The Role of FNDC5/Irisin in the Nervous System and as a Mediator for Beneficial Effects of Exercise on the Brain

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Abstract Exercise can improve cognitive function and the outcome of neurodegenerative diseases like Alzheimer's disease. This effect has been linked to the increased expression of brain-derived neurotrophic factor (BDNF). However, the underlying molecular mechanisms driving the elevation of this neurotrophin remain unknown. Recently, we have reported a PGC-1α-FNDC5/irisin pathway that is activated by exercise in the hippocampus in mice and induces a neuroprotective gene program, including *Bdnf*. This review will focus on FNDC5 and its secreted form "irisin," a newly discovered myokine, its role in the nervous system and its therapeutic potential. In addition, we will briefly discuss the role of other exercise-induced myokines in positive brain effects.

Introduction

Exercise, especially endurance exercise, is known to have beneficial effects on brain health and cognitive function (Cotman et al. 2007; Mattson 2012; Voss et al. 2013). This improvement in cognitive function with exercise has been most prominently observed in the aging population (Colcombe and Kramer 2003). Exercise has also been reported to ameliorate outcomes in neurological diseases such as depression, epilepsy, stroke, and Alzheimer's and Parkinson's disease (Ahlskog 2011; Arida et al. 2008; Buchman et al. 2012; Russo-Neustadt et al. 1999; Zhang et al. 2012). The effects of exercise on the brain are most apparent in the hippocampus and the dentate gyrus, a part of the brain involved in learning and memory. Specific beneficial effects of exercise in the brain have been reported to include increases in the size of, and blood flow to, the hippocampus in humans and morphological changes in dendrites and dendritic spines, increased synapse plasticity and, importantly, de novo neurogenesis in the dentate gyrus in various mouse models of exercise (Cotman

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et al. 2007; Mattson 2012). De novo neurogenesis in the adult brain is observed in only two areas; the dentate gyrus of the hippocampus is one of them. Exercise is one of the few known stimuli of this de novo neurogenesis (Kobilo et al. 2011).

One important molecular mediator of these beneficial responses in the brain to exercise is the induction of neurotrophins/growth factors, most notably brain-derived neurotrophic factor (BDNF). In animal models, BDNF is induced in various regions of the brain with exercise, most robustly in the hippocampus (Cotman et al. 2007). BDNF promotes many aspects of brain development, including neuronal cell survival, differentiation, migration, dendritic arborization, synaptogenesis and plasticity (Greenberg et al. 2009; Park and Poo 2013). In addition, BDNF is essential for synaptic plasticity, hippocampal function, and learning (Kuipers and Bramham 2006). Highlighting the relevance of BDNF in humans, individuals carrying the Val66Met mutation in the *Bdnf* gene exhibit decreased secretion of BDNF, decreased volume of specific brain regions, deficits in episodic memory function and increased anxiety and depression (Egan et al. 2003; Hariri et al. 2003). Blocking BDNF signaling with anti-TrkB antibodies attenuates the exercise-induced improvement of acquisition and retention of a spatial learning task, as well as the exercise-induced expression of synaptic proteins (Vaynman et al. 2004, 2006). However, the underlying mechanism that induces BDNF in exercise remains incompletely understood.

We recently described a role for the newly discovered "exercise-hormone," FNDC5 (Bostrom et al. 2012), and its secreted form, "irisin," in the protective effects of exercise on the brain. *Fndc5* expression is induced by exercise in the hippocampus in mice; it can, in turn, activate BDNF and other neuroprotective genes (Wrann et al. 2013). Importantly, peripheral delivery of FNDC5 to the liver via adenoviral vectors, resulting in elevated blood irisin, induces expression of *Bdnf* and other neuroprotective genes in the hippocampus. These data indicate that either irisin itself can cross the blood-brain-barrier to induce gene expression changes or irisin induces a "factor x" that can, which has significant implications for irisin as a novel therapeutic target. This review will examine previous literature about FNDC5/irisin as well as its therapeutic potential for treating neurodegenerative disease.

Discovery of FNDC5/Irisin

In 2002, two groups independently cloned a novel gene termed either PeP or, alternatively, Frcp2, that contained a fibronectin type III (FNIII) domain; it is now named FNDC5 (Ferrer-Martinez et al. 2002; Teufel et al. 2002). Recently, our group identified FNDC5 as a PGC-1α-dependent myokine that is secreted from muscle during exercise and induces some major metabolic benefits of exercise (Bostrom et al. 2012).

FNDC5 is a glycosylated type I membrane protein. It contains a N-terminal signal peptide [amino acid (aa) 1-28], a FNIII domain (aa 33–124), a transmembrane domain (aa 150–170), and a cytoplasmic tail (aa 171–209) (www.uniporot.org) (Fig. 1). The secreted form of FNDC5 contains 112 amino acids (aa 29-140), named irisin, and is generated by proteolytic cleavage and is released into the circulation.

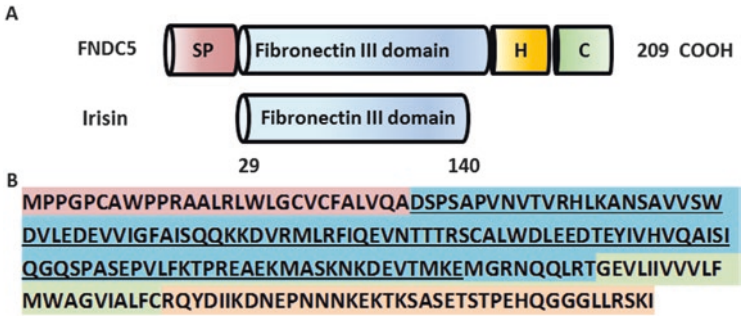

Fig. 1 Analysis of Irisin Peptides by Mass Spectrometry. (**a**) Scheme of the murine FNDC5 protein structure (top) and murine irisin protein structure (bottom). *SP* signal peptide, *H* hydrophobic domain, *C* cytoplasmic domain. (**b**) Murine FNDC5 amino acid sequence with corresponding domains colored. The irisin sequence is underlined

The protease/sheddase responsible for that cleavage has not yet been identified. Irisin has been crystallized and its structure has been solved (Schumacher et al. 2013). Interestingly, the FNIII-like domain shows an unusual confirmation, with a continuous intersubunit beta-sheet dimer, that has not been previously described for any other FNIII protein. Subsequent biochemical experiments confirmed the existence of irisin (bacterial recombinant) as a homodimer.

Irisin in Humans

Irisin is a highly conserved polypeptide across mammals and is, in fact, 100% identical in mice and humans (Bostrom et al. 2012). Such a high degree of conservation is often the result of evolutionary pressure to conserve function. Interestingly, the human FNDC5 has an atypical start of translation, ATA in place of ATG, as compared to mouse Fndc5. While it is now known that a few percent of eukaryotic mRNAs begin translation with non-ATG start codons (Ingolia et al. 2011; Ivanov et al. 2011; Peabody 1989) and are often associated with regulation on the translational level (Chang and Wang 2004; Starck et al. 2012), recent reports (Albrecht et al. 2015; Raschke et al. 2013) have argued that this ATA codon in human FNDC5 was a "null mutation" or a "myth" and, as a result, human irisin would not be produced. Furthermore, many reports from other groups measuring irisin in humans by Western blot or ELISA have suggested results to be artefacts of poor antibody specificity (Albrecht et al. 2015; Erickson 2013; Raschke et al. 2013), even though an earlier study had detected irisin circulating in human plasma using mass spectrometry, an unbiased method independent of the quality of existing antibodies (Jedrychowski et al. 2015; Lee et al. 2014). To identify and quantify irisin in human plasma, we used targeted mass spectrometry with control peptides enriched with stable isotopes as internal standards. This precise, state-of-the-art method demonstrated that human irisin was mainly translated from its non-canonical ATA start

codon (Jedrychowski et al. 2015). In addition, it showed that, in sedentary individuals, irisin circulated at ~3.6 ng/ml and that it was significantly increased in individuals undergoing aerobic interval training. This study determined that, at the atomic level, human irisin exists, and is regulated by certain forms of aerobic exercise.

FNDC5/Irisin in Exercise

FNDC5/irisin was first described as an exercise-induced myokine by Bostrom et al. in 2012, where they observed upregulation of *Fndc5* gene expression in skeletal muscle and increased serum irisin levels after prolonged endurance exercise in both mice and humans. Increasing the circulating levels of irisin by overexpression of FNDC5 from adenoviral vectors in the liver led to an increase in "browning" of the white inguinal adipose tissue, i.e., the upregulation of mitochondrial gene expression, especially of *Ucp1*, and an increased glucose tolerance in mice. Both are among the major metabolic benefits of endurance exercise. By now, there are around 50 published papers that investigate the role of FNDC5 and/or irisin in exercise, including both rodent studies and clinical trials in humans. Induction of *Fndc5* mRNA in skeletal muscle by endurance exercise has been confirmed in several studies in both mice (Quinn et al. 2015; Tiano et al. 2015; Wrann et al. 2013) and humans (Albrecht et al. 2015; Lecker et al. 2012; Norheim et al. 2014) using qPCR or RNA sequencing. As with all clinical studies, there are a lot of variables to consider, such as retrospective studies vs. interventional trials, age and fitness level of the subjects and, most importantly, the type of exercise protocol used and time point of sampling. However, a consensus is building, supported by studies that reported positive associations between irisin plasma level and exercise, performed early sampling and high intensity training protocols levels (Daskalopoulou et al. 2014; Huh et al. 2014; Kraemer et al. 2014; Malcolm Eaton et al. 2017; Norheim et al. 2014). Plasma levels of irisin and BDNF have been shown to be positively correlated with cognitive function in endurance athletes (Belviranli et al. 2016).

The brief rise in circulating irisin levels after exercise is suggestive of an acute shedding event of irisin during exercise. There is little to no evidence thus far that FNDC5 or irisin is upregulated by resistance exercise in mouse or human This is not unexpected, since endurance exercise activates PGC-1α1, which has been shown to be the upstream regulator of Fndc5 gene expression, whereas resistance exercise activates a different isoform of PGC-1α1, PGC-1α4 (Ruas et al. 2012).

FNDC5/Irisin in Neuronal Development

Fndc5 is highly expressed in the brain, including the Purkinje cells of the cerebellum (Dun et al. 2013; Ferrer-Martinez et al. 2002; Teufel et al. 2002). Irisin, the shed form of FNDC5, was identified in human cerebrospinal fluid by Western blot (Piya

et al. 2014). In addition, immunoreactivity against the extracellular domain of FNDC5/irisin was detected in human hypothalamic sections, especially paraventricular neurons (Piya et al. 2014). Other tissues with high FNDC5 levels include skeletal muscle and the heart. *Fndc5* gene expression increases during differentiation of rat pheochromocytoma-derived PC12 cells into neuron-like cells (Ostadsharif et al. 2011). FNDC5 levels are enhanced after the differentiation of human embryonic stem cell-derived neural cells into neurons (Ghahrizjani et al. 2015) as well as during the maturation of primary cortical neurons in culture and during brain development in vivo (Wrann et al. 2013).

Knockdown of FNDC5 in neuronal precursors impaired their development into mature neurons (and astrocytes), suggesting a developmental role for FNDC5 in neurons (Hashemi et al. 2013). Despite this finding, forced expression of FNDC5 during neuronal precursor formation from mouse embryonic stem cells increased mature neuronal markers (Map2, b-tubulinIII and Neurocan) and an astrocyte marker (GFAP) and BDNF. However, overexpression of FNDC5 in undifferentiated mouse embryonic stem cells did not have these effects, indicating that FNDC5 supports neural differentiation rather than lineage commitment (Forouzanfar et al. 2015). Pharmacological doses of recombinant irisin increased cell proliferation in the mouse H19-7 hippocampal cell line (Moon et al. 2013). Furthermore, forced expression of FNDC5 in primary cortical neurons increased cell survival in culture, whereas knockdown of FNDC5 had the opposite effect (Wrann et al. 2013).

FNDC5/Irisin: Other Effects in the CNS

The group of Dr. Mulholland (University of Michigan) had taken in interest in the central nervous effects of irisin. In a first study, they injected irisin either into third ventricle of rats or intravenously measured the effects on blood pressure and cardiac contractibility (Zhang et al. 2015a). Central administration of irisin activated neurons in the paraventricular nuclei of the hypothalamus, as indicated by increased c-fos immunoreactivity. Central irisin administration also increased both blood pressure and cardiac contractibility. In contrast, i.v. injection of irisin reduced blood pressure in both control and spontaneously hypertensive rats. In a second study, Zhang et al. showed that central treatment of rats with irisin-Fc led to an increase in physical activity as measured as total travel distance, ambulatory counts and time, and vertical counts and time compared to control animals receiving IgG Fc peptide (Zhang et al. 2015b). In addition, the centrally applied irisin also induced significant increases in oxygen consumption, carbon dioxide production and heat production, indicating an increase in metabolic activity- possibly through SNS activation. Similarly, intra-hypothalamic injection of irisin decreased food intake in rats possibly by stimulating anorexigenic peptides and inhibiting dopamine, norepinephrine and orexin-A (Ferrante et al. 2016).

A recent study investigated the neuroprotective potential of irisin treatments in cerebral ischemia. Irisin improved survival of cultured PC12 neuronal cells in

oxygen glucose deprivation. I.v. injection of recombinant irisin reduced brain infarct and edema volume and improved the neurological score in MCAO stroke model (Li et al. 2017). Systemic irisin administration has also been shown to ameliorate depressive-like behavior in a chronic unpredictable stress model in rats (Wang and Pan 2016).

Exercise Induces Hippocampal BDNF Through a PGC-1α/FNDC5 Pathway

In a recent study, we have shown that FNDC5 is also elevated in the hippocampus of mice undergoing endurance exercise regimen of 30-days free-wheel running. Neuronal *Fndc5* gene expression is regulated by PGC-1α and Pgc1a$^{-/-}$ mice show reduced *Fndc5* expression in the brain. Forced expression of FNDC5 in primary cortical neurons increases *Bdnf* expression, whereas RNAi-mediated knockdown of FNDC5 reduces *Bdnf*. Importantly, peripheral delivery of FNDC5 to the liver via adenoviral vectors, resulting in elevated blood irisin, induces expression of *Bdnf* and other neuroprotective genes in the hippocampus. Taken together, our findings link endurance exercise and the important metabolic mediators, PGC-1α and FNDC5, with BDNF expression in the brain. Interestingly, a recent study investigating the effects of the flavonoid quercetin hypobaric hypoxia, reported that quercetin administration to hyperbaric hypoxic rats increased expression of PGC-1α, FNDC5, and BDNF in the hippocampus (Liu et al. 2015). While more research will be required to determine whether the FNDC5/irisin protein can improve cognitive function in animals, this study suggests that a hormone administered peripherally could induce some of the effects of endurance exercise on the brain (Fig. 2).

Other Circulating Factors from the Muscle

While FNDC5/irisin is a very interesting molecule that holds therapeutic promise, this is not to say that we think that FNDC5/irisin captures all the benefits of exercise on the brain or that is the only important secreted molecule from muscle in exercise. In fact, other such molecules have been described, including BDNF, IGF-1, and VEGF, kynurenic acid, cathepsin B, as well as a variety of cytokines and chemokines, to name a few (Agudelo et al. 2014; Moon et al. 2016; Phillips et al. 2014; Voss et al. 2013). We expect that in the future, additional molecules will be discovered and some may reach their full therapeutic potential.

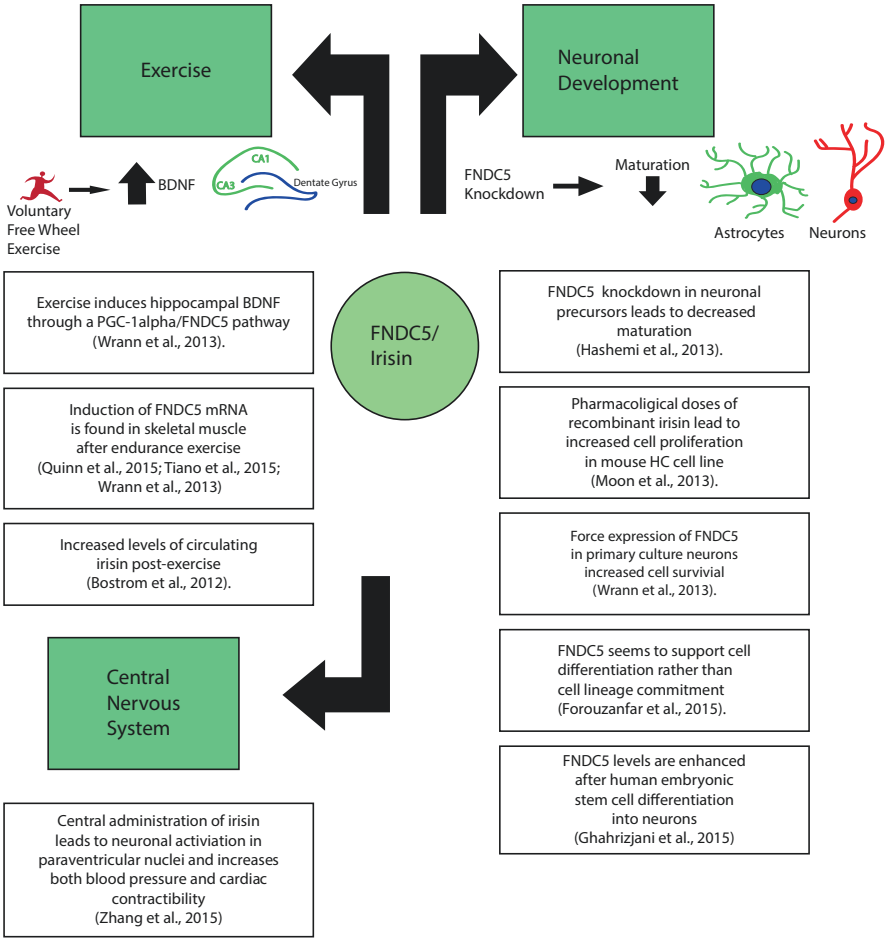

Fig. 2 Summary of FNDC5/irisin effects on the brain

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