BDNF in hippocampal neurons to enhance synaptic plasticity, thereby effectively alleviating cognitive deficits in PD mice (Tang et al., 2023). In terms of stroke, the increase in FNDC5 levels is associated with hypertension-related stroke, while the decrease in FNDC5 blood concentration is related to poor prognosis in patients with acute ischemic stroke (Chen et al., 2019; Tu et al., 2018). Other studies have shown that FNDC5 can play a neuroprotective role in stroke-induced brain damage by protecting the permeability of the blood-brain barrier, reducing cortical cell apoptosis, and increasing the expression of BDNF protein (Guo et al., 2019; Asadi et al., 2018; Li et al., 2017). Jin et al. (Jin et al., 2021) further explored the effects of the exercise factor FNDC5 on cognitive function in a cerebral ischemia mouse model. The results showed that FNDC5 could alleviate oxidative stress by upregulating the expression of the Klotho gene, thereby improving cognitive dysfunction after cerebral ischemic injury.

In summary, FNDC5/Irisin plays a significant role in various clinically common brain-related disorders, and this will contribute to the development of biomarkers and therapeutic targets related to disease occurrence and prognosis, and provide new avenues for the prevention and treatment of neurological disorders. However, the mechanism by which FNDC5 improves cognitive impairment caused by neurological diseases has not been fully investigated. Most studies have focused on FNDC5's promotion of BDNF expression to improve cognitive function, with only a few experiments suggesting the involvement of specific signaling pathways. In addition, the studies on the relationship between FNDC5 and other neurological disorders such as autism, schizophrenia, and epilepsy are currently very limited, and there are almost no available data in major international databases. Therefore, future studies should explore the effects of exercise-induced muscle factor FNDC5 on various neurological disorders and related cognitive impairments at both clinical and animal levels. It is necessary to investigate the specific mechanisms of FNDC5 in neuroprotection, inflammation regulation, and molecular signaling pathways, and provide a theoretical basis for the development of new treatment strategies and medications in clinical settings.

4 Exercise-mediated improvement of cognitive function through FNDC5

A large body of research indicates that exercise is a significant factor in regulating FNDC5 expression in skeletal muscle and brain tissue, in both humans and animals, and different forms of exercise have varying effects on FNDC5 expression. Animal experiments have demonstrated that aerobic exercise can increase the levels of FNDC5 protein, in both acute exercise (Pang et al., 2018) and chronic exercise (Ren et al., 2022; Wang et al., 2023). In human experiments, researchers found that a single session of acute exercise can increase Irisin levels in the blood of healthy untrained women by 9.5%, and after 6 weeks of whole-body vibration training, the Irisin levels in their blood increased by 18.1% (Huh et al., 2014b). This suggests that long-term exercise training may have a more significant impact on FNDC5/Irisin secretion than single exercise sessions, over a certain duration. Additionally, Kim et al. (Kim and Song, 2017) divided 24 eight-week-old rats randomly into a lean control group, a diabetic control group, and a diabetic exercise-trained group, and the results showed that diabetic rats, after 12 weeks of resistance training (3 times/week), had an increase in FNDC5/Irisin levels in

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their blood from 1.9 ng/mL before training to 2.3 ng/mL after. Nygaard et al. (Nygaard et al., 2015) found that the concentration of Irisin in the blood of healthy subjects temporarily increased after a single session of strength and endurance exercise, and individuals with a lower lean body mass ratio showed a more pronounced increase in Irisin levels after resistance exercise. In summary, exercise is closely related to the secretion of FNDC5, and different exercise protocols and sampling time points may lead to variations in research findings, but it is certain that exercise does not decrease the expression of FNDC5. Based on this, researchers further explored the relationship between exercise, FNDC5, and cognitive function, and investigated various mechanisms through which exercise regulates FNDC5 to improve cognitive function, providing a theoretical basis for the treatment of cognitive impairments in neurodegenerative diseases (Fig. 3).

4.1 Exercise regulates FNDC5 to inhibit neuroinflammation

Neuroinflammation refers to a series of immune responses mediated by glial cells in the central nervous system, including microglia and astrocytes. When these glial cells are excessively activated, they release large amounts of pro-inflammatory cytokines with neurotoxic effects, leading to damage in the central nervous system and ultimately resulting in cognitive impairments (Sha et al., 2021; Leng and Edison, 2021). It was found that exercise factor FNDC5 can alleviate neuronal damage induced by oxygen and glucose deprivation (OGD), in part by inhibiting the reactive oxygen species (ROS)/NOD-like receptor thermal protein domain associated protein-3 (NLRP-3) inflammasome signaling pathway, suggesting an inhibitory effect of FNDC5 on inflammatory responses in the brain (Peng et al., 2017). In vitro studies showed that, in astrocytes, FNDC5 reduced the release of inflammatory cytokines IL-6 and IL-1β, inhibited the expression of pro-inflammatory mediator cyclooxygenase-2 (COX-2), and suppressed the phosphorylation of protein kinase B (AKT), thereby inhibiting inflammatory responses and cell damage (Wang et al., 2018). These findings suggest the anti-inflammatory role of FNDC5 in neurodegenerative diseases. Exercise, as a non-pharmacological treatment, plays an important role in a variety of diseases associated with immune system activation, and it has been shown to improve cognitive function by regulating the expression of FNDC5 and suppressing neuroinflammation mediated by glial cells. Human experiments have demonstrated that long-term exercise training leads to improvements in cognitive function, and the increased levels of serum Irisin are positively correlated with reduced inflammation (Gmiąt et al., 2018; Briken et al., 2016). In high-fat diet (HFD) and STZ-induced T2DM mice, 8 weeks of running exercise increases FNDC5 expression, reverses glial cell activation in the hippocampus of T2DM mice, reduces the expression levels of pro-inflammatory cytokines IL-1β, IL-6, and TNF-α, and increases the expression levels of anti-inflammatory cytokines IL-10 and transforming growth factor-beta1 (TGF-β1), which alleviates inflammatory responses in the hippocampus of the mice, and improves the cognitive deficits in diabetic mice (Lang et al., 2020).

In summary, exercise can increase FNDC5 expression and suppress the expression of inflammatory cytokines in the brain, thereby improving cognitive impairment. However, current research only confirms the correlation between exercise-induced FNDC5 and neuroinflammation, and the specific molecular mechanisms by which it regulates the inflammatory response have yet to be elucidated; this needs to be explored in depth by further studies. Furthermore, Toll-like receptors (TLRs) are the main receptors on the surface of glial cells that recognize antigens and activate them, playing a crucial role in the inflammatory response process of neurodegenerative diseases, which have become a focus of attention and research for scientists in recent years (Dendrou et al., 2016). It is unclear whether the process of exercise regulating FNDC5 to reduce brain inflammation is related to the inhibition of TLRs, which could be investigated in the future.

4.2 Exercise regulates FNDC5 to improve hippocampal neurogenesis

The hippocampus is the primary brain region responsible for regulating cognitive and memory function. Hippocampal neurogenesis is the process by which neural stem cells (NSCs) in the hippocampus differentiate and generate new neurons. It is a significant manifestation of brain structural plasticity, and maintaining the normal function of hippocampal neurogenesis is of great importance for learning and memory (Abbott and

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Nigussie, 2020). It was shown that knocking down the precursor of Irisin, FNDC5, inhibited neural differentiation in mouse embryonic stem cells, and pharmacological doses of recombinant Irisin (50-100 nM) could promote cell proliferation in mouse hippocampal neurons through the activation of the STAT9 signaling pathway, suggesting that the exercise factor FNDC5 plays a positive role in hippocampal neurogenesis (Wrann, 2015; Moon et al., 2013). As one of the ways to influence FNDC5 secretion, exercise can improve hippocampal neurogenesis through the regulation of FNDC5. The experimental study has shown that 4 weeks of low/moderate-intensity running exercise can increase FNDC5 levels in the hippocampus of mice, improve cell proliferation and survival in the hippocampal region, and reduce immobility time in FST and TST, thereby exhibiting antidepressant effects (Siteneski et al., 2020). Hwang et al. (Hwang et al., 2023) showed that treadmill exercise can increase the expression of FNDC5 in the mouse hippocampus, inducing neurogenesis and improving the mice's memory abilities. In both wild-type $BDNF^{Val/Val}$ mice and genetically altered $BDNF^{Met/Met}$ mice models, running wheel exercise can activate the expression of FNDC5 in both skeletal muscle and the hippocampus, and promote the survival of newborn neurons (Ieraci et al., 2016). Based on the results provided in the above studies, it is reasonable to speculate that the increase of FNDC5/Irisin levels induced by exercise in the hippocampus may be the basis for the promotion of hippocampal neurogenesis through physical exercise. Therefore, additional studies are necessary to determine the causal relationship between these effects. A further study by Choi et al. (Choi et al., 2018) in an AD mouse model has found that exercise can activate hippocampal neurogenesis by increasing the levels of FNDC5, BDNF, IL-6, and synaptic markers, thereby mitigating the pathological process of AD and improving the cognitive deficits in mice.

In summary, the increase in FNDC5 levels induced by exercise is important for improving hippocampal neurogenesis, and provides new avenues and therapeutic targets for improving cognitive dysfunction resulting from neurological damage. However, most current studies are conducted in animal models without disease phenotypes, which can only help us understand the normal physiological role of the exercise factor FNDC5 in hippocampal neurogenesis. Future research should consider exploring the effects of this factor on hippocampal neurogenesis and cognitive function in various types of brain injury models, such as ischemic brain injury models, traumatic brain injury models, and neurodegenerative disease models, to clarify its impact in the context of brain damage.

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4.3 Exercise regulates FNDC5 to improve hippocampal synaptic plasticity

Synapses are structures in the brain that connect neurons and transmit information. Synaptic plasticity refers to the adaptive changes in the structure or function of synapses in response to physiological activities or external stimuli, and is categorized into structural and functional plasticity. In the central nervous system, the structure, quantity, and functional status of synapses are closely related to learning and memory, and synaptic plasticity is the neural basis for learning and memory formation (Feng et al., 2022). The exercise-induced factor FNDC5/Irisin was found to be directly involved in the regulation of synaptic plasticity, and intraventricular injection of FNDC5/Irisin can enhance the expression of genes related to synaptic plasticity in the prefrontal cortex and hippocampus (Siteneski et al., 2018). Lourenco et al. (Lourenco et al., 2019) found that FNDC5 levels were reduced in the brains and cerebrospinal fluid of human AD patients and in the hippocampus of an AD mouse model. Knocking down FNDC5 expression in the brains of C57BL/6 mice impaired the maintenance of hippocampal long-term potentiation (LTP) and novel object recognition (NOR) memory ability, while increasing FNDC5 levels in the brain improved synaptic plasticity and memory function in AD mice. Based on this, further experimental design showed that peripheral overexpression of FNDC5 improved memory impairment induced by AβOs, whereas peripheral blockade of FNDC5 weakens the protective effect of exercise on synaptic plasticity and memory function in AD mice, indicating that FNDC5 may be an important mediator of the beneficial effects of exercise on synaptic function and memory in AD models. Another study showed that both high-intensity interval training (HIIT) and moderate-intensity continuous training (MICT) could increase the levels of FNDC5 in the hippocampus of healthy rats, upregulate the expression of factors involved in neural plasticity, such as BDNF, IGF-1, and VEGF, and improve synaptic plasticity in the hippocampus, and that HIIT

has superior improvement effects compared to MICT (Constans et al., 2021; Hugues et al., 2022). In the CUMS-induced depression model, both 8-week aerobic exercise and resistance training improved depressive behavior in rats, decreased the apoptosis rate of hippocampal neurons, enhanced LTP in the CA1 region of the hippocampus, and improved synaptic plasticity (Kang et al., 2020). However, the molecular mechanisms underlying the modulation of hippocampal synaptic plasticity by the two exercise modalities were different. Aerobic exercise may activate the PGC-1α/ERRα/FDNC5 signaling pathway, while resistance training tends to upregulate the IGF-1/IGF-1R/Akt/mTOR signaling pathway. Additionally, BDNF has a wide range of regulatory effects in the nervous system. It can promote the expression of SYN and postsynaptic density protein 95 (PSD95), increase synaptic density and complexity, and enhance synaptic transmission efficiency, which plays a crucial regulatory role in cognitive processes in the brain (Kowiański et al., 2018). A recent study has shown that treadmill exercise-induced activation of FNDC5 protein expression upregulates the levels of BDNF in the hippocampus and increases dopaminergic synaptic connections between the substantia nigra pars compacta (SNpc) and the hippocampus, thereby improving hippocampal synaptic plasticity and reversing cognitive dysfunction in the PD mouse model (Tang et al., 2023).

In summary, different types of exercise can influence the level of FNDC5 and upregulate the expression of factors related to synaptic plasticity through this pathway, thereby improving hippocampal synaptic plasticity and alleviating cognitive dysfunction. However, different exercise modalities seem to regulate hippocampal synaptic plasticity via different signaling pathways, and aerobic exercise appears to have a better regulatory effect on the PGC-1α/ERRα/FNDC5 signaling pathway; however, the specific mechanisms are not yet clear and require further research for clarification. In addition, synaptic plasticity manifests as LTP and long-term depression (LTD), with LTP being the most extensively studied form of synaptic plasticity and considered the cellular basis of learning and memory (Vints et al., 2022; Bin Ibrahim et al., 2022). Currently, there is a research gap regarding the specific mechanisms linking the increase in FNDC5 levels mediated by exercise and their impact on LTP. In the future, the application of patch-clamp techniques on brain slices can be used for in-depth exploration of this connection.

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5 Conclusion and outlook

In conclusion, as a factor induced by exercise, FNDC5 plays a crucial role in the nervous system. It not only promotes neuronal differentiation and maturation and protects the neural function of organisms, but also improves the cognitive impairments caused by diseases such as AD, DM, depression, and stroke, and can be considered as a novel target in the prevention and treatment of cognitive impairments. In addition, exercise, as a non-pharmacological intervention, has been extensively studied and shown to improve hippocampal cognitive impairments by modulating the expression of FNDC5, where the mechanisms involved include the inhibition of neuroinflammation, the induction of hippocampal neurogenesis, and the enhancement of hippocampal synaptic plasticity. However, there are several pressing issues that need to be addressed in the current research in this field. Firstly, while studies have confirmed that exercise factor FNDC5 can improve cognitive function through various pathways, most of the research has focused on the role of FNDC5 in promoting BDNF expression and improving brain function, and only a small portion of experiments suggest the involvement of specific signaling pathways. In the future, further exploration is needed to identify the specific downstream targets through which FNDC5 influences cognitive function. Secondly, the studies on the effects of exercise intervention on regulating FNDC5 and hippocampal cognitive function are still not sufficient. In the future, it is important to conduct more studies on exercise intervention in animal models with other neurological pathologies such as AD, PD, schizophrenia, and epilepsy, compare the mechanisms and effects of FNDC5 in improving cognitive function in different disease models, and lay the foundation for its application in clinical practice. Finally, exercise is a complex variable, and different exercise modalities, durations, intensities, and frequencies may have varying effects on FNDC5 levels. Currently, there is a lack of specific exercise standards and protocols for mediating FNDC5 regulation of hippocampal cognitive function improvement, and further in-depth research is still

needed in this area.

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Author contributions

Ruobing ZHAO drafted the manuscript; Xuchang ZHOU, Dongxue WANG, Haifeng TANG and Guoxin NI revised the manuscript. All authors have read and approved the final manuscript, and therefore, have full access to all the data in the study and take responsibility for the integrity and security of the data.

Compliance with ethics guidelines

Ruobing ZHAO, Xuchang ZHOU, Dongxue WANG, Haifeng TANG and Guoxin NI declare that they have no conflict of interest.

This article does not contain any studies with human or animal subjects performed by any of the authors.

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Table 1. Regulatory role of FNDC5 in different tissues.

Study	Experimental Model	Target Tissue	Target Cells in Researches	Main Effect
Boström et al., 2012	In vitro	Adipose tissue	Murine preadipocytes	FNDC5 induces browning of WAT-derived murine preadipocytes.
Huh et al., 2014	In vitro	Adipose tissue	Mature human adipocytes	FNDC5 can regulate adipocyte metabolism.
Qiao et al., 2016	In vitro	Bone	Osteoblast	FNDC5 promotes osteoblast proliferation, differentiation, and mineralization.
Jia et al., 2022	In a rat OA model/ In vitro	Bone	Chondrocytes	FNDC5 alleviates chondrocyte inflammation and ameliorates chondrocyte pyroptosis.
Chen et al., 2020	In vitro	Bone	BMSCs	FNDC5 enhances osteogenic differentiation by stimulating autophagy in BMSCs.
Mazur-Bialy, 2017	In vitro	Immunocompetent cells	Murine RAW 264.7 macrophages	FNDC5 changes macrophage activity and improves their phagocytosis ability.
Tan et al., 2019	In a mouse septic cardiomyopathy model/ In vitro	Heart	Cardiomyocyte	FNDC5 attenuates sepsis-mediated myocardial depression and cardiomyocyte death.
Ren et al., 2019	In a mouse AP model/ In vitro/ In humans	Pancreas	Pancreatic cells	FNDC5 can treat acute pancreatitis by restoring mitochondrial function.
Park et al., 2015	In vitro	Liver	Hepatocytes	FNDC5 prevents hepatic steatosis by reducing oxidative stress.
Gaggini et al., 2017	In humans	Liver	Hepatocytes	FNDC5 has a protective effect against liver damage.
Wrann et al., 2013	In a mouse model/ In vitro	Brain	Neural cells	Forced expression of FNDC5 increases BDNF expression in brain tissue.
Forouzanfar et al., 2015	In vitro	Brain	mESCS	FNDC5 facilitates neural differentiation.
Hashemi et al., 2013	In vitro	Brain	mESCS	FNDC5 expression is required for the appropriate neural differentiation of mESCs

FNDC5: fibronectin type III domain-containing protein 5; WAT: white adipose tissues; OA: osteoarthritis; BMSCs: bone marrow mesenchymal stem cells; AP: acute pancreatitis; BDNF: brain-derived neurotrophic factor; mESCS: mouse embryonic stem cells

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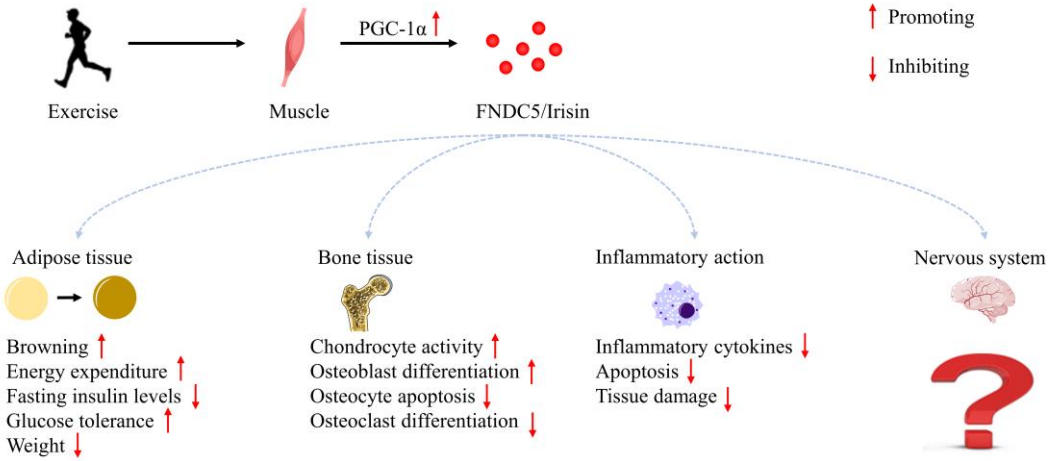

Fig. 1 The biological function of FNDC5.
FNDC5, fibronectin type III domain-containing protein 5. PGC-1α: peroxisome proliferators-activated receptor-γcoactivator-1α.

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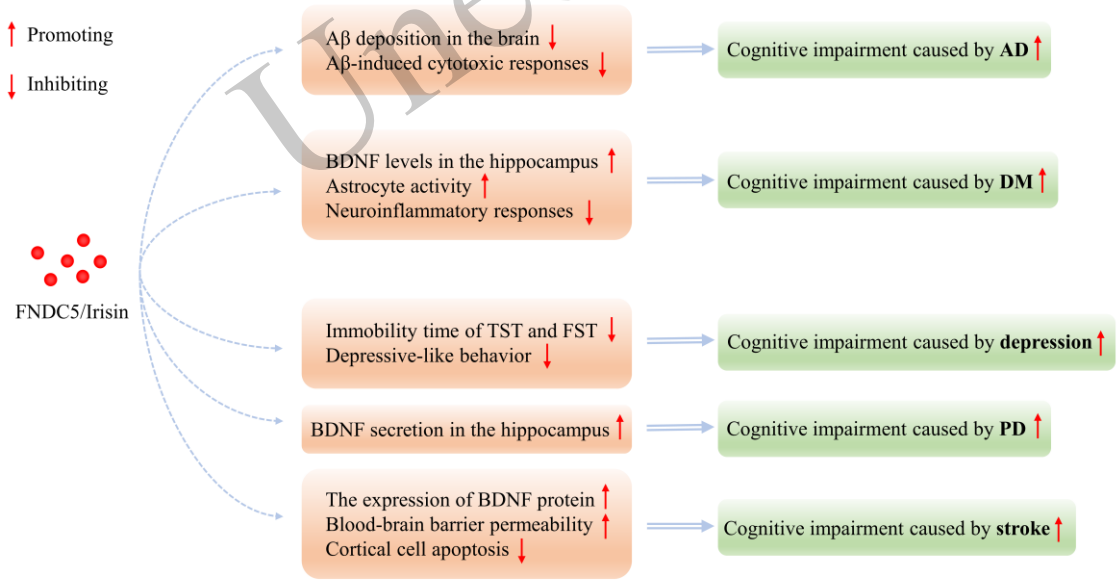

Fig. 2 Exercise-induced FNDC5 improves cognitive dysfunction caused by various diseases.
FNDC5, fibronectin type III domain-containing protein 5. Aβ, amyloid beta protein. BDNF, brain-derived neurotrophic factor. TST, tail suspension test. FST, forced swimming test. AD: Alzheimer's disease. DM: diabetes mellitus. PD: Parkinson's disease.

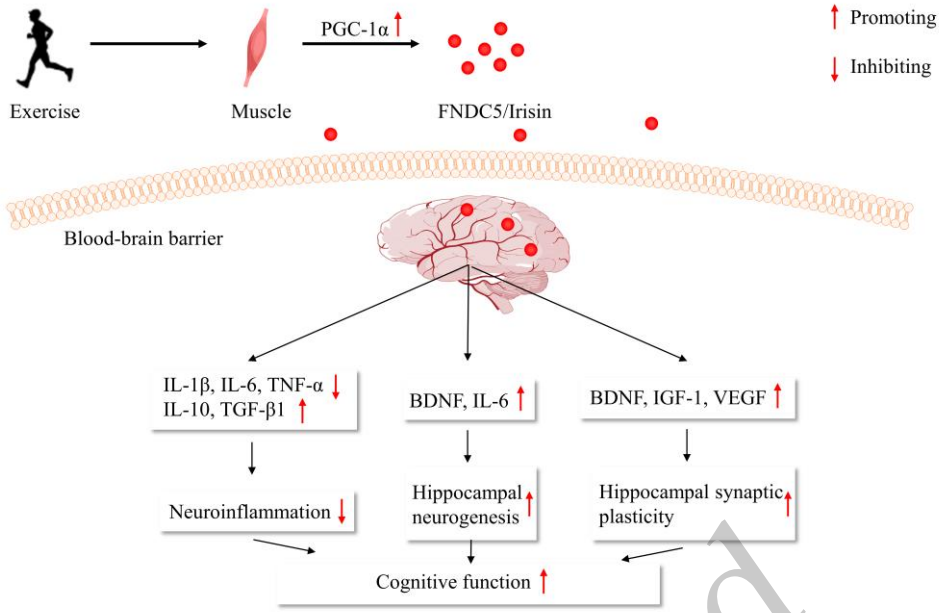

Fig. 3 The mechanism by which exercise regulates FNDC5 to improve cognitive function.

FNDC5, fibronectin type III domain-containing protein 5. PGC-1α: peroxisome proliferators-activated receptor-γcoactivator-1α. IL-1β, interleukin-1β. IL-6, interleukin-6. TNF-α, tumor necrosis factor-α. IL-10, interleukin-10. TGF-β1, transforming growth factor-β1. BDNF, brain-derived neurotrophic factor. IGF-1, insulin-like growth factor-1. VEGF, vascular endothelial growth factor.

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