 doi:10.20944/preprints201712.0023.v1

Review

Does Irisin Link Physical Exercise with Alzheimer's Disease?

Dewan Md. Sumsuzzman [1,2,3], Yunho Jin [1,2,3], Yonggeun Hong [1,2,3,4,*]

[1] Department of Rehabilitation Science, Graduate School of Inje University, Gimhae, Korea; dewanpavelpharm@gmail.com (D.Md.S); jynh33@naver.com (Y.J.)
[2] Biohealth Products Research Center (BPRC), Inje University, Gimhae, Korea
[3] Ubiquitous Healthcare & Anti-aging Research Center (u-HARC), Inje University, Gimhae, Korea
[4] Department of Physical Therapy, College of Healthcare Medical Science & Engineering, Gimhae, Korea
* Correspondence: Yonggeun Hong(DVM, PhD); Mailing address: Department of Rehabilitation Science, Graduate School of Inje University, Inje University, 197 Inje-ro, Gimhae, Gyeongnam 50834, Republic of Korea; Tel.: +82-55-320-3681; Fax: +82-55-329-1678; E-mail: yonghong@inje.ac.kr(yonguary12@gmail.com)

Abstract: The skeletal muscle-secreted myokine irisin, which is produced in response to physical exercise, has several protective functions both in the central and peripheral nervous systems, including regulation of brain-derived neurotrophic factor, modification of telomere length, inhibition of the endoplasmic reticulum stress response, and anti-inflammatory and anti-apoptotic effects that may be of benefit in neurodegenerative diseases such as Alzheimer's disease (AD). The present review is based on the hypothesis that irisin connects physical exercise with AD progression. We herein describe current knowledge of the physiology of irisin and its potential role in AD. We conclude that, although current and ongoing research on irisin is very promising, further research is required to clarify its potential as a meaningful target for drugs to treat human diseases.

Keywords: physical exercise; irisin; neurodegeneration; aging; Alzheimer's disease

1. Introduction

Alzheimer's disease (AD) is a devastating age-associated neurodegenerative disorder characterized by progressive cognitive and functional decline. Extracellular amyloid-β (Aβ) aggregation and intracellular neurofibrillary tangles are considered the pathological hallmarks of AD. Notwithstanding several previous studies, the etiology of AD is largely unknown. However, a series of neurodegenerative events in the hippocampus, as well as microglial activation, neuroinflammation, oxidative stress, metabolic energy failure, and consequent neuronal apoptosis are believed to be closely correlated with the pathogenesis of AD [1–6].

Physical exercise is currently advocated as a behavioral intervention to ameliorate neurological impairments [7]; however, the precise cellular mechanism remains elusive. Many studies have highlighted the effects of exercise in various organs, such as the liver, brain, adipose tissue, and heart. Unlike other organs, skeletal muscle is directly affected by exercise [8]. Skeletal muscle has been identified as a secretary organ since it produces and releases cytokines and other peptides that function similarity to hormones [9]. These secretions may underlie the beneficial effects of exercise. The identification of several hundred components in the 'secretome' of skeletal muscle provides the basis for understanding how muscle communicates with other organs [8]. Irisin was recently identified as a muscle-derived myokine is released from skeletal muscle immediately after exercise. In this review, we discuss the plausible mechanism of the protective effects of irisin against AD.

 doi:10.20944/preprints201712.0023.v1

2. Association between neuroinflammation and AD

Neuroinflammation in AD is characterized by glial activation and the release of inflammatory mediators, which provoke a ferocious cycle of neuroinflammatory attack [10]. As the first defensive response against brain injury, microglia shows their diverse phenotypes in response to specific signals from the microenvironment [11]. Two major phenotypes of activated microglia have been proposed: 1) a classically activated M1 pro-inflammatory phenotype that releases destructive pro-inflammatory mediators (e.g., interleukin [IL]-1β, IL-6, and tumor necrosis factor [TNF]-alpha, and 2) a selectively activated M2 repair/anti-inflammatory phenotype that secretes neuroprotective, anti-inflammatory factors (e.g., IL-4 and IL-10) [10, 11]. Interestingly, divergent roles for M1 and M2 polarized microglia have been reported in several neurodegenerative diseases, including AD, stroke, and spinal cord injury [11, 14–16], which raise the possibility that modulation of the microglial phenotype could yield translational benefits in these neurodegenerative disorders.

In addition to a role for neuroinflammation, there is adequate evidence that oxidative stress plays an important pathogenic role in AD [17–19]. It was previously demonstrated that oxidative stress leads to irreversible impairment of biological systems due to the oxidation of most of the major biomolecules in cells, including DNA, RNA, proteins, and lipids [20]. In fact, oxidation leading to a buildup of damaging oxidative byproducts has been consistently reported in AD progression, surprisingly at the preliminary stage before crucial senile plaques have formed [21–23]. Furthermore, the accumulation of reactive oxygen species in mitochondria causes subsequent destruction of the electron transfer chain leading to metabolic energy failure and mitochondrial dysfunction [24–26], which is crucial in AD pathology [27, 28].

3. Irisin as a mediator of the beneficial effects of exercise on the brain

Exercise, particularly endurance exercise, has salutary effects on brain health and cognitive function [29-31]. The improvement in cognitive function following exercise may be beneficial to older adults [32]. Exercise has also been reported to ameliorate negative outcomes in neurological diseases, such as depression, epilepsy, stroke, AD, and Parkinson's disease (PD) [33–38]. The beneficial effects of exercise on the brain are most discernible in the hippocampus and its dentate gyrus, a region of the brain associated with learning and memory. The markedly favorable effects of exercise on the brain include increases in the size of, and blood flow to, the hippocampus in humans, morphological variations in dendrites and dendritic spines, increased synaptic plasticity and, importantly, de novo neurogenesis in the dentate gyrus in various animal models [29, 30]. De novo neurogenesis in the mature brain is believed to occur in only two areas, one of which is the dentate gyrus of the hippocampus; exercise is one of the few known stimuli of this de novo neurogenesis [39].

The discovery of the "exercise hormone" irisin has attracted a great deal of attention [40]. Irisin was identified as a communicator between skeletal muscle and adipocytes; thus, it acts as a potent messenger of the positive effects of physical exercise on target organs other than muscle [41] (Figure 1). Human studies have demonstrated that 10 weeks of physical training resulted in increased plasma levels of irisin [40]. Subsequent studies substantiated acute exercise-altered irisin levels [42, 43]. The results were, however, more equivocal with respect to physical training interventions delivered over several weeks [44–47]. The observations that irisin administration increased the proliferation of hippocampal cells in vitro [48], and that the expression of fibronectin type III domain-containing 5 (FNDC5) resulted in elevated irisin concentrations and brain-derived neurotropic factor (BDNF) gene expression in culture [49], suggest that irisin could be a therapeutic target in neurodegenerative disorders [50–52].

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 4 December 2017 doi:10.20944/preprints201712.0023.v1

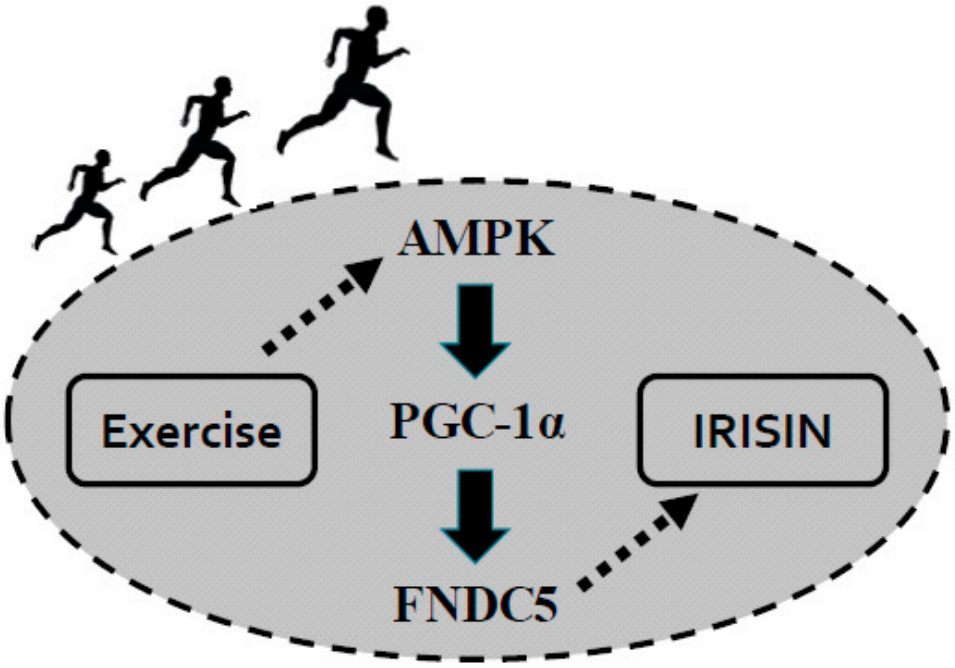

Figure 1. Mechanisms of irisin biogenesis in the human body. 5′-adenosine monophosphate-activated protein kinase (AMPK) leads to the creation of proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α). In turn, fibronectin type III domain-containing 5 (FNDC5) is expressed during prolonged exercise. FNDC5 is cleaved by an unknown peptidase and secreted as irisin.

4. Irisin

Irisin, a newly discovered skeletal muscle-derived myokine secreted during exercise, is also synthesized in various tissues of different species [53]. It is secreted from FNDC5 after cleavage of its extracellular portion [54]. The production of irisin occurs similarly to the shedding and release of other hormones and hormone-like polypeptides, such as epidermal growth factor and transforming growth factor α, from transmembrane precursors. After the N-terminal signal peptide is withdrawn, the peptide is proteolytically cleaved from the C-terminal moiety, glycosylated, and released as a hormone of 112 amino acids. This molecule upregulates uncoupling protein 1 (UCP1) and transforms white adipose tissue (WAT) into brown adipose tissue (BAT), thereby increasing thermogenesis and the energy consumption of adipose tissue [51]. In addition, it ameliorates insulin resistance, lowers blood glucose, and promotes weight loss. Studies have shown that irisin further encourages cell proliferation and inhibits cell apoptosis. Previous studies have also indicated that irisin sustains the levels, and increases the proliferation, of human umbilical vein endothelial cells [55]. Irisin was also shown to increase the proliferation of H19-7 mouse hippocampal neurons [56]. Meanwhile, irisin suppresses the high-glucose-induced apoptosis of vascular endothelial cells and improves their function via the extracellular signal-regulated kinase (ERK) and the 5′-adenosine monophosphate-activated protein kinase (AMPK)-PI3K-protein kinase B (Akt)-eNOS signaling pathways [55, 57, 58]. Furthermore, by interfering with oxidative stress and inflammation, irisin protects against palmitic acid-induced apoptosis in liver cells [59].

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 4 December 2017 doi:10.20944/preprints201712.0023.v1

5. AMPK/FNDC5/IRISIN/BDNF signaling

There are many good reasons to be physically active, including to reduce the odds of developing heart disease, stroke, and diabetes. The activation of various signaling pathways, such as AMPK pathway, contributes to the beneficial effects of exercise [60, 61]. As irisin is an exercise-induced hormone, the intriguing question of whether it links physical activity with brain function has been raised. Wrann et al. reported that irisin is elevated in the hippocampal tissue of mice by endurance exercise [62]. Moreover, they showed that forced expression of FNDC5 in primary cortical neurons increased BDNF expression, and peripheral delivery of FNDC5 to the liver induced BDNF expression in the hippocampus [62]. Because BDNF is a critical regulator of neural plasticity, irisin may act as a key regulator of neuronal survival following neurodegenerative diseases such as AD (Figure 2).

As one of the well-known neurotrophins, BDNF is responsible for regulating the growth, function, and survival of neurons, as well as synaptic stabilization and branching [63]. BDNF is believed to be involved in the pathophysiology of central nervous system diseases associated with neuroinflammation [63]. Neuroinflammation refers to the inflammation of nervous tissue and can lead to neurodegenerative disorders, including AD. Evidence from human neuropathological studies has indicated that the levels of neurotrophins-nerve growth factor and BDNF are lower in AD [64]. These studies demonstrated that BDNF mRNA levels were significantly reduced at very early stages of amyloid pathology in a transgenic rat model of AD. Furthermore, ileocecal valve Aβ-treated rats manifested a memory deficit and significantly decreased BDNF levels, with a concurrent increase in mitochondrial oxidative damage and inflammatory mediators in the hippocampus [65].

In summary, it is hypothesized that a decrease in irisin levels may cause AD pathogenesis and cognitive deficits. These phenomena are highly associated with neuroinflammation and apoptosis, mediated by a dramatic decrease of BDNF.

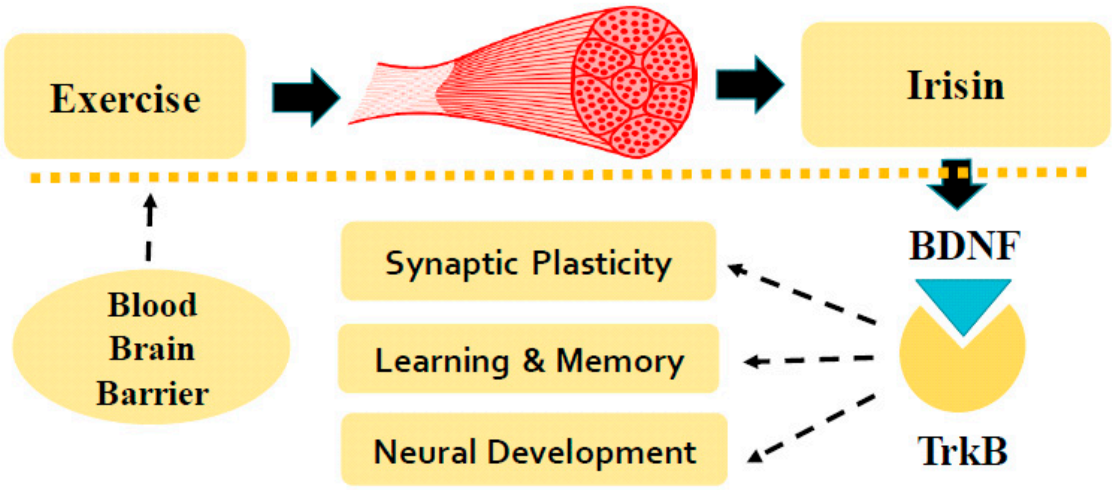

Figure 2. Cross-talk between irisin and neurohormones in the brain. Exercise improves cognitive function and the outcomes of neurodegenerative diseases, such as AD. This effect has been linked to the increased expression of brain-derived neurotropic factor (BDNF). Particularly, in the brain, BDNF is activated by binding with the TrkB receptor, resulting in synaptic plasticity, learning, memory, and neural development. Importantly, irisin is a key player that increases the expression of BDNF and acts as a mediator between exercise and brain development.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 4 December 2017 doi:10.20944/preprints201712.0023.v1

6. IRISIN/AKT/ERK signaling pathway

Irisin was previously reported to be expressed in the brain, as well as skeletal muscle and the heart [66]. This hormone largely inhibits brain infarct volume and reduces neuroinflammation and post-ischemic oxidative stress. One group of scientists demonstrated that irisin activates the Akt and ERK1/2 signaling pathways in brain tissue [67]. Previous studies have also shown that irisin stimulates ERK1/2 signaling in adipocytes [68], endothelial cells [69], and bone marrow stromal cells [70], and activates Akt signaling in hepatocytes [71]. These results indicate that the activation of both Akt and ERK1/2 may be important for the neuroprotective effects of irisin because specific chemical inhibitors of the Akt and ERK1/2 pathways abolished the neuroprotection conferred by irisin. The same group also proved that mouse plasma irisin levels are negatively correlated with plasma TNF-α and IL-6 levels [67]. Finally, they demonstrated that the novel exercise-induced hormone irisin protects against neuronal injury via activation of the Akt and ERK1/2 signaling pathways [67]. These results suggest that irisin contributes to the neuroprotective effects of physical exercise in cerebral ischemia and is a promising agent for the prevention and treatment of ischemic stroke. Recent research has disclosed a role for chronic neuroinflammation in the pathophysiology of neurodegenerative diseases such as AD, and attention has focused the use of anti-TNF and TNF-modulating agents for prevention and treatment [72]. The brains of treated animals exhibited a significant reduction in pro-inflammatory TNF-α, and a diminished burden of neurofibrillary tangles, amyloid precursor protein, and β-amyloid plaques. The brief discussion above allows a clearer mechanistic understanding of the role of proinflammatory mediators such as TNF-α in AD, and suggests that irisin could be a novel target to reduce proinflammatory mediators for the prevention or treatment of AD.

7. Irisin, as a biomarker of age-dependent telomere shortening, is associated with AD pathogenesis

Telomeres are the caps at the end of each DNA strand that preserve our chromosomes, similar to the plastic tips at the ends of shoelaces [73]. Without this coating, shoelaces become frayed until they can no longer do their job; in the same manner, without telomeres DNA strands become damaged so that our cells cannot perform their job. Telomere shortening is associated with all aspects of the aging process on a cellular level. Telomere length (TL) describes our biological age as opposed to our chronological age. Numerous empirical studies have uncovered a strong connection between short telomeres and cellular aging [74]. For example, the immune system, which normally atrophies as we age, is highly sensitive to telomere shortening [75]. Telomere shortening has been confirmed to play a causative role in age-related neurodegenerative diseases, including AD. Telomere shortening has also been associated with cognitive impairment, amyloid pathology, and hyper-phosphorylation of Tau in AD, and plays a significant role in the pathogenesis of AD via the mechanisms of oxidative stress and inflammation [76]. A shorter TL in leukocytes has been connected to age-related diabetes, and cardiovascular and heart diseases, as well as an elevated risk of neurodegenerative diseases, including dementia [77]. It seems that long-term chronic inflammation and/or oxidative stress accelerate telomere shortening in monocytes [78]. In addition, since TL is shortened by aging, elderly populations are more susceptible to AD. Interestingly, microglia also exhibit shorter telomeres in the brains of AD subjects, suggesting that these cells undergo early replicative senescence, which could be due to the intense amyloid plaque profusion seen in AD [79]. Monocytes migrate through the blood-brain barrier in AD and convert into microglial cells in the brain, and microglial activation has been reported to be associated with amyloid-plaques in the AD brain [80]. Additionally, increased expression of chemokine receptors and cytokines in the peripheral blood mononuclear cells of AD patients has been reported [81]. Previous studies have reported that lifestyle factors, including exercise, can have a notable impact on the accumulation of DNA damage and TL [82]. The discovery of irisin, which prompts a peroxisome proliferator-activated receptor gamma coactivator 1-alpha

 doi:10.20944/preprints201712.0023.v1

(PGC1-α)- dependent 'browning' of WAT to a BAT-like phenotype, and upregulates thermogenesis and energy expenditure, may represent a novel mechanism by which modest exercise attenuates age-related decline. Recently, Karan et al. [83] demonstrated that plasma irisin levels showed a significant correlation with TL. The shortening of TL with aging is well-understood and, as expected, shows an inverse relationship with age. Since plasma irisin is likely associated with TL, irisin may exhibit anti-aging properties. Previous research has reported that exercise, which increases plasma irisin, can modulate TL [84-86]. The data presented herein describe a potential mechanism by which exercise is associated with an increased TL. Previously published data have uncovered that irisin activates signaling pathways connected to the regulation of cellular proliferation, including p38 MAPK [87], which regulates cellular proliferation and the expression of human telomere reverse transcriptase [88]. In summary, it is hypothesized the age-related decrease of irisin may be a cause of AD pathogenesis and cognitive impairments. This association is highly linked to telomere shortening induced by oxidative stress and inflammation.

8. Reduction of endoplasmic reticulum (ER) stress responses by irisin in AD

The ER is associated with several crucial cellular functions (e.g., protein folding, quality control, maintenance of Ca2+ balance, and cholesterol synthesis). Many genetic and environmental insults can disrupt the function of the ER, resulting in ER stress. Therefore, it is not surprising that a number of studies have reported that ER stress is linked with several neurodegenerative diseases [89-91]. The unfolded protein response (UPR) induced by ER stress involves both immediate protein kinase responses and subsequent changes in the expression of hundreds of target genes [92, 93]. Evidence of activated UPR signaling has been revealed in AD, PD, and Huntington's disease, as well as in amyotrophic lateral sclerosis [94, 89-91]. Furthermore, cerebral ischemia can trigger the UPR, although this is clearly reduced by the concomitant dramatic decline in protein synthesis [95]. Recent studies have shown that ER stress can generate signals that warn neighboring cells and elicit inflammatory responses to prevent extensive tissue damage [96, 97]. In fact, moderate ER stress improves cellular protection by a series of changes called the 'hormetic response', which is characterized by alteration of the transcriptome and proteome of the cell, thus elevating the adaptive capacity of the ER [98, 99-102]. However, the prolonged ER stress manifested in neurodegenerative diseases is believed to disrupt the protective effects of the UPR, leading to the activation of inflammatory and apoptotic programs that promote neurotoxicity. Therefore, prolonged ER stress disrupts the protective mechanism of the UPR, leading to inflammation and apoptosis, which promote AD pathogenesis. Exercise believed to improve physical fitness and prevent chronic diseases and age-related disorders. Exercise promotes the expression of several myokines such as irisin, which is linked to the transcription factor PGC-1α and is not related to ER-stress, whereas typical ER-stress-induced cytokines, such as fibroblast growth factor 21 and growth/differentiation factor 15 are not exercise-induced myokines under normal physiological conditions [103]. Recent studies have revealed that irisin dramatically suppresses the expression of phosphorylated PERK (protein kinase R-like endoplasmic reticulum kinase) and eIF2α induces by oxidized low-density lipoprotein (ox-LDL) and tunicamycin, indicating that irisin alleviates ox-LDL-induced apoptosis via PERK/eIF2α/CHOP/Bcl-2 CHOPERS signaling pathways [104]. It was previously reported that, among the four eIF2α kinases, PERK is emerging as a key regulator of the memory impairments and neurodegeneration that characterize AD [105]. In summary, it is hypothesized that a sedentary lifestyle and aging are fundamental to irisin deficiency, which is directly followed by the development of AD. This is correlated with ER stress-induced disruption of the protective effects of the UPR and subsequent inflammation, apoptosis and, ultimately, AD (Figure 3).

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 4 December 2017 doi:10.20944/preprints201712.0023.v1

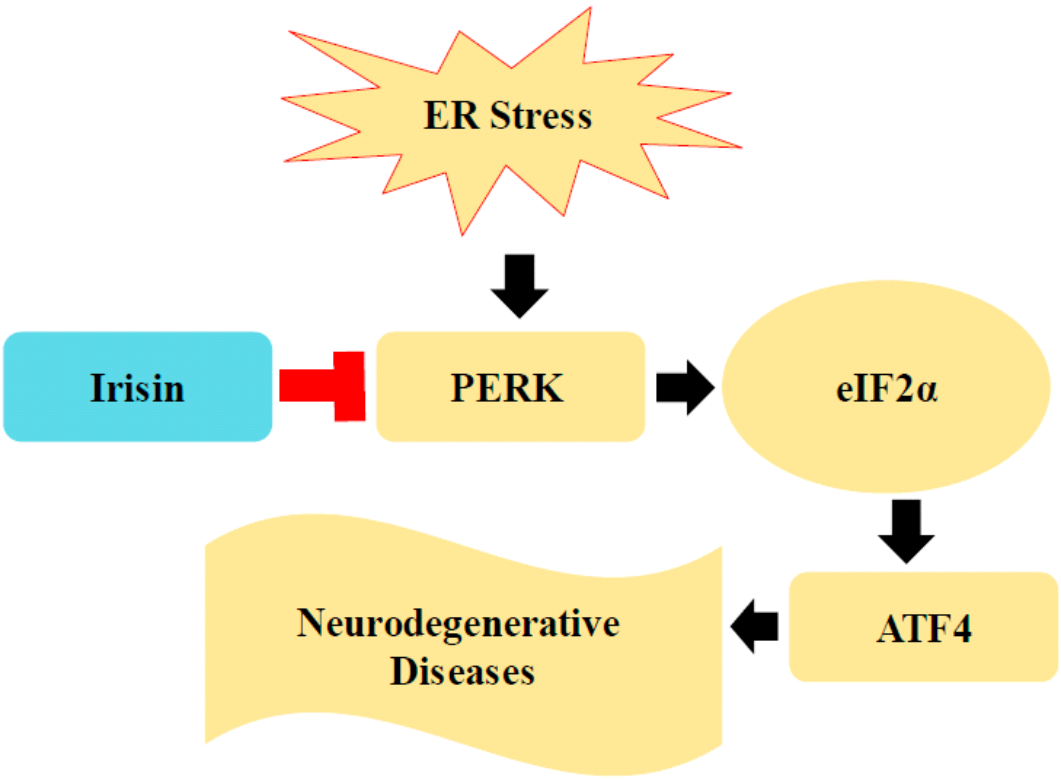

Figure 3. Interrelationship between irisin and endoplasmic reticulum (ER) stress responses in degenerative brain diseases. Brain ER stress is caused by several disease-associated stressors, including amyloid-β (Aβ) in Alzheimer's disease (AD). In such disorders, abnormal ER stress leads to activation of the protein kinase R-like endoplasmic reticulum kinase (PERK)/eIF2α signaling pathway. ATF4 is a transcription factor that is activated translationally by eIF2α phosphorylation and plays a role in the transcriptional activation of CHOP in the integrated stress response. Abnormally high eIF2α-P levels increase ATF4 production and impair translation. Excessive eIF2α-P signaling and its downstream effectors impair cell function and may result in brain dysfunction and neurodegeneration. Since irisin strongly inhibits PERK/eIF2 α signaling, it may serve as become a novel therapeutic agent [104].

9. Conclusions

Several studies suggest that neuroinflammation in the brain may play a role in neurodegeneration during aging. Reduced irisin levels in elderly populations may be a factor increasing the risk of AD. During aging, chronic irisin deficiency may disrupt BDNF signaling, increase proinflammatory mediators, shorten the TL, and upregulate the ER stress response. These age-related changes accompany Aβ production, causing neuroinflammation and neurodegeneration. Regarding its neuroprotective roles, including the regulation of BDNF signaling, age-dependent telomere shortening, and anti-inflammatory and anti-apoptotic effects, irisin can be regarded as a therapeutic candidate to prevent and treat AD (Figure 4).

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 4 December 2017 doi:10.20944/preprints201712.0023.v1

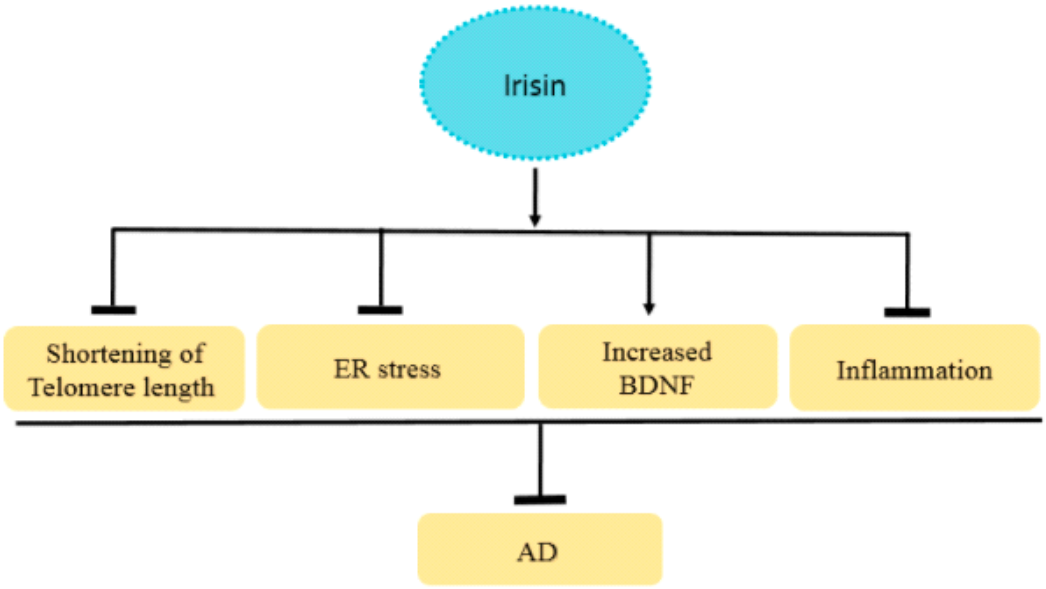

Figure 4. A hypothetical model demonstrating the role of irisin in AD. A schematic diagram depicting the potential molecular mechanisms underlying irisin-conferred protection against AD, i.e., by inhibiting telomere shortening, reducing endoplasmic reticulum (ER) stress, increasing BDNF and decreasing inflammation.

Acknowledgments: This work was supported by the grants from the National Research Foundation (NRF-2013R1A2A2A01067169 to Y.H., NRF-2017R1A2A2A01067169 to Y.H.), and by the KRIBB Research Initiative Program (KGM4611714 to Y.H.). This work was also supported by the 2017 Creative Research Program of Inje University, Republic of Korea.

Author Contributions: This review was conceptualized and designed by Yonggeun Hong; Dewan Md. Sumsuzzman, Yunho Jin and Yonggeun Hong wrote the manuscript; Dewan Md. Sumsuzzman and Yunho Jin collected the references and created the figures appearing in the manuscript under supervision by Yonggeun Hong. All authors commented on the manuscript and approved the final form of manuscript.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Simonian, N.A.; Coyle, JT. Oxidative stress in neurodegenerative diseases. *Annu. Rev. Pharmacol. Toxicol.* **1996**, 36, 83-106.
2. Behl, C.; Holsboer, F. Oxidative stress in the pathogenesis of Alzheimer's disease and antioxidant neuroprotection. *Fortschr. Neurol. Psychiatr.* **1998**, 66, 113-121.
3. Koliatsos, V.E.; Kecojevic, A.; Troncoso, J.C.; Gastard, M.C.; Bennett, D.A.; Schneider, J.A. Early involvement of small inhibitory cortical interneurons in Alzheimer's disease. *Acta. Neuropathol.* **2006**, 112, 147–162.
4. Akama, K.T.; Van Eldik L.J. Beta-amyloid stimulation of inducible nitric-oxide synthase in astrocytes is interleukin-1beta- and tumor necrosis factor-alpha (TNF alpha)-dependent, and involves a TNF alpha receptor-associated factor- and NF kappa B-inducing kinase-dependent signaling mechanism. *J. Biol. Chem.* **2000,** 275, 7918–7924.
5. Behl, C.; Davis, J.B.; Lesley, R.; Schubert, D. Hydrogen peroxide mediates amyloid beta protein toxicity. *Cell.* **1994**, 77, 817–827.
6. Griffin, W.S.; Mrak R.E. Interleukin-1 in the genesis and progression of and risk for development of neuronal degeneration in Alzheimer's disease. *J. Leukoc. Biol.* **2002**, 72, 233–238.

7. Kim, S.E.; Ko, I.G.; Park, C.Y.; Shin, M.S.; Kim, C.J.; Jee, Y.S. Treadmill and wheel exercise alleviate lipopolysaccharide-induced short-term memory impairment by enhancing neuronal maturation in rats. *Mol. Med. Rep.* **2013**, 7, 31-36.
8. Pedersen, B.K.; Febbraio, MA. Muscles, exercise and obesity: skeletal muscle as a secretory organ. *Nat. Rev. Endocrinol.* **2012**, 8, 457-465.
9. Bortoluzzi, S.; Scannapieco, P.; Cestaro, A.; Danieli, G.A.; Schiaffino, S. Computational reconstruction of the human skeletal muscle secretome. *Proteins.* **2006**, 62, 776-792.
10. Wilkins, H.M.; Carl, S.M.; Weber, S.G.; Ramanujan, S.A.; Festoff, B.W.; Linseman, D.A.; Swerdlow, R.H. Mitochondrial lysates induce inflammation and Alzheimer's disease-relevant changes in microglial and neuronal cells. *J. Alzheimers. Dis.* **2015**, 45, 305–318.
11. Kristina, A.K.; John, C.G.; Daniel, P.A.; Jessica, K.A.; Dustin, J.D.; Phillip, G.P. Identification of two distinct macrophage subsets with divergent effects causing either neurotoxicity or regeneration in the injured mouse spinal cord. *J. Neurosci.* **2009**, 29, 13435-13444.
12. Durafourt, B.A.; Moore, C.S.; Zammit, D.A.; Johnson, T.A.; Zaguia, F.; Guiot, M.C.; Bar-Or, A.; Antel, J.P. Comparison of polarization properties of human adult microglia and blood-derived macrophages. *Glia.* **2012**, 60, 717–727.
13. Goerdt, S.; Politz, O.; Schledzewski, K.; Birk, R.; Gratchev, A.; Guillot, P.; Hakiy, N.; Klemke, C.D. Dippel, E.; Kodelja, V.; et al. Alternative versus classical activation of macrophages. *Pathobiology.* **1999**, 67, 222–226.
14. Hu, X.; Li, P.; Guo, Y.; Wang, H.; Leak, R.K.; Chen, S.; Gao, Y.; Chen, J. Microglia/macrophage polarization dynamics reveal novel mechanism of injury expansion after focal cerebral ischemia. *Stroke.* **2012**, 43, 3063-3070.
15. Zhu, D.; Yang, N.; Liu, Y.Y.; Zheng, J.; Ji, C.; Zuo, P.P. M2 macrophage transplantation ameliorates cognitive dysfunction in amyloid-β-treated rats through regulation of microglial polarization. *J. Alzheimers. Dis*. **2016**, 52, 483-495.
16. Jiang, T.; Zhang, Y.D.; Chen, Q.; Gao, Q.; Zhu, X.C.; Zhou, J.S.; Shi, J.Q.; Lu, H.; Tan, L.; Yu, J.T. TREM2 modifies microglial phenotype and provides neuroprotection in P301S tau transgenic mice. *Neuropharmacology.* **2016**, 105, 196-206.
17. Moreira, P.I.; Carvalho, C.; Zhu, X.; Smith, M.A.; Perry, G. Mitochondrial dysfunction is a trigger of Alzheimer's disease pathophysiology. *Biochim. Biophys. Acta.* **2010**, 1802, 2-10.
18. Moreira, P.I.; Duarte, A.I.; Santos, M.S.; Rego, A.C.; Oliveira, C.R. An integrative view of the role of oxidative stress, mitochondria and insulin in Alzheimer's disease. *J. Alzheimers. Dis.* **2009**, 16, 741-761.
19. Von, B.R.; Eugenin, V.L.; Eugenin, J. Microglial cell dysregulation in brain aging and neurodegeneration. *Front. Aging. Neurosci.* **2015**, 7, 124.
20. Wang, X.; Wang, W.; Li, L.; Perry, G.; Lee, H.G.; Zhu.; X. Oxidative stress and mitochondrial dysfunction in Alzheimer's disease. *Biochim. Biophys. Acta.* **2014**, 1842, 1240-1247.
21. Mufson, E.J.; Chen, E.Y.; Cochran, E.J.; Beckett, L.A.; Bennett, D.A.; Kordower, J.H. Entorhinal cortex beta-amyloid load in individuals with mild cognitive impairment. *Exp. Neurol.* **1999**, 158, 469–490.
22. Markesbery, W.R.; Schmitt, F.A.; Kryscio, R.J.; Davis, D.G.; Smith, C.D.; Wekstein, D.R. Neuropathologic substrate of mild cognitive impairment. *Arch. Neurol***. 2006**, 63, 38–46.
23. Price, J.L.; McKeel, D.W.; Buckles, V.D.; Roe, C.M.; Xiong, C.; Grundman, M.; Hansen, L.A.; Petersen, R.C.; Parisi, J.E.; Dickson, D.W.; et al. Neuropathology of nondemented aging: Presumptive evidence for preclinical Alzheimer disease. *Neurobiol. Aging.* **2009**, 30, 1026-1036.
24. Yamane, T.; Ikari, Y.; Nishio, T.; Ishii, K.; Ishii, K.; Kato, T.; Ito, K.; Silverman, D.H.; Senda, M.; Asada, T.; et al. Visual-statistical interpretation of (18) F-FDG-PET images for characteristic Alzheimer patterns in a multicenter study: Inter-rater concordance and relationship to automated quantitative evaluation. *AJNR. Am. J. Neuroradiol.* **2014**, 35, 244–249.
25. Shokouhi, S.; Claassen, D.; Kang, H.; Ding, Z.; Rogers, B.; Mishra, A. Longitudinal progression of cognitive decline correlates with changes in the spatial pattern of brain 18F-FDG PET. *J. Nucl .Med.* **2013**, 54, 1564–1569.
26. Landau, S.M.; Harvey, D.; Madison, C.M.; Koeppe, R.A.; Reiman, E.M.; Foster, N.L.; Weiner, M.W.; Jagust, W.J. Associations between cognitive, functional, and FDG-PET measures of decline in AD and MCI. *Neurobiol. Aging.* **2011**, 32, 1207–1218.
27. de la Torre J.C. Pathophysiology of neuronal energy crisis in Alzheimer's disease. *Neurodegener. Dis.* **2008**, 5, 126–132.

28. Parihar, M.S.; Brewer, G.J. Mitoenergetic failure in Alzheimer disease. *Am. J. Physiol. Cell. Physiol.* **2007**, 292, C8–23.
29. Cotman, C.W.; Berchtold, N.C.; Christie, L.A. Exercise builds brain health: Key roles of growth factor cascades and inflammation. *Trends. Neuro. Sci.* **2007**, 30, 464-472.
30. Mattson, M.P. Energy intake and exercise as determinants of brain health and vulnerability to injury and disease. *Cell. Metabolism.* **2012**, 16, 706-722.
31. Voss, M.W.; Vivar, C.; Kramer, A.F.; Van, P.H. Bridging animal and human models of exercise-induced brain plasticity. *Trends. Cogn. Sci.* **2013**, 17, 525-544.
32. Colcombe, S.; Kramer, A.F. Fitness effects on the cognitive function of older adults: A meta-analytic study. *Psychol. Sci.* **2003**, 14, 125-130.
33. Ahlskog, J.E. Does vigorous exercise have a neuroprotective effect in Parkinson disease? *Neurology.* **2011**, 77, 288-294.
34. Arida, R.M.; Cavalheiro, E.A.; Silva, A.C.; Scorza, F.A. Physical activity and epilepsy: Proven and predicted benefits. *Sports. Med.* **2008**, 38, 607-615.
35. Buchman, A.S.; Boyle, P.A.; Yu, L.; Shah, R.C.; Wilson, R.S.; Bennett, D.A. Total daily physical activity and the risk of AD and cognitive decline in older adults. *Neurology.* **2012**, 78, 1323-1329.
36. Russo.; N.A, Beard, R.C.; Cotman, C.W. Exercise, antidepressant medications, and enhanced brain derived neurotrophic factor expression. *Neuropsychopharmacolog.* **1999**, 21, 679-682.
37. Zhang, Q.; Wu, Y.; Zhang, P.; Sha, H.; Jia, J.; Hu, Y. Exercise induces mitochondrial biogenesis after brain ischemia in rats. *Neuroscience.* **2012**, 205, 10-17.
38. Mattson, M.P. Energy intake and exercise as determinants of brain health and vulnerability to injury and disease. *Cell Metabolism.* **2012**, 16, 706-722.
39. Kobilo, T.; Liu, Q.R.; Gandhi, K.; Mughal, M.; Shaham, Y.; Van, P.H. Running is the neurogenic and neurotrophic stimulus in environmental enrichment. *Learn. Mem.* **2011**, 18, 605-609.
40. Bostrom, P.; Wu, J.; Jedrychowski, M.P.; Korde, A.; Ye, L.; Lo, J.C.; Rasbach, K.A.; Boström, E.A.; Choi, J.H.; Long, J.Z.; et al. A PGC1-α-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. *Nature.* **2012**, 481, 463–468.
41. Kelly, D.P. Irisin, light my fire. *Science.* **2012**, 336, 42–43.
42. Huh, J.Y.; Mougios, V.; Kabasakalis, A.; Fatouros, I.; Siopi, A.; Douroudos, I.I.; Filippaios, A.; Panagiotou, G.; Park, K.H.; Mantzoros, C.S. Exercise-induced irisin secretion is independent of age or fitness level and increased irisin may directly modulate muscle metabolism through AMPK activation. *J. Clin. Endocrinol. Metab.* **2014**, 99, E2154–2161.
43. Norheim, F.; Langleite, T.M.; Hjorth, M.; Holen, T.; Kielland, A.; Stadheim, H.K. The effects of acute and chronic exercise on PGC-1alpha, irisin and browning of subcutaneous adipose tissue in humans. *FEBS. J.* **2014**, 281, 739–749.
44. Hecksteden, A.; Wegmann, M.; Steffen, A.; Kraushaar, J.; Morsch, A.; Ruppenthal, S.; Kaestner, L.; Meyer, T. Irisin and exercise training in humans–results from a randomized controlled training trial. *BMC. Med.* **2013**, 11, 235.
45. Miyamoto, M.E.; Sato, K.; Kurihara, T.; Hasegawa, N.; Fujie, S.; Fujita, S.; Sanada, K.; Hamaoka, T.; Tabata, I.; Iemitsu, M. Endurance training-induced increase in circulating irisin levels is associated with reduction of abdominal visceral fat in middle-aged and older adults. *PLoS. One.* **2015**, 10, 0120354.
46. Timmons, J.A.; Baar, K.; Davidsen, P.K.; Atherton, P.J. Is irisin a human exercise gene? E9-10; discussion. *Nature.* **2012**, 488, E09–10.
47. Qiu, S.; Cai, X.; Sun, Z.; Schumann, U.; Zügel, M.; Steinacker, J.M. Chronic exercise training and circulating irisin in adults: A meta-analysis. *Sports. Med.* **2015**, 45, 1577–1588.
48. Moon, H.S.; Dincer, F.; Mantzoros, C.S. Pharmacological concentrations of irisin increase cell proliferation without influencing markers of neurite outgrowth and synaptogenesis in mouse H19-7 hippocampal cell lines. *Metabolism.* **2013**, 62, 1131–1136.
49. Wrann, C.D.; White, J.P.; Salogiannnis, J.; Laznik, B.D.; Wu, J.; Ma, D. Lin, J.D.; Greenberg, M.E.; Spiegelman, B.M. Exercise induces hippocampal BDNF through a PGC-1alpha/FNDC5 pathway. *Cell Metab.* **2013**, 18, 649–659.
50. Jodeiri, F.M.; Ghaedi, K.; Megraw, T.L.; Curtiss, J.; Shirani, F.M.; Vaziri, P.; Nasr-Esfahani, M.H. Does PGC1alpha/FNDC5/BDNF elicit the beneficial effects of exercise on neurodegenerative disorders? *Neuromolecular. Med.* **2016**, 18, 1-15.

51. Novelle, M.G.; Contreras, C.; Romero, P.A.; Lopez, M.; Dieguez, C. Irisin, two years later. *Int. J. Endocrinol.* **2013**, 2013, 746281..
52. Xu, B. BDNF (I)rising from exercise. *Cell Metab.* **2013**, 18, 612–614.
53. Peng, J.; Deng, X.; Huang, W.; Yu, J.H.; Wang, J.X.; Wang, J.P.; Yang, S.B.; Liu, X.; Wang, L.; Zhang, Y.; et al. Irisin protects against neuronal injury induced by oxygen-glucose deprivation in part depends on the inhibition of ROS-NLRP3 inflammatory signaling pathway. *Mol. Immunol.* **2017**, 91, 185-194.
54. Bostrom, P.; Wu, J.; Jedrychowski, M.P.; Korde, A.; Ye, L.; Lo, J.C.; Rasbach, K.A.; Boström, E.A.; Choi, J.H.; Long, J.Z.; et al. A PGC1-alpha-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. *Nature.* **2012**, 48, 463-468.
55. Song, H.; Wu, F.; Zhang, Y.; Zhang, Y.; Wang, F.; Jiang, M.; Li, S.; Yang, L. Irisin promotes human umbilical vein endothelial cell proliferation through the ERK signaling pathway and partly suppresses high glucose-induced apoptosis. *PLoS. One.* **2014**, 9, e110273.
56. Moon, H.S.; Dincer, F.; Mantzoros, C.S. Pharmacological concentrations of irisin increase cell proliferation without influencing markers of neurite outgrowth and synaptogenesis in mouse H19-7 hippocampal cell lines. *Metabolism.* **2013**, 62, 1131-1136.
57. Lu, J.; Xiang, G.; Liu, M.; Mei, W.; Xiang, L.; Dong, J. Irisin protects against endothelial injury and ameliorates atherosclerosis in apolipoprotein E-Null diabetic mice. *Atherosclerosis.* **2015**, 243, 438-448.
58. Han, F.; Zhang, S.; Hou, N.; Wang, D.; Sun, X. Irisin improves endothelial function in obese mice through the AMPK-eNOS pathway. *Am. J. Physiol. Heart. Circ. Physiol.* **2015**, 309, H1501-508.
59. Park, M.J.; Kim, D.I.; Choi, J.H.; Heo, Y.R.; Park, S.H. New role of irisin in hepatocytes: The protective effect of hepatic steatosis in vitro. *Cell Signal.* **2015**, 27, 1831-1839.
60. Liu, X.; Niu, Y.; Yuan, H.; Huang, J.; Fu, L. AMPK binds to Sestrins and mediates the effect of exercise to increase insulin sensitivity through autophagy. *Metabolism.* **2015**, 64, 658–665.
61. Ray, HRD.; Yamada, T.; Ishizawa, R.; Saito, Y.; Masuda, K. Curcumin treatment enhances the effect of exercise on mitochondrial biogenesis in skeletal muscle by increasing cAMP levels. *Metabolism.* **2015**, 66, 1334–1347.
62. Wrann, C.D.; White, J.P.; Salogiannnis, J.; Laznik, B.D.; Wu, J.; Ma, D.; Lin, J.D.; Greenberg, M.E.; Spiegelman, B.M. Exercise induces hippocampal BDNF through a PGC-1alpha/FNDC5 pathway. *Cell Metab.* **2013**, 18, 649–659.
63. Kazak, F.; Yarim, G.F. Neuroprotective effects of acetyl-l-carnitine on lipopolysaccharide-induced neuroinflammation in mice: Involvement of brain-derived neurotrophic factor. *Neurosci. Lett.* **2017**, 658, 32-36.
64. Iulita, M.F.; Bistué, Millón, M.B.; Pentz, R.; Aguilar, L.F.; Do, Carmo S.; Allard, S.; Michalski, B.; Wilson, E.N.; Ducatenzeiler, A.; Bruno M.A.; et al. Differential deregulation of NGF and BDNF neurotrophins in a transgenic rat model of Alzheimer's disease. *Neurobiol. Dis.* **2017**, 108, 307-323.
65. Prakash, A.; Kumar, A. Role of nuclear receptor on regulation of BDNF and neuroinflammation in hippocampus of β-amyloid animal model of Alzheimer's disease. *Neurotox. Res.* **2014**, 25, 335-347.
66. Dun, S.L.; Lyu, R.M.; Chen, Y.H.; Chang, J.K.; Luo, J.J.; Dun, N.J. Irisin-immunoreactivity in neural and non-neural cells of the rodent. *Neuroscience.* **2013**, 240, 155–162.
67. Li, D.J.; Li, Y.H.; Yuan, H.B.; Qu, L.F.; Wang, P. 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.* **2017**, 68, 31-42.
68. Zhang, Y.; Li, R.; Meng, Y.; Li, S.; Donelan, W.; Zhao, Y.; Qi, L.; Zhang, M.; Wang, X.; Cui, T.; et al. Irisin stimulates browning of white adipocytes through mitogenactivated protein kinase p38 MAP kinase and ERK MAP kinase signaling. *Diabetes.* **2014**, 63, 514–525.
69. Song, H.; Wu, F.; Zhang, Y.; Zhang, Y.; Wang, F.; Jiang, M.; Wang, Z.; Zhang, M.; Li, S.; Yang, L.; et al. Irisin promotes human umbilical vein endothelial cell proliferation through the ERK signaling pathway and partly suppresses high glucose-induced apoptosis. *PLoS. One.* **2014**, 9, e110273.
70. Colaianni, G.; Cuscito, C.; Mongelli, T.; Pignataro, P.; Buccoliero, C.; Liu, P.; Lu, P.; Sartini, L.; Di, Comite M.; Mori, G.; et al. The myokine irisin increases cortical bone mass. *Proc. Natl. Acad. Sci. U S A.* **2015**, 11, 12157–12162.
71. Liu, T.Y.; Shi, C.X.; Gao, R.; Sun, H.J.; Xiong, X.Q.; Ding, L.; Chen, Q.; Li, Y.H.; Wang, J.J.; Kang, Y.M.; et al. Irisin inhibits hepatic gluconeogenesis and increases glycogen synthesis via the PI3K/Akt pathway in type 2 diabetic mice and hepatocytes. *Clin. Sci. (Lond).* **2015**, 129, 839–850.

72. Shamim, D.; Laskowski, M. Inhibition of Inflammation Mediated Through the Tumor Necrosis Factor α Biochemical Pathway Can Lead to Favorable Outcomes in Alzheimer Disease. *J. Cent. Nerv. Syst. Dis.* **2017**, 9, 1179573517722512.
73. Blackburn, E.H.; Epel, E.S. Telomeres and adversity: Too toxic to ignore. *Nature.* **2012**, 490, 169-171.
74. Armanios, M.; Blackburn, E.H. The telomere syndromes. *Nature. Reviews. Genetics.* **2012**, 13, 693-704.
75. Kaszubowska, L. Telomere shortening and ageing of the immune system. *J. Physiol. Pharmacol.* **2008**, 59, 169-186.
76. Cai, Z.; Yan, L.J.; Ratka, A. Telomere shortening and Alzheimer's disease. *Neuromolecular Med.* **2013**, 15, 25-48.
77. Honig, L.S.; Schupf, N.; Lee, J.H.; Tang, M.X.; Mayeux, R.; Shorter telomeres are associated with mortality in those with APOE epsilon4 and dementia. *Ann. Neurol.* **2006**, 60, 181–187.
78. Von, Zglinicki T.; Serra, V.; Lorenz, M.; Saretzki, G.; Lenzen, Grossimlighaus R.; Gessner, R.; Risch, A.; Steinhagen, Thiessen E. Short telomeres in patients with vascular dementia: an indicator of low antioxidative capacity and a possible risk factor? *Lab. Invest.* **2000**, 80, 1739–1747.
79. Flanary, B.E.; Sammons, N.W.; Nguyen, C.; Walker, D.; Streit, W.J. Evidence that aging and amyloid promote microglial cell senescence. *Rejuvenation. Res.* **2007**, 10, 61–74.
80. Floris, S.; Ruuls, S.R.; Wierinckx, A.; van der Pol, S.M.; Döpp, E.; van der Meide, P.H.; Dijkstra, C.D.; De Vries, H.E. Interferon-beta directly influences monocyte infiltration into the central nervous system. *J. Neuroimmunol.* **2002**, 127, 69–79.
81. Reale, M.; Iarlori, C.; Feliciani, C.; Gambi, D. Peripheral chemokine receptors, their ligands, cytokines and Alzheimer's disease. *J. Alzheimers Dis*. **2008**,14, 147–159.
82. Song, Z.; von Figura, G.; Liu, Y.; Kraus, J.M.; Torrice, C.; Dillon, P.; Rudolph-Watabe, M.; Ju, Z.; Kestler, H.A.; Sanoff, H.; Lenhard Rudolph, K.; Lifestyle impacts on the aging-associated expression of biomarkers of DNA damage and telomere dysfunction in human blood. *Aging. Cell.* **2010**, 9, 607-615.
83. Karan, S.R.; Muhammad, A.; Eric, J.H.; Sarah, A.; David, A.N.; Alan Nevill, Harpal S. Randeva, Clifford J. Bailey, Srikanth Bellary, James E. Brown. Plasma irisin levels predict telomere length in healthy adults. *Age. (Dordr).* **2014**, 36, 995–1001.
84. Kim, S.; Parks, CG.; DeRoo, L.A.; Chen, H.; Taylor, J.A.; Cawthon, R.M.; Sandler, D.P. Obesity and weight gain in adulthood and telomere length. *Cancer. Epidemiol. Biomarkers. Prev*. **2009**, 18, 816-820.
85. Ludlow, A.T.; Zimmerman, J.B.; Witkowski, S.; Hearn, J.W.; Hatfield, B.D.; Roth, S.M. Relationship between physical activity level, telomere length, and telomerase activity. *Med. Sci. Sports. Exerc*. **2008**, 40, 1764-1771.
86. Cherkas, L.F.; Hunkin, J.L.; Kato, B.S.; Richards, J.B.; Gardner, J.P.; Surdulescu, G.L.; Kimura, M.; Lu, X.; Spector, T.D.; Aviv, A. The association between physical activity in leisure time and leukocyte telomere length. *Arch. Intern. Med.* **2008**, 168, 154-158.
87. Zhang, Y.; Li, R.; Meng, Y.; Li, S.; Donelan, W.; Zhao, Y.; Qi, L.; Zhang, M.; Wang, X.; Cui, T.; Yang, L.J.; Tang, D. Irisin stimulates browning of white adipocytes through mitogen-activated protein kinase p38 MAP kinase and ERK MAP kinase signaling. *Diabetes.* **2014**, 63, 514-525.
88. Matsuo, T.; Shimose, S.; Kubo, T.; Fujimori, J.; Yasunaga, Y.; Sugita, T.; Ochi, M. Correlation between p38 mitogen-activated protein kinase and human telomerase reverse transcriptase in sarcomas. *J. Exp. Clin. Cance.r Res.* **2012**, 31, 5.
89. Lindholm, D.; Wootz, H.; Korhonen, L. ER stress and neurodegenerative diseases. *Cell. Death. Differ*. **2006**, 13, 85-392.
90. Paschen, W.; Mengesdorf, T. Cellular abnormalities linked to endoplasmic reticulum dysfunction in cerebrovascular disease therapeutic potential. *Pharmacol. Ther.* **2005**, 108, 362-375.
91. Scheper, W.; Hoozemans, J. Endoplasmic reticulum protein quality control in neurodegenerative disease: the good, the bad and the therapy. *Curr. Med. Chem*. **2009**, 16, 615-626.
92. Ron, D.; Walter, P. Signal integration in the endoplasmic reticulum unfolded protein response. *Nat. Rev. Mol. Cell. Biol.* **2007**, 8, 519-529.
93. Kim, I.; Xu, W.; Reed, J.C. Cell death and endoplasmic reticulum stress: disease relevance and therapeutic opportunities. *Nat. Rev. Drug.Discov. 2008*, 7, 1013-1030.
94. Hoozemans, J.J,; van, Haastert.; E.S.; Nijholt, D.A.; Rozemuller A.J.; Eikelenboom, P.; Scheper, W. The unfolded protein response is activated in pretangle neurons in Alzheimer's disease hippocampus. *Am J Pathol*. **2009**, 174, 1241-1251.

 doi:10.20944/preprints201712.0023.v1

95. DeGracia, D.J.; Montie, H.L. Cerebral ischemia and the unfolded protein response. *J Neurochem*. **2004**, 91, 1-8.
96. Zhang, K.; Kaufman, R.J. From endoplasmic-reticulum stress to the inflammatory response. *Nature.* **2008**, 454, 455-462.
97. Kaser, A.; Blumberg, R.S. Endoplasmic reticulum stress in the intestinal epithelium and inflammatory bowel disease. *Semin Immunol.* **2009**, 21, 156–163.
98. Hetz, C.; Mollereau, B. Disturbance of endoplasmic reticulum proteostasis in neurodegenerative diseases. *Nat. Rev. Neurosci*. **2014**, 15, 233-49.
99. Inagi, R.; Kumagai, T.; Nishi, H.; Kawakami, T.; Miyata, T.; Fujita, T. Preconditioning with endoplasmic reticulum stress ameliorates mesangioproliferative glomerulonephritis. *J Am Soc Nephrol.* **2008**, 19, 915-22.
100. Mercado, G.; Valdes, P.; Hetz, C. An ERcentric view of Parkinson's disease. *Trends Mol Med. 2013*, 19, 165-75.
101. Fouillet, A.; Levet, C.; Virgone, A.; Robin, M.; Dourlen, P.; Rieusset, J. ER stress inhibits neuronal death by promoting autophagy. *Autophagy.* **2012**, 8, 915-26.
102. Calabrese, V.; Cornelius, C.; Dinkova-Kostova, A.T.; Calabrese, E.J.; Mattson, M.P. Cellular stress responses, the hormesis paradigm, and vitagenes: novel targets for therapeutic intervention in neurodegenerative disorders. *Antioxid. Redox. Signal*. **2010**, 13, 1763-811.
103. Ost, M.; Coleman, V.; Kasch, J.; Klaus, S. Regulation of myokine expression: Role of exercise and cellular stress. *Free Radic Biol Med.* **2016**, 98, 78-89.
104. Zheng G.; Li, H.; Zhang, T.; Yang, L.; Yao, S.; Chen, S.; Zheng, M.; Zhao, Q.; Tian, H. Irisin protects macrophages from oxidized low density lipoprotein-induced apoptosis by inhibiting the endoplasmic reticulum stress pathway. *Saudi. Journal. of. Biological. Sciences.* **2017**.
105. Ohno, M. PERK as a hub of multiple pathogenic pathways leading to memory deficits and neurodegeneration in Alzheimer's disease. Brain Res Bull. 2017, S0361-9230, 30393-3.