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The role of physical activity in prevention of neurodegenerative diseases via irisin synthesis – a contemporary review

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ABSTRACT
Background:
Neurodegenerative diseases (NDDs) such as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis (ALS) pose as a growing clinical and socioeconomic challenge due to population aging and the lack of causal therapies. Shared pathological mechanisms include oxidative stress, mitochondrial dysfunction, and chronic neuroinflammation. Regular physical activity shows neuroprotective effects, and irisin—an exercise-induced myokine generated by proteolytic cleavage of FNDC5 under PGC-1α control—may be an important mediator of the muscle–brain axis.
Aim:
To present the current state of knowledge on irisin, with particular emphasis on its role in the pathogenesis, diagnosis, and potential treatment of neurodegenerative diseases.
Material and methods:
This narrative review summarizes available evidence on the biological properties of irisin, its proposed mechanisms of action (including signaling via αV/β5 integrin receptors and MAPK, AMPK, and PI3K/AKT pathways), and its effects on energy metabolism, inflammation, oxidative stress, and neuroplasticity in the context of NDDs.
Results*:*
Experimental studies indicate that irisin increases hippocampal BDNF expression, promotes neurogenesis and synaptic plasticity, and reduces neuronal apoptosis. In Alzheimer's disease models, FNDC5/irisin levels were reduced in the hippocampus and cerebrospinal fluid, whereas increasing FNDC5/irisin improved memory and attenuated amyloid-related pathology. In Parkinson's disease models, irisin reduced α-synuclein aggregation, protected dopaminergic neurons, and improved motor performance. In ALS, irisin has been proposed to modulate oxidative stress and neuroinflammation through NRF2 activation and NF-κB inhibition, although clinical evidence remains limited.
Conclusions:
Irisin is a promising biomarker and potential therapeutic target in neurodegenerative diseases. Despite encouraging preclinical results, clinical translation requires well-designed human studies. At present, regular physical activity remains the most practical strategy to modulate endogenous irisin levels and may support prevention and management of NDDs.

Keywords:
irisin; FNDC5; neurodegenerative diseases; Alzheimer's disease; Parkinson's disease; amyotrophic lateral sclerosis; physical activity; BDNF; muscle–brain axis

1. Introduction

Neurodegenerative diseases (NDDs), characterised by the progressive degeneration of the structure and function of the nervous system, result in a variety of symptoms and impairments. [1] Although these conditions present differently, they share certain mechanisms, including the formation of misfolded protein aggregates and abnormal protein accumulation. These disorders affect millions of people worldwide and their etiology is complex. Age is considered to play a significant role in the pathogenesis of neurodegenerative disorders, however, genetics, environmental and lifestyle factors also contribute. [2-4] Increasing life expectancy has led to a corresponding rise in the prevalence of NDDs, resulting in a growing socio-economic burden associated with neurodegenerative diseases. NDDs are often chronic and debilitating with no curative treatment, making them a significant challenge for both patients and healthcare providers. [5]

Physical activity is acknowledged as a safe, feasible and effective intervention to improve metabolic and neurological health. [6] Due to its highly modifiable characteristics and potential as a non-pharmacological strategy for the prevention of several chronic diseases, it has been extensively investigated in the medical field. Studies have shown that MVPA (moderate-to-vigorous physical activity) is correlated with a decreased incidence of neurodegenerative diseases, like Parkinsonism and dementia. Moreover, cardiovascular disorders and their traditional risk factors, such as active lifestyle, are known to be strongly linked with the development of NDDs. [7-9]

Myokines, secreted by myocytes in response to muscle contractions, especially during resistance and high-intensity exercise, exert autocrine, paracrine, and endocrine effects on tissues. Some myokines can cross the blood-brain barrier, providing neuroprotective and neuromodulatory effects and forming part of the muscle-brain axis (MBA), through which muscle activity influences CNS function. Key myokines mediating exercise-induced brain benefits include BDNF, IGF-1, cathepsin B, VEGF, L-lactate, and irisin. [10-11] Irisin has been shown to counteract processes such as insulin resistance, inflammation, and cognitive decline. These effects play a key role in the prevention of NDDs. Increased irisin levels have been associated with improved cognitive function and memory performance. [12-13] Owing to these properties, irisin represents a potential therapeutic target for the prevention and treatment of metabolic disorders, neurodegenerative diseases, and related conditions.

In this work we aim to present the current state of knowledge on irisin, with a particular focus on its role in the diagnosis and treatment of neurodegenerative diseases. We review the available literature to summarize its biological functions, mechanisms of action, and potential clinical applications. This overview highlights the therapeutic and diagnostic relevance of irisin in the context of neurodegenerative pathology

2. Irisin – characteristics and biological role

Discovery and origin

Irisin is an exercise-induced myokine discovered in 2002, primarily characterized as an unknown gene expressed in the heart, brain, skeletal muscles and other tissues of mice; it was then named PeP - peroxisomal protein or FRCP2 - fibronectin type III repeat containing protein 2 [14,15]. Later, this gene became annotated as fibronectin type III domain containing protein 5 (FNDC5) and that is how it is known today. Irisin came into the spotlight again in 2012 when it was identified as one of the target genes of peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α; PPARGC1A), a multispecific transcriptional coactivator induced in muscle by exercise [16]. It was reported to be a molecule capable of inducing changes in adipose tissue and named after Iris, the Greek messenger goddess [16]. The main source of irisin secretion is skeletal muscles [16]; however, it has also been found to be expressed in the pancreas, testicles, liver, spleen, stomach and other organs [17]. Physical exercise elevates the level of irisin in the human body by stimulating the expression of peroxisome proliferator-activated receptor γ coactivator-1α (PGC-1α), thereby enhancing the transcription of FNDC5, which leads to increased synthesis and secretion of irisin [18]. Therefore, systemic concentration of irisin varies between individuals: in those with a sedentary lifestyle, irisin circulates at approximately 3.6 ng/ml, whereas in individuals undergoing aerobic interval training it reaches about 4.3 ng/ml [19]. Apart from exercise, irisin secretion has also been shown to be stimulated by other factors, such as obesity, high temperature, and exposure to cold [17,20,21].

Structure and mechanism of action

From a molecular point of view, irisin is a polypeptide composed of 112 amino acids. It is produced by cleavage of FNDC5 (a transmembrane glycoprotein encoded by the FNDC5 gene) under the control of PGC-1α [22,23]. Irisin acts as a link between skeletal muscles and other tissues. Although the receptor for irisin has not been fully identified, it has been suggested that this myokine exerts its effects via binding to αV/β5 integrins [24]. Integrins are transmembrane heterodimers located on the surface of the cell, serving as major adhesion receptors, transmitting signals across the plasma membrane [25]. At the intracellular level, there are several signaling pathways through which irisin elicits its biological functions, the main being the MAPK signaling pathways. Other signaling cascades include the AMPK, PI3K/AKT and STAT3/Snail pathway [26].

Functions of irisin

The function of irisin in the human body is multi-target and multi-effect. It has been shown to promote the conversion of white adipose tissue into brown adipose tissue, thereby increasing glucose and lipid metabolism as well as overall energy expenditure [27]. Moreover, irisin inhibits the secretion of pro-inflammatory cytokines, such as IL-6 and TNF-α, therefore reducing systemic inflammation. It also exhibits antioxidative properties by decreasing oxidative stress in macrophages and increasing the expression of antioxidant enzymes [28,29]. It was also found to promote antidepressant effects through activation of the PGC-1α/BDNF pathway [30]. Irisin also contributes to bone health - it reduces the risk of bone fractures and bone loss, as well as stimulates bone formation and mineralization [31–33]. The myokine can also contribute to adipocyte function modulation, improving insulin sensitivity and decreasing inflammation in adipose tissue. Due to its properties, irisin plays a role in maintaining cardiovascular health and preventing arterial stiffness and cardiovascular diseases. [34]. Moreover, risin was reported to affect the nervous system. It was discovered that irisin stimulates the expression of brain-derived neurotrophic factor (BDNF) in the hippocampus—a brain region associated with learning and memory—therefore promoting synaptic plasticity and neurogenesis [35]. BDNF enhances neuronal survival and migration as well as reduces neuronal damage caused by oxidative stress [36–38]. This raises the possibility that irisin could be a protective agent against neurodegenerative disorders and a key mediator of the beneficial effect of exercise on cognitive function. The myokine also plays a crucial role in the activation of autophagy, therefore exhibiting a protective role against inflammation [39]. It was also suggested that irisin alleviates the neuronal apoptosis and post-ischemic inflammation and reduces ischemia-induced neuronal injury [40,41].

3. Neurodegenerative diseases – a brief review

Alzheimer’s disease

AD is an incurable, neurodegenerative, fatal disorder. It is rather sporadic than familial and has a multifactorial etiology, as both environmental factors and genetic predispositions influence its development. The main risk factors for AD include age, level of education, social relationships, and polymorphism of the APOE (apolipoprotein E) gene, which is the only well-documented genetic risk factor. Rare forms of AD may be caused by mutations in single genes. Currently, three forms of AD have been identified: APP, PSEN1, and PSEN2 mutations. The pathophysiology of AD is based on the accumulation of extracellular β-amyloid (Aβ) deposits and intracellular aggregations of hyperphosphorylated tau protein. These plaques promote apoptosis of neural cells, which ultimately leads to a reduction in neurotransmitter levels in the brain [42].

Parkinson's disease

Parkinson's disease (PD) is a progressive neurodegenerative disorder associated with degeneration of brain structures, the exact etiology of which remains largely unclear. Current evidence suggests multifactorial causes, including both environmental and genetic factors, mainly related to mitochondrial genome dysfunction. PD is characterized by a slowly progressive, idiopathic loss of dopaminergic neurons in the substantia nigra, as well as glial proliferation. Parkinson's disease presents with both motor and non-motor symptoms [43]. Currently, PD is considered a generalized synucleinopathy. In the cytoplasm of neurons, α-synuclein and ubiquitin aggregates form Lewy bodies, which are a distinctive sign of central nervous system degeneration. During disease progression, dopamine levels are gradually reduced. Pathological changes initially occur in the substantia nigra and subsequently spread to the midbrain and cerebral cortex [44].

Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is an incurable disease of the nervous system characterized by progressive neurodegeneration of motor neurons. The damage affects both upper and lower motor neurons, leading to progressive muscle weakness and impairment of movement, communication and swallowing. The etiology of ALS is not fully understood; however, approximately 7.5% of cases are familial and genetically determined. A characteristic feature of ALS is fasciculations presented as muscle twitches. Over time, muscles undergo atrophy, eventually resulting in respiratory failure due to weakening of the respiratory muscles [45]. Oxidative stress has been reorted as a possible factor contributing to the development of the disease. By analyzing ALS mouse models. It has been reported that nerve terminals are sensitive to ROS (reactive oxygen species), indicating that oxidative stress, compromised mitochondria, and increased intracellular $Ca2+$ amplify the presynaptic decline in neuromuscular junctions (NMJ). Further, inflammatory agents and the loss of trophic support are conducive to neurodegeneration. [46].

4. Irisin in neurodegenerative disorders

Alzheimer's disease

Alzheimer's disease is the most common cause of dementia worldwide.[47] It is estimated that 6.7 million Americans aged 65 and older currently live with Alzheimer's dementia, with a projected increase to 13.8 million by 2060. Alzheimer's disease has been officially listed as the sixth leading cause of death in the United States.[48] Although the incidence of Alzheimer's disease is gradually increasing worldwide, no effective therapeutic solutions have been found. Due to the scale of the problem and its impact on healthcare in many countries, it is the subject of interest for scientists around the world who are looking for potential new avenues of treatment and therapy for the disease. Currently, researchers are looking for it in irisin.

Studies have shown its presence in many brain structures, including cerebrospinal fluid, the hypothalamus [49], Purkinje cells of the cerebellum, and intercellular nerve endings [50].

In rodents, FNDC5 is expressed in several brain regions, including the midbrain and hippocampus [51]. Studies have shown that FNDC5/irisin expression levels are reduced in the hippocampus and cerebrospinal fluid in Alzheimer's disease, impairing long-term synaptic strengthening and recognition memory of new objects in mice. Conversely, increasing FNDC5/irisin levels in the brain restored synaptic plasticity and memory in mice with Alzheimer's disease. Overexpression of FNDC5/irisin in the peripheral system alleviated the symptoms of dementia.[52] Irisin is essential for neuronal differentiation in mouse embryonic stem cells [53]. Studies have shown that irisin affects hippocampal neurogenesis and induces neuronal proliferation.[54], inhibits oxidative stress-induced neuronal damage and attenuates pro-inflammatory cytokine secretion [55]. Integrin αV/β5 has recently been detected in the hippocampus and cerebral cortex [56], indicating that irisin binds to integrin αV/β5, exerting a protective effect on the brain. It is a protein that acts as a key energy sensor, maintaining energy balance and mitochondrial haemostasis [57]. It has been suggested that irisin contributes to neuronal differentiation by modulating metabolic responses in the central nervous system [58] via BDNF production stimulation [59]. BDNF is a neurotrophic factor of brain origin, a widely distributed neurotrophin in the brain, playing a significant role in synapse function [60]. It inhibits the cytotoxic response of neurons and moderates learning deficits in relation to Aβ toxicity in Alzheimer's disease [61], controls dopamine-3 signalling pathways, affecting the action of dopamine on the central nervous system [62], and modulates synaptic plasticity and neurogenesis in the amygdala, prefrontal cortex, and hippocampus [63]. BDNF induces LTP and increases synaptic strength [64]. Furthermore, BDNF is essential for hippocampal neurogenesis and hippocampal neural circuitry [65]. Recent studies have shown that the irisin-BDNF axis may enhance learning and memory functions [66]. Several studies have shown that administering BDNF to patients with Alzheimer's disease alleviates the symptoms of the disease [67]. FNDC5/irisin contributes to increased learning and reward motivation by increasing BDNF production [66]. Furthermore, increased FNDC5 expression in primary cortical neurons promotes BDNF expression, while decreased FNDC5 expression leads to decreased BDNF expression [68]. Overexpression of BDNF mitigated neurodegeneration and restored impaired memory in non-human primates [69]. Given that BDNF expression can potentially improve cognitive function in Alzheimer's disease [70], stimulation of the BDNF-irisin axis in the brain may be a promising avenue for the treatment of Alzheimer's disease, since increased irisin levels have been observed after aerobic exercise. [71]. Alzheimer's Disease International recommends 150 minutes of moderate aerobic exercise or 75 minutes of vigorous aerobic exercise per week for adults to maintain proper heart function, weight control and mental health. There is evidence that exercise can be an effective intervention in the early stages of Alzheimer's disease [72].

Interestingly, recent studies have highlighted the link between metabolic disorders and Alzheimer's disease (AD). It has been shown that a high-fat diet increases APP expression and APP processing enzyme levels [73]. In addition, rats fed a high-fat diet showed increased levels of the APP-cleaving enzyme and Aβ in the hippocampus [74]. Clinical studies have shown that obesity causes cognitive decline, disrupts the blood-brain barrier, and increases the risk of Alzheimer's disease [75]. For this reason, the potential use of irisin in the treatment of Alzheimer's disease is being explored. It has been proven that irisin levels are higher in patients with metabolic syndrome than in healthy individuals [76], and its reduction is associated with the onset of insulin resistance [77]. Increased expression of FNDC5/irisin improves insulin resistance and lowers blood glucose levels in mice fed a high-fat diet [78]. Given the link between metabolic disorders and the onset of Alzheimer's disease, the use of irisin in the prevention or treatment of this neurodegenerative disorder seems promising.

Parkinson’s disease

Parkinson’s disease (PD) is the second most common neurodegenerative disorder after Alzheimer’s disease. Its prevalence is expected to double over the next 30 years and an accurate diagnosis remains challenging. [79-80] Besides pharmacotherapy, physical exercise has shown promising effects in PD patients, including reduced of postural and gait instability, improved overall mobility and cognitive functions, as well as lower deterioration on daily living activities. [81-82]

Kam et al. used the α-synuclein preformed fibril (a-syn PFF) model of Parkinson’s disease, showing that irisin reduces α-synuclein pathology and neuronal loss. Irisin protected cultured neurons, preserved dopaminergic neurons and striatal dopamine in vivo and improved motor performance in mice. The study indicates that irisin reduces α-synuclein pathology through at least three distinct mechanisms: downregulating ApoE4, reduction of a-syn internalization by neurons and promoting its degradation via the endolysosomal pathway. [83]

Zarbakhsh et al. developed a rat model of Parkinson’s disease using intranasal administration of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). They showed that co-treatment with irisin and bone marrow stromal cells (BMSCs) protected dopaminergic neurons from apoptosis and degeneration. In particular, irisin promoted the migration of BMSCs to the damaged brain regions, increased the number of tyrosine hydroxylase positive neurons in substantia nigra and striatum and improved PD-related symptoms. [84]

In PD patients, plasma α-synuclein levels increase while irisin levels decrease as the disease progresses with a negative correlation between the two. Irisin levels are inversely related to motor symptom severity (UPDRS-III) and positively related to cognitive function (MoCA). Higher irisin levels are associated with improved striatal DOPA uptake, particularly on the side opposite the affected limb, suggesting a neuroprotective role through α-synuclein reduction and enhanced striatal function. [85]

In Parkinson’s disease, CREB is crucial for expressing neuroprotective genes like NURR1, essential for dopaminergic neuron survival, and its inactivation worsens neuronal degeneration [86] Irisin can activate upstream pathways such as AKT and MAPK1/3, potentially enhancing CREB activity and supporting neuroprotection. While direct evidence in PD is limited, irisin’s effects suggest it may help modulate CREB-mediated neuroprotective mechanisms [87]

Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease affecting upper and lower motor neurons. While the exact causes of neuronal damage are unclear, neuroinflammation—driven by activated microglia and astrocytes releasing pro-inflammatory cytokines—plays a key role in disease progression. [88]

Irisin has been reported to activate the NRF2 pathway, leading to increased expression of antioxidant enzymes and reduced oxidative stress. Additionally, irisin inhibits NF-κB activation, thereby reducing the production of pro-inflammatory cytokines. These effects suggest that irisin may offer therapeutic potential in ALS by modulating oxidative stress and inflammation pathways. Studies in genetically modified SOD1 mice, the main model for ALS, have shown elevated levels of the peripheral canonical PGC1α system, whereas specific PGC1α isoforms are decreased in the CNS. These results imply that disruptions in the PGC1α system may be involved in the neurodegenerative processes of ALS. [89-90]

A human study demonstrated that ALS patients with metabolic disturbances exhibited higher serum irisin levels compared to normo-metabolic ALS patients and healthy controls. [91]

No studies have yet directly linked irisin to ALS, but given its anabolic effects on skeletal muscle and the muscle damage seen in ALS, irisin may hold potential as a biomarker for muscle degeneration in neurodegenerative diseases.

5. Irisin as a potential therapeutic factor

Correlation between irisin levels and particular exercise types

Irisin, being a myokine secreted by skeletal muscles during physical exercise and simultaneously promoting hippocampal neurogenesis, may mediate the beneficial effects of physical activity on the brain, thereby contributing to improvements in cognitive functions.[92-93] This suggests that exercise may represent an effective strategy for modulating irisin levels, gaining importance in the prevention and treatment of cognitive disorders. Research findings indicate that the exercise-induced increase in irisin levels is not uniform and depends on multiple variables, such as exercise intensity, type of physical activity, the individual's training status, duration of activity, and the timing of blood sample collection after exercise.

A study by Nygaard et al. demonstrated that both intense endurance exercise and heavy resistance training led to a transient increase in circulating irisin concentrations. Peak levels were observed immediately after endurance exercise and one hour after resistance training, followed by a gradual return to baseline values. Moreover, the increase in irisin concentration in response to resistance exercise consistently showed a strong negative correlation with lean body mass proportions.[94]

Similarly, Daskalopoulou et al. (2014) reported that irisin levels increased after exercise, with a greater rise observed at maximal workload.[95]

In the context of regular physical activity, numerous studies have also documented changes in irisin concentrations. In a systematic review and meta-analysis by Torabi et al., statistical analysis revealed a significant increase in serum irisin levels in overweight and obese individuals who engaged in exercise compared to a passive control group. High-intensity interval training (HIIT) exerted a more pronounced effect on increasing serum irisin levels than other types of exercise. Additionally, exercise effectiveness varied depending on participants' body mass status (significant changes in overweight individuals and non-significant changes in obese individuals), age (significant changes in individuals under 40 years of age and non-significant changes in those over 40), and sex (significant changes in men and non-significant changes in women).[96]

Studies conducted by Huh et al. also reported an increase in irisin levels immediately after high-intensity interval exercise (HIIE), continuous moderate exercise (CME), and resistance exercise (RE), followed by a decrease after one hour. The increase was greater in response to resistance exercise compared with high-intensity or continuous moderate exercise. Changes in irisin concentrations in response to exercise did not differ between individuals with and without metabolic syndrome.[97]

In research conducted by Cosio et al. (2023), an analysis of studies involving a single exercise session in healthy adults showed that continuous endurance training resulted in a significant increase in irisin levels, whereas interval training did not produce a significant change.[98]

Potential applications of irisin in therapy (experimental perspective)

Irisin exerts a significant influence on the pathogenesis of neurodegenerative diseases by modulating inflammation and oxidative stress, affecting energy metabolism and mitochondrial function, as well as pathways related to neuroplasticity and cognitive functions.[99-100] Consequently, interest in irisin as a therapeutic target for these disorders has increased.

Studies conducted by Bretland et al. demonstrated that irisin treatment significantly reduced levels of phosphorylated tau (PTAU) and TNFα in the hippocampus and serum of female HTAU mice compared to control groups, while no changes in PTAU levels were observed in male HTAU mice.[101]

Wang et al. reported that irisin administration stimulated the expression of mitochondrial transcription factor A (TFAM), thereby counteracting microglial aging and alleviating cognitive decline in P301S mice. This finding suggests a promising new avenue for therapeutic strategies targeting tauopathies.[102]

However, therapeutic applications of irisin remain largely at the experimental stage. Barriers to its clinical use include the lack of standardized dosing regimens and routes of administration in preclinical studies, as well as the absence of large-scale clinical trials confirming the efficacy and safety of such interventions. In practice, within the field of neurodegeneration, the most readily implementable application of the irisin concept remains exercise and movement-based therapy, whereas strictly "irisin-based" strategies should currently be regarded as a research direction rather than a clinical solution.

6. Conclusions

Available evidence indicates that irisin is a biologically plausible link between physical activity and neuroprotection in neurodegenerative diseases. Experimental studies demonstrate that FNDC5/irisin signaling influences the pathogenic processes of Alzheimers disease and Parkinsons disease and possibly amyotrophic lateral sclerosis. The signaling contributes to BDNF-dependent synaptic plasticity, reduces the α-synuclein and tau pathology, lowers oxidative stress by NRF2 activation, suppresses NF-κB-driven neuroinflammation, enhances mitochondrial function and cellular energy balance. The multimodal effect of irisin positions it as a molecule that targets several converging neurodegenerative pathways. Moreover, earlier studies indicate that an increase or restoration of FNDC5/irisin alleviates cognitive deficits, maintains dopamine neurons, and enhances behavior. The clinical studies indicate that the level of irisin in the blood is related to the severity of the disease and cognitive function, which could be a useful biomarker. Nevertheless, human studies remain limited and somewhat conflicting, hence there is a need to standardize measurement techniques and conduct proper long-term studies to establish cause-effect relationships and predictive value. Although mechanistic and experimental research shows potential, irisin-based pharmacological interventions are still in the primary investigative phase. Its receptor interactions have not been fully characterized, optimal therapeutic dosing has not been established, and there is inadequate clinical trial evidence to evaluate its effectiveness and safety. Overall, existing research findings justify further translational research of the FNDC5/irisin pathway as a promising diagnostic biomarker and therapeutic intervention in neurodegenerative diseases. Until pharmacological approaches are established, physical activity is still the most evidence-based and clinically feasible approach to regulate endogenous irisin levels and promote neuroprotective effects. More studies on the molecular mechanisms and clinical implications of irisin may contribute to the development of new mechanism-based therapies to prevent neurodegenerative disorders.

Disclosure

Author's contribution:

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References

1. Williams A. Defining neurodegenerative diseases. *BMJ*. 2002;324(7352):1465–1466. https://doi.org/10.1136/bmj.324.7352.1465

2. Ricci C. Neurodegenerative disease: from molecular basis to therapy, 2nd edition. *Int J Mol Sci*. 2025;26(5):1929. https://doi.org/10.3390/ijms26051929

3. Checkoway H, Lundin JI, Kelada SN. Neurodegenerative diseases. *IARC Sci Publ*. 2011;(163):407–419.

4. Veronese, N., Nova, A., Fazia, T., Riggi, E., Yang, L., Piccio, L., Huang, B. H., Ahmadi, M., Barbagallo, M., Notarnicola, M., Giannelli, G., De Pergola, G., Stamatakis, E., Cereda, E., Bernardinelli, L., & Fontana, L. (2024). Contribution of Nutritional, Lifestyle, and Metabolic Risk Factors to Parkinson's Disease. *Movement disorders : official journal of the Movement Disorder Society*, *39*(7), 1203–1212. https://doi.org/10.1002/mds.29778

5. Heemels MT. Neurodegenerative diseases. *Nature*. 2016;539(7628):179. https://doi.org/10.1038/539179a

6. Di Liegro CM, Schiera G, Proia P, Di Liegro I. Physical activity and brain health. *Genes (Basel)*. 2019;10(9):720. https://doi.org/10.3390/genes10090720

7. Bonanni, R., Cariati, I., Tarantino, U., D'Arcangelo, G., & Tancredi, V. (2022). Physical Exercise and Health: A Focus on Its Protective Role in Neurodegenerative Diseases. *Journal of functional morphology and kinesiology*, *7*(2), 38. https://doi.org/10.3390/jfmk7020038

8. Liu, Y., Yan, T., Chu, J. M., Chen, Y., Dunnett, S., Ho, Y. S., Wong, G. T., & Chang, R. C. (2019). The beneficial effects of physical exercise in the brain and related pathophysiological mechanisms in neurodegenerative diseases. *Laboratory investigation; a journal of technical methods and pathology*, *99*(7), 943–957. https://doi.org/10.1038/s41374-019-0232-y

9. Huang, L. Y., Ou, Y. N., Yang, Y. X., Wang, Z. T., Tan, L., & Yu, J. T. (2023). Associations of cardiovascular risk factors and lifestyle behaviors with neurodegenerative disease: a Mendelian randomization study. *Translational psychiatry*, *13*(1), 267. https://doi.org/10.1038/s41398-023-02553-9

10. Vints WAJ, Gökçe E, Langeard A, et al. Myokines as mediators of exercise-induced cognitive changes in older adults: protocol for a comprehensive living systematic review and meta-analysis. *Front Aging Neurosci*. 2023;15:1213057. https://doi.org/10.3389/fnagi.2023.1213057

11. Oudbier SJ, Goh J, Looijaard SMLM, et al. Pathophysiological mechanisms explaining the association between low skeletal muscle mass and cognitive function. *J Gerontol A Biol Sci Med Sci*. 2022;77(10):1959–1968. https://doi.org/10.1093/gerona/glac121

12. Küster OC, Laptinskaya D, Fissler P, et al. Novel blood-based biomarkers of cognition, stress, and physical or cognitive training in older adults at risk of dementia. *J Alzheimers Dis*. 2017;59(3):1097–1111. https://doi.org/10.3233/JAD-170447

13. Zhang Y, Zhang X, Lin S. Irisin: a bridge between exercise and neurological diseases. *Heliyon*. 2022;8(12):e12352. https://doi.org/10.1016/j.heliyon.2022.e12352

14. Ferrer-Martínez, A., Ruiz-Lozano, P., & Chien, K. R. (2002). Mouse PeP: a novel peroxisomal protein linked to myoblast differentiation and development. *Developmental dynamics : an official publication of the American Association of Anatomists*, *224*(2), 154–167. https://doi.org/10.1002/dvdy.10099

15. Teufel, A., Malik, N., Mukhopadhyay, M., & Westphal, H. (2002). Frcp1 and Frcp2, two novel fibronectin type III repeat containing genes. *Gene*, *297*(1-2), 79–83. https://doi.org/10.1016/s0378-1119(02)00828-4

16. Boström P, Wu J, Jedrychowski MP, et al. A PGC1-α-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. *Nature*. 2012;481(7382):463–468. https://doi.org/10.1038/nature10777

17. Aydin S, Kuloglu T, Aydin S, et al. A comprehensive immunohistochemical examination of the distribution of the fat-burning protein irisin in biological tissues. *Peptides*. 2014;61:130–136. https://doi.org/10.1016/j.peptides.2014.09.014

18. Flori L, Testai L, Calderone V. The "irisin system": from biological roles to pharmacological and nutraceutical perspectives. *Life Sci*. 2021;267:118954. https://doi.org/10.1016/j.lfs.2020.118954

19. Jedrychowski MP, Wrann CD, Paulo JA, et al. Detection and quantitation of circulating human irisin by tandem mass spectrometry. *Cell Metab*. 2015;22(4):734–740. https://doi.org/10.1016/j.cmet.2015.08.001

20. Lee P, Linderman JD, Smith S, et al. Irisin and FGF21 are cold-induced endocrine activators of brown fat function in humans. *Cell Metab*. 2014;19(2):302–309. https://doi.org/10.1016/j.cmet.2013.12.017

21. Roca-Rivada A, Castelao C, Senin LL, et al. FNDC5/irisin is not only a myokine but also an adipokine. *PLoS One*. 2013;8(4):e60563. https://doi.org/10.1371/journal.pone.0060563

22. Wang YT, Zheng SY, Jiang SD, et al. Irisin in degenerative musculoskeletal diseases: functions in system and potential in therapy. *Pharmacol Res*. 2024;210:107480. https://doi.org/10.1016/j.phrs.2024.107480

23. Lourenco MV, Frozza RL, de Freitas GB, et al. Exercise-linked FNDC5/irisin rescues synaptic plasticity and memory defects in Alzheimer's models. *Nat Med*. 2019;25(1):165–175. https://doi.org/10.1038/s41591-018-0275-4

24. Kim H, Wrann CD, Jedrychowski M, et al. Irisin mediates effects on bone and fat via αV integrin receptors. *Cell*. 2018;175(7):1756–1768.e17. https://doi.org/10.1016/j.cell.2018.10.025

25. Hynes RO. Integrins: bidirectional, allosteric signaling machines. *Cell*. 2002;110(6):673–687. https://doi.org/10.1016/S0092-8674(02)00971-6

26. Rabiee F, Lachinani L, Ghaedi S, et al. New insights into the cellular activities of FNDC5/irisin and its signaling pathways. *Cell Biosci*. 2020;10:51.

https://doi.org/10.1186/s13578-020-00413-3

27. Shi H, Hao X, Sun Y, et al. Exercise-inducible circulating extracellular vesicle irisin promotes browning and the thermogenic program in white adipose tissue. *Acta Physiol (Oxf)*. 2024;240(1):e14103. https://doi.org/10.1111/apha.14103

28. Slate-Romano JJ, Yano N, Zhao TC. Irisin reduces inflammatory signaling pathways in inflammation-mediated metabolic syndrome. *Mol Cell Endocrinol*. 2022;552:111676. https://doi.org/10.1016/j.mce.2022.111676

29. Mazur-Bialy AI, Pocheć E, Zarawski M. Anti-inflammatory properties of irisin, mediator of physical activity, are connected with TLR4/MyD88 signaling pathway activation. *Int J Mol Sci*. 2017;18(4):701. https://doi.org/10.3390/ijms18040701

30. de Oliveira Bristot VJ, de Bem Alves AC, Cardoso LR, et al. The role of PGC-1α/UCP2 signaling in the beneficial effects of physical exercise on the brain. *Front Neurosci*. 2019;13:292. https://doi.org/10.3389/fnins.2019.00292

31. Kornel A, den Hartogh DJ, Klentrou P, Tsiani E. Role of the myokine irisin on bone homeostasis: review of the current evidence. *Int J Mol Sci*. 2021;22(17):9136. https://doi.org/10.3390/ijms22179136

32. Polyzos SA, Anastasilakis AD, Efstathiadou ZA, et al. Irisin in metabolic diseases. *Endocrine*. 2018;59(2):260–274. https://doi.org/10.1007/s12020-017-1476-1

33. Colaianni G, Cuscito C, Mongelli T, et al. The myokine irisin increases cortical bone mass. *Proc Natl Acad Sci U S A*. 2015;112(39):12157–12162. https://doi.org/10.1073/pnas.1516622112

34. Liu C, Wei A, Wang T. Irisin, an effective treatment for cardiovascular diseases? *J Cardiovasc Dev Dis*. 2022;9(9):305. https://doi.org/10.3390/jcdd9090305

35. Wrann CD, White JP, Salogiannis J, et al. Exercise induces hippocampal BDNF through a PGC-1α/FNDC5 pathway. *Cell Metab*.2013;18(5):649–659. https://doi.org/10.1016/j.cmet.2013.09.008

36. Korta P, Pocheć E, Mazur-Biały A. Irisin as a multifunctional protein: implications for health and certain diseases. *Medicina (Kaunas)*. 2019;55(8):485. https://doi.org/10.3390/medicina55080485

37. Moon HS, Dincer F, Mantzoros CS. Pharmacological concentrations of irisin increase cell proliferation without influencing markers of neurite outgrowth and synaptogenesis. *Metabolism*. 2013;62(8):1131–1136.

https://doi.org/10.1016/j.metabol.2013.04.007

38. Qi JY, Yang LK, Wang XS, et al. Irisin: a promising treatment for neurodegenerative diseases. *Neuroscience*. 2022;498:289–299. https://doi.org/10.1016/j.neuroscience.2022.07.018

39. Pesce M, Ballerini P, Paolucci T, et al. Irisin and autophagy: first update. *Int J Mol Sci*. 2020;21(20):7587. https://doi.org/10.3390/ijms21207587

40. Jin Z, Guo P, Li X, et al. Neuroprotective effects of irisin against cerebral ischemia/reperfusion injury via Notch signaling pathway. *Biomed Pharmacother*. 2019;120:109452. https://doi.org/10.1016/j.biopha.2019.109452

41. Li DJ, Li YH, Yuan HB, et al. The novel exercise-induced hormone irisin protects against neuronal injury via activation of the Akt and ERK1/2 signaling pathways. *Metabolism*. 2017;68:31–42. https://doi.org/10.1016/j.metabol.2016.12.003

42. Scheltens P, De Strooper B, Kivipelto M, et al. Alzheimer's disease. *Lancet*. 2021;397(10284):1577–1590. https://doi.org/10.1016/S0140-6736(20)32205-4

43. Cattaneo C, Jost WH. Pain in Parkinson's disease: pathophysiology, classification and treatment. *J Integr Neurosci*. 2023;22(5):132. https://doi.org/10.31083/j.jin2205132

44. Day JO, Mullin S. The genetics of Parkinson's disease and implications for clinical practice. *Genes (Basel)*. 2021;12(7):1006. https://doi.org/10.3390/genes12071006

45. Eisen A, Vucic S, Mitsumoto H. History of ALS and the competing theories on pathogenesis. *Clin Neurophysiol Pract*. 2023;9:1–12. https://doi.org/10.1016/j.cnp.2023.11.004

46. Teleanu DM, Niculescu AG, Lungu II, et al. An overview of oxidative stress, neuroinflammation, and neurodegenerative diseases. *Int J Mol Sci*. 2022;23(11):5938. https://doi.org/10.3390/ijms23115938

47. Zhang XX, Tian Y, Wang ZT, et al. The epidemiology of Alzheimer's disease modifiable risk factors and prevention. *J Prev Alzheimers Dis.* 2021;8(3):313–321. https://doi.org/10.14283/jpad.2021.15

48. 2023 Alzheimer's disease facts and figures. *Alzheimers Dement.* 2023;19(4):1598–1695. https://doi.org/10.1002/alz.13016

49. Quinn, L.S., Anderson, B.G., Conner, J.D. *et al.* Circulating irisin levels and muscle FNDC5 mRNA expression are independent of IL-15 levels in mice. *Endocrine* 50, 368–

377 (2015). https://doi.org/10.1007/s12020-015-0607-9

50. Piya, M. K., Harte, A. L., Sivakumar, K., Tripathi, G., Voyias, P. D., James, S., Sabico, S., Al-Daghri, N. M., Saravanan, P., Barber, T. M., Kumar, S., Vatish, M., & McTernan, P. G. (2014). The identification of irisin in human cerebrospinal fluid: influence of adiposity, metabolic markers, and gestational diabetes. *American journal of physiology. Endocrinology and metabolism*, *306*(5), E512–E518. https://doi.org/10.1152/ajpendo.00308.2013

51. Phillips, C., Baktir, M. A., Srivatsan, M., & Salehi, A. (2014). Neuroprotective effects of physical activity on the brain: a closer look at trophic factor signaling. *Frontiers in cellular neuroscience*, *8*, 170. https://doi.org/10.3389/fncel.2014.00170

52. Lourenco, M. V., Frozza, R. L., de Freitas, G. B., Zhang, H., Kincheski, G. C., Ribeiro, F. C., Gonçalves, R. A., Clarke, J. R., Beckman, D., Staniszewski, A., Berman, H., Guerra, L. A., Forny-Germano, L., Meier, S., Wilcock, D. M., de Souza, J. M., Alves-Leon, S., Prado, V. F., Prado, M. A. M., Abisambra, J. F., … De Felice, F. G. (2019). Exercise-linked FNDC5/irisin rescues synaptic plasticity and memory defects in Alzheimer's models. *Nature medicine*, *25*(1), 165–175. https://doi.org/10.1038/s41591-018-0275-4

53. Hashemi, M. S., Ghaedi, K., Salamian, A., Karbalaie, K., Emadi-Baygi, M., Tanhaei, S., Nasr-Esfahani, M. H., & Baharvand, H. (2013). Fndc5 knockdown significantly decreased neural differentiation rate of mouse embryonic stem cells. *Neuroscience*, *231*, 296–304. https://doi.org/10.1016/j.neuroscience.2012.11.041

54. Moon, H. S., Dincer, F., & Mantzoros, C. S. (2013). Pharmacological concentrations of irisin increase cell proliferation without influencing markers of neurite outgrowth and synaptogenesis in mouse H19-7 hippocampal cell lines. *Metabolism: clinical and experimental*, *62*(8), 1131–1136. https://doi.org/10.1016/j.metabol.2013.04.007

55. Li, D. J., Li, Y. H., Yuan, H. B., Qu, L. F., & Wang, P. (2017). The novel exercise-induced hormone irisin protects against neuronal injury via activation of the Akt and ERK1/2 signaling pathways and contributes to the neuroprotection of physical exercise in cerebral ischemia. *Metabolism: clinical and experimental*, *68*, 31–42. https://doi.org/10.1016/j.metabol.2016.12.003

56. Jackson, T.C., Gorse, K., Herrmann, J.R. *et al.* Hippocampal and Prefrontal Cortical Brain Tissue Levels of Irisin and GDF15 Receptor Subunits in Children. *Mol Neurobiol* 58, 2145–2157 (2021). https://doi.org/10.1007/s12035-020-02250-4

57. Toyama, E. Q., Herzig, S., Courchet, J., Lewis, T. L., Jr, Losón, O. C., Hellberg, K., Young, N. P., Chen, H., Polleux, F., Chan, D. C., & Shaw, R. J. (2016). Metabolism. AMP-activated protein kinase mediates mitochondrial fission in response to energy stress.

Science (New York, N.Y.), *351*(6270), 275–281. https://doi.org/10.1126/science.aab4138

58. Zhang, W., Chang, L., Zhang, C., Zhang, R., Li, Z., Chai, B., Li, J., Chen, E., & Mulholland, M. (2015). Irisin: A myokine with locomotor activity. *Neuroscience letters*, *595*, 7–11. https://doi.org/10.1016/j.neulet.2015.03.069

59. Wrann, C. D., White, J. P., Salogiannnis, J., Laznik-Bogoslavski, D., Wu, J., Ma, D., Lin, J. D., Greenberg, M. E., & Spiegelman, B. M. (2013). Exercise induces hippocampal BDNF through a PGC-1α/FNDC5 pathway. *Cell metabolism*, *18*(5), 649–659. https://doi.org/10.1016/j.cmet.2013.09.008

60. Diniz, B. S., & Teixeira, A. L. (2011). Brain-derived neurotrophic factor and Alzheimer's disease: physiopathology and beyond. *Neuromolecular medicine*, *13*(4), 217–222. https://doi.org/10.1007/s12017-011-8154-x

61. Arancibia, S., Silhol, M., Moulière, F., Meffre, J., Höllinger, I., Maurice, T., & Tapia-Arancibia, L. (2008). Protective effect of BDNF against beta-amyloid induced neurotoxicity in vitro and in vivo in rats. *Neurobiology of disease*, *31*(3), 316–326. https://doi.org/10.1016/j.nbd.2008.05.012

62. Guillin, O., Griffon, N., Bezard, E., Leriche, L., Diaz, J., Gross, C., & Sokoloff, P. (2003). Brain-derived neurotrophic factor controls dopamine D3 receptor expression: therapeutic implications in Parkinson's disease. *European journal of pharmacology*, *480*(1-3), 89–95. https://doi.org/10.1016/j.ejphar.2003.08.096

63. Camandola, S., & Mattson, M. P. (2017). Brain metabolism in health, aging, and neurodegeneration. *The EMBO journal*, *36*(11), 1474–1492. https://doi.org/10.15252/embj.201695810

64. Yan, Q. S., Feng, M. J., & Yan, S. E. (2005). Different expression of brain-derived neurotrophic factor in the nucleus accumbens of alcohol-preferring (P) and -nonpreferring (NP) rats. *Brain research*, *1035*(2), 215–218. https://doi.org/10.1016/j.brainres.2004.12.039

65. Lee, J., Duan, W., & Mattson, M. P. (2002). Evidence that brain-derived neurotrophic factor is required for basal neurogenesis and mediates, in part, the enhancement of neurogenesis by dietary restriction in the hippocampus of adult mice. *Journal of neurochemistry*, *82*(6), 1367–1375. https://doi.org/10.1046/j.1471-4159.2002.01085.x

66. Zsuga, J., Tajti, G., Papp, C., Juhasz, B., & Gesztelyi, R. (2016). FNDC5/irisin, a molecular target for boosting reward-related learning and motivation. *Medical hypotheses*, *90*, 23–28. https://doi.org/10.1016/j.mehy.2016.02.020

67. Chen, Z. Y., Cao, L., Wang, L. M., Guo, C., Ye, J. L., Chai, Y. F., & Yan, Z. Y. (2001). Development of neurotrophic molecules for treatment of neurodegeneration. *Current protein & peptide science*, *2*(3), 261–276. https://doi.org/10.2174/1389203013381125

68. Liu, P., Zou, D., Yi, L., Chen, M., Gao, Y., Zhou, R., Zhang, Q., Zhou, Y., Zhu, J., Chen, K., & Mi, M. (2015). Quercetin ameliorates hypobaric hypoxia-induced memory impairment through mitochondrial and neuron function adaptation via the PGC-1α pathway. *Restorative neurology and neuroscience*, *33*(2), 143–157. https://doi.org/10.3233/RNN-140446

69. Nagahara, A. H., Merrill, D. A., Coppola, G., Tsukada, S., Schroeder, B. E., Shaked, G. M., Wang, L., Blesch, A., Kim, A., Conner, J. M., Rockenstein, E., Chao, M. V., Koo, E. H., Geschwind, D., Masliah, E., Chiba, A. A., & Tuszynski, M. H. (2009). Neuroprotective effects of brain-derived neurotrophic factor in rodent and primate models of Alzheimer's disease. *Nature medicine*, *15*(3), 331–337. https://doi.org/10.1038/nm.1912

70. Longo, F. M., Yang, T., Knowles, J. K., Xie, Y., Moore, L. A., & Massa, S. M. (2007). Small molecule neurotrophin receptor ligands: novel strategies for targeting Alzheimer's disease mechanisms. *Current Alzheimer research*, *4*(5), 503–506. https://doi.org/10.2174/156720507783018316

71. Jedrychowski, M. P., Wrann, C. D., Paulo, J. A., Gerber, K. K., Szpyt, J., Robinson, M. M., Nair, K. S., Gygi, S. P., & Spiegelman, B. M. (2015). Detection and Quantitation of Circulating Human Irisin by Tandem Mass Spectrometry. *Cell metabolism*, *22*(4), 734–740. https://doi.org/10.1016/j.cmet.2015.08.001

72. De la Rosa, A., Olaso-Gonzalez, G., Arc-Chagnaud, C., Millan, F., Salvador-Pascual, A., García-Lucerga, C., Blasco-Lafarga, C., Garcia-Dominguez, E., Carretero, A., Correas, A. G., Viña, J., & Gomez-Cabrera, M. C. (2020). Physical exercise in the prevention and treatment of Alzheimer's disease. *Journal of sport and health science*, *9*(5), 394–404. https://doi.org/10.1016/j.jshs.2020.01.004

73. Puig, K. L., Floden, A. M., Adhikari, R., Golovko, M. Y., & Combs, C. K. (2012). Amyloid precursor protein and proinflammatory changes are regulated in brain and adipose tissue in a murine model of high fat diet-induced obesity. *PloS one*, *7*(1), e30378. https://doi.org/10.1371/journal.pone.0030378

74. Zhang, T., Pan, B. S., Zhao, B., Zhang, L. M., Huang, Y. L., & Sun, F. Y. (2009). Exacerbation of poststroke dementia by type 2 diabetes is associated with synergistic increases of beta-secretase activation and beta-amyloid generation in rat brains. *Neuroscience*, *161*(4), 1045–1056. https://doi.org/10.1016/j.neuroscience.2009.04.032

75. Droogsma, E., van Asselt, D., Bieze, H., Veeger, N., & De Deyn, P. P. (2015). The relationship of weight change trajectory with medial temporal lobe atrophy in patients with

mild Alzheimer's disease: results from a cohort study. *Alzheimer's research & therapy*, *7*(1), 18. https://doi.org/10.1186/s13195-015-0098-1

76. Park, K. H., Zaichenko, L., Peter, P., Davis, C. R., Crowell, J. A., & Mantzoros, C. S. (2014). Diet quality is associated with circulating C-reactive protein but not irisin levels in humans. *Metabolism: clinical and experimental*, *63*(2), 233–241. https://doi.org/10.1016/j.metabol.2013.10.011

77. Choi, Y. K., Kim, M. K., Bae, K. H., Seo, H. A., Jeong, J. Y., Lee, W. K., Kim, J. G., Lee, I. K., & Park, K. G. (2013). Serum irisin levels in new-onset type 2 diabetes. *Diabetes research and clinical practice*, *100*(1), 96–101. https://doi.org/10.1016/j.diabres.2013.01.007

78. Xiong, X. Q., Chen, D., Sun, H. J., Ding, L., Wang, J. J., Chen, Q., Li, Y. H., Zhou, Y. B., Han, Y., Zhang, F., Gao, X. Y., Kang, Y. M., & Zhu, G. Q. (2015). FNDC5 overexpression and irisin ameliorate glucose/lipid metabolic derangements and enhance lipolysis in obesity. *Biochimica et biophysica acta*, *1852*(9), 1867–1875. https://doi.org/10.1016/j.bbadis.2015.06.017

79. GBD 2016 Parkinson's Disease Collaborators. Global, regional, and national burden of Parkinson's disease, 1990–2016: a systematic analysis. *Lancet Neurol.* 2018;17(11):939–953. https://doi.org/10.1016/S1474-4422(18)30295-3

80. Tolosa E, Garrido A, Scholz SW, Poewe W. Challenges in the diagnosis of Parkinson's disease. *Lancet Neurol.* 2021;20(5):385–397. https://doi.org/10.1016/S1474-4422(21)00030-2

81. Johansson, M. E., Cameron, I. G. M., Van der Kolk, N. M., de Vries, N. M., Klimars, E., Toni, I., Bloem, B. R., & Helmich, R. C. (2022). Aerobic Exercise Alters Brain Function and Structure in Parkinson's Disease: A Randomized Controlled Trial. *Annals of neurology*, *91*(2), 203–216. https://doi.org/10.1002/ana.26291

82. Tsukita, K., Sakamaki-Tsukita, H., & Takahashi, R. (2022). Long-term Effect of Regular Physical Activity and Exercise Habits in Patients With Early Parkinson Disease. *Neurology*, *98*(8), e859–e871. https://doi.org/10.1212/WNL.0000000000013218

83. Kam TI, Park H, Chou SC, et al. Amelioration of pathologic alpha-synuclein-induced Parkinson's disease by irisin. *Proc Natl Acad Sci U S A.* 2022;119(36):e2204835119. https://doi.org/10.1073/pnas.2204835119

84. Zarbakhsh, S., Safari, M., Aldaghi, M. R., Sameni, H. R., Ghahari, L., Khaleghi Lagmouj, Y., Rahimi Jaberi, K., & Parsaie, H. (2019). Irisin protects the substantia nigra dopaminergic neurons in the rat model of Parkinson's disease. *Iranian journal of basic*

medical sciences, *22*(7), 722–728. https://doi.org/10.22038/ijbms.2019.33444.7987

85. Shi X, Gu Q, Fu C, et al. Relationship of irisin with disease severity and dopamine uptake in Parkinson's disease. *Neuroimage Clin.* 2024;41:103555. https://doi.org/10.1016/j.nicl.2023.103555

86. Xu, X., He, X., Ma, S., Li, M., & Huang, Q. (2021). Nurr1 downregulation is caused by CREB inactivation in a Parkinson's disease mouse model. *Neuroscience letters*, *759*, 136045. https://doi.org/10.1016/j.neulet.2021.136045

87. Zhu, M., Peng, Q., Li, S., Zhang, G., & Zhang, Z. (2025). Irisin promotes autophagy and attenuates NLRP3 inflammasome activation in Parkinson's disease. *International immunopharmacology*, *149*, 114201. https://doi.org/10.1016/j.intimp.2025.114201

88. Kwon, H.S., Koh, SH. Neuroinflammation in neurodegenerative disorders: the roles of microglia and astrocytes. *Transl Neurodegener* 9, 42 (2020). https://doi.org/10.1186/s40035-020-00221-2

89. Bayer H, Lang K, Buck E, et al. ALS-causing mutations affect PGC-1α expression. *Neurobiol Dis.* 2017;97(Pt A):36–45. https://doi.org/10.1016/j.nbd.2016.11.001

90. Petri S, Körner S, Kiaei M. Nrf2/ARE signaling pathway in ALS. *Neurol Res Int.* 2012;2012:878030. https://doi.org/10.1155/2012/878030

91. Lunetta C, Lizio A, Tremolizzo L, et al. Serum irisin in ALS patients. *J Neurol.* 2018;265(12):3001–3008. https://doi.org/10.1007/s00415-018-9093-3

92. Pignataro, P., Dicarlo, M., Zerlotin, R., Zecca, C., Dell'Abate, M. T., Buccoliero, C., Logroscino, G., Colucci, S., & Grano, M. (2021). FNDC5/Irisin System in Neuroinflammation and Neurodegenerative Diseases: Update and Novel Perspective. *International journal of molecular sciences*, *22*(4), 1605. https://doi.org/10.3390/ijms22041605

93. Young, M. F., Valaris, S., & Wrann, C. D. (2019). A role for FNDC5/Irisin in the beneficial effects of exercise on the brain and in neurodegenerative diseases. *Progress in cardiovascular diseases*, *62*(2), 172–178. https://doi.org/10.1016/j.pcad.2019.02.007

94. Nygaard H, Slettaløkken G, Vegge G, et al. Irisin in blood increases transiently after single sessions of intense endurance exercise and heavy strength training. *PLoS One.* 2015;10(3):e0121367. https://doi.org/10.1371/journal.pone.0121367

95. Daskalopoulou SS, Cooke AB, Gomez YH, et al. Plasma irisin levels progressively increase in response to increasing exercise workloads. *Eur J Endocrinol.*

2014;171(3):343–352. https://doi.org/10.1530/EJE-14-0204

96. Torabi, A., Reisi, J., Kargarfard, M., & Mansourian, M. (2024). Differences in the Impact of Various Types of Exercise on Irisin Levels: A Systematic Review and Meta-Analysis. *International journal of preventive medicine*, *15*, 11. https://doi.org/10.4103/ijpvm.ijpvm_76_23

97. Huh, J. Y., Panagiotou, G., Mougios, V., Brinkoetter, M., Vamvini, M. T., Schneider, B. E., & Mantzoros, C. S. (2012). FNDC5 and irisin in humans: I. Predictors of circulating concentrations in serum and plasma and II. mRNA expression and circulating concentrations in response to weight loss and exercise. *Metabolism: clinical and experimental*, *61*(12), 1725–1738. https://doi.org/10.1016/j.metabol.2012.09.002

98. Cosio, P. L., Pelaez, M., Cadefau, J. A., & Farran-Codina, A. (2023). Systematic Review and Meta-Analysis of Circulating Irisin Levels Following Endurance Training: Results of Continuous and Interval Training. *Biological research for nursing*, *25*(3), 367–381. https://doi.org/10.1177/10998004221142580

99. Muzaffar S, Tyagi A, Pugazhenthi S. Therapeutic Potential of Irisin in Neurodegenerative Diseases. *International Journal of Molecular Sciences*. 2025; 26(23):11348. https://doi.org/10.3390/ijms262311348

100. Minuti, A., Raffaele, I., Scuruchi, M., Lui, M., Muscarà, C., & Calabrò, M. (2025). Role and Functions of Irisin: A Perspective on Recent Developments and Neurodegenerative Diseases. *Antioxidants (Basel, Switzerland)*, *14*(5), 554. https://doi.org/10.3390/antiox14050554

101. Bretland, K. A., Lin, L., Bretland, K. M., Smith, M. A., Fleming, S. M., & Dengler-Crish, C. M. (2021). Irisin treatment lowers levels of phosphorylated tau in the hippocampus of pre-symptomatic female but not male htau mice. *Neuropathology and applied neurobiology*, *47*(7), 967–978. https://doi.org/10.1111/nan.12711

102. Wang, C., Wang, X., Sun, S., Chang, Y., Lian, P., Guo, H., Zheng, S., Ma, R., & Li, G. (2024). Irisin inhibits microglial senescence via TFAM-mediated mitochondrial metabolism in a mouse model of tauopathy. *Immunity & ageing : I & A*, *21*(1), 30. https://doi.org/10.1186/s12979-024-00437-0