REVIEW ARTICLE

Irisin, A Fascinating and Multifunctional Protein: Implication for Health

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Abstract

BACKGROUND: Fibronectin type III domain-containing protein 5 (FNDC5), or also known as irisin, has been identified for two decades but almost completely disregarded for 10 years. It is present in skeletal muscle, heart, and brain, and in reaction to exercise can transform white adipose tissue into brown. Since then, irisin has gained a lot of attention for its potencies in treating metabolic disorders. In this review article, the potential future of irisin especially on metabolism and aging process will be discussed.

CONTENT: Sedentary lifestyle is acknowledged as risk factor for type 2 diabetes mellitus, obesity, immune system issues, asthma, and neurological or heart illness. Irisin is secreted by muscle cells when exercising, produced after the proteolytic cleavage of FNDC5 protein. Irisin has positive impacts on maintaining physiological balance including reducing inflammation, keeping the bone homeostasis, as well as influencing metabolic processes and the neurological system function. Due to these many and advantageous characteristics, irisin could be a possible choice for preventing and managing disorders associated with modern society, and finding the agents to increase irisin can be beneficial.

SUMMARY: Irisin offers a fresh potential basis for kinesitherapy and shows promise as a therapeutic target due to its various biological activities. Irisin pathway can be activated through dietary changes, the use of natural substances and drugs and can interact with this signalling pathway which involved peroxisome proliferator-activated receptor-γ coactivator 1α (PGC-1α) and uncoupling protein mRNA 1 (UCP1) to resolve obesity and its metabolic comorbidities.

KEYWORDS: irisin, FNDC5, exercise, inflammation, obesity, nervous system

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Introduction

Exercises have been proved to deliver benefit not only to improve metabolic diseases such as obesity, diabetes, heart diseases, but also the brain function. Irisin was released from skeletal muscle as extracellular portion of a transmembrane protein known as fibronectin type III domain-containing protein 5 (FNDC5). Irisin levels in the blood increases shortly after high-intensity exercises, and enhances the metabolic well-being in animals and humans. It also encourages the activation of a possible gene program that protects the brain, especially in the hippocampus.(1)

Muscle peroxisome proliferator-activated receptor-γ coactivator 1α (PGC-1α) is seen as an important factor in how exercise can enhance metabolic condition. A study focusing on the search of precise element that might facilitates PGC-1α-triggered metabolic improvements found a novel myokine, known as irisin, which has the ability to activate muscle PGC-1α and promote the browning of white

adipose tissue (WAT). Additionally, it helps in reducing diet-induced obesity and insulin resistance. More studies found the association of irisin and non-metabolic disorders such as sarcopenia, osteoporosis, and cardiovascular disease (CVD). Therefore, irisin is seen as a significant factor in the positive effects of exercise on both metabolic and non-metabolic conditions, such as chronic diseases.(2)

By promoting brown adipose tissue (BAT), the essential role of irisin is potentially regulating thermogenesis. Irisin enhance the expression of the receptor triggered by PGC-1α, and promotes mitochondrial uncoupling protein mRNA 1 (UCP1) for mitochondrial biogenesis.(3,4) Meanwhile, another study discovered that treating with r-irisin increases UCP1 levels via enhancing the phosphorylation of p38 mitogen-activated protein kinase (p38 MAPK) and regulatory kinases.(5) Thus, irisin is suggested as a hormone that can increase energy expenditure, promote weight loss, and reduce insulin resistance caused by the diet.(6)

Skeletal muscle is the biggest organ that influences the body's insulin sensitivity and metabolic balance. Exercises may deliver its protective features against chronic disease such as type 2 diabetes mellitus (T2DM), cardiovascular illnesses, cancer, dementia, and depression by releasing protective myokines including irisin during muscle contraction, and this could potentially explain the connection between diseases and physical inactivity. These myokines include irisin, myostatin, interleukin (IL)-4, IL-6, IL-7, IL-15, myonectin, follistatin-like 1, and leukaemia inhibitory factor. Myokines have been identified to mediate of fat browning, and their function can be influenced by adipokines, indicating the communication between skeletal muscle and adipose tissue in controlling thermogenesis and energy expenditure.(7)

Irisin has properties that reduce inflammation, oxidative stress, and cell death. It has been demonstrated to affect many pathways in order to protect different tissues from stressful stimuli. It causes activities that prevent cell death by limiting the activity of certain enzymes, preventing the movement of a protein called Bcl-2 associated agonist of cell death (BAD) from one part of the cell to another, and decreasing the production of another protein called Bcl-2 associated X-protein (BAX). In addition, its caspase-dependent anti-apoptotic effects include reducing the activity of caspase-3, 8, 9, Bax, and increasing the levels of Bcl-2. Irisin seems to hinder oxidative stress through the AMP-dependent protein kinase (AMPK)-phosphoinositide 3-kinases (PI3K)-Akt-endothelial nitric oxide synthase (eNOS) signaling pathway. Irisin possesses anti-inflammatory effects as it can decrease the production of inflammatory cytokines such as tumor necrosis factor (TNF), IL-6, and nuclear factor kappaB (NF-κB), and the attraction of inflammatory cells such as T-cells and lymphocytes.(8) In this review, the beneficial properties of irisin on metabolism and aging process as well as its mechanisms will be discussed to highlight the potential future of irisin.

The Generation of Irisin

Irisin is a hormone consisting of 112 amino acids (aa), named after *Iris*, a Greek deity associated with messengers and rainbows. Irisin is believed to be produced by the cleavage of the transmembrane protein FNDC5. The FNDC5 precursor is composed of a signal peptide, a fibronectin III domain, a linker domain, a hydrophobic transmembrane domain, and a cytoplasmic domain. Due to the fibronectin III domain, FNDC5 bears resemblance to several cytokine receptors. Therefore, FNDC5 might also function as a receptor for a ligand that has not yet been discovered. Once the signal peptide is removed, the FNDC5 precursor needs to undergo N-glycosylation. There are two possible N-glycosylation sites, Asn36 and Asn81 (Asn39 and Asn84 in humans). Site alterations of Asn36 or Asn81 prevent N-glycosylation, thereby reducing the stability of irisin and causing FNDC5 to be retained in the endomembrane system. The FNDC5 precursor is subsequently converted into mature FNDC5 and moves to the membrane, where an unidentified protease breaks down FNDC5 between Glu140 and Met141 (Glu143 and Met144 in humans) to release irisin.(9)

However, the intricacies of FNDC5 cleavage are still not well understood. An enzyme from the A disintegrin and metalloproteinase domain-containing protein (ADAM) family, maybe ADAM-10, is a potential protease that breaks down FNDC5. Angiotensin II has the ability to increase the expression of ADAM-10, and may enhance the cleavage of FNDC5.(10) Interesting data found a protein in human plasma that includes a portion of the FNDC5 C-terminal domain having the region from Gln146 to Ile175 (Gln149 to Ile178 in humans), which was not expected to be present in irisin. Proteolysis can occur not only between Glu140 and Met141 but also at other sites. Furthermore, jogging downhill, which can result in muscle damage and inflammation, on the other side leads to a higher rise in irisin levels compared to running on level ground. This suggests that the rupture of muscle fibers may also release FNDC5 into the bloodstream. Therefore, irisin including a portion of the C-terminal domain or possibly entire FNDC5 protein might potentially be released into the bloodstream.(11)

Irisin is primarily generated by muscle, counted about ~72% including both skeletal and cardiac muscles. While skeletal muscle is generally seen as the main supplier of circulating irisin, cardiac muscle appears to generate more irisin than skeletal muscle during brief swimming sessions in animals.(12) Importantly, other tissues can also produce FNDC5 and release irisin, such as the liver, thyroid, adrenal gland, WAT, and the central nervous system (CNS) but only in a very small number. Adipose tissues provide the remaining less than 28% in rats, but in human the secretion of FNDC5 is 100-200 times lower in adipose tissue compared to skeletal muscle.(13,14) Physical activity was previously thought to be a primary factor in the rise in irisin levels, however further research has found that factors such as temperature, nutrition, and certain medications including fenofibrate, metformin, and all-trans retinoic acid can have an impact on irisin levels, but exercise is still become a significant trigger of irisin.(15)

Irisin levels increases as a result of prolonged or intense activity, with the highest increase observed during exercises of maximum intensity cycling at 80% of maximum oxygen uptake (VO_2max) for 50 minutes, or graded exercise until exhaustion, all raise levels of irisin up to 19% from the baseline right after the exercise and keep declining until one hour post exercise. On the other hand, running at a moderate intensity of 70% of maximum heart rate (HRmax) for 40 minutes and cycling at 60% of VO_2max for 60 minutes do not cause an increase in irisin. interestingly, intense running (at 85% VO_2max for 30 minutes) did not impact the level of irisin too (16), whereas running at a moderate intensity of 50-55% VO_2max for 40 minutes raised the levels of irisin up to 20% (17,18). Regardless of these findings, the majority of investigations appear to support the idea that acute exercise is a stronger trigger for the production of irisin. (19) Some data showed that short-term physical activity has minimal impact on muscle FNDC5 mRNA expression (20-22), while another study discovered that a single session of resistance training increases FNDC5 mRNA levels without influencing circulating irisin levels (23). Regular exercise increases FNDC5 in skeletal muscle, but without any change in irisin level. Another study showed an increasing in irisin level of 22.5-93.7 % range by 12-weeks of resistance training.(24) Therefore, the levels of irisin and the expression of FNDC5 may not be in sync throughout training. The contradictive results on irisin level after prolonged regular exercise suggest that regular exercise may enhance the effectiveness of irisin secretion caused by acute exercise. One suggestion is that long-term exercise may increase muscle FNDC5 expression, and a single instance of short-term exercise might therefore encourage greater FNDC5 cleavage.(25)

The levels of irisin exhibit significant variability following different frequency, type, intensity, duration of exercise, and subject's metabolic condition and age. Overall, the significant increasing of irisin level can be reached in moderate to high intensity exercises marked with graduate exhaustion during exercise, or in chronic resistance training for at least 12 weeks. As a result, the circulating value of irisin is influenced by the timing of blood and muscle sampling. The release of irisin in the heart muscle (12) and adipose tissue (26) could potentially be influenced by physical activity. While there is no proof that physical activity can stimulate the secretion of irisin from the heart muscle and fatty tissue, we cannot dismiss the chance that the levels of circulating irisin are influenced by the irisin secreted from these tissues. A 6-weeks running exercise increases FNDC5 expression in several tissues, such as the pancreas, kidney, WAT, BAT, and brain.(27) Importantly, regular exercise over a long period of time can strongly impact these tissues and potentially have significant effects on overall metabolic health, including changes in the expression of FNDC5 and the release of irisin.(5)

The glycosylation mechanism of FNDC5/irisin is not well understood. The FNDC5 sequence has three possible N-glycosylation sites, and two of these, specifically Asn-36 and Asn-81, are filled by N-glycans. Yet, the structure has not been determined until now, but it is known that the lack of oligosaccharides has a significant impact on the stability of the molecule. By using site-directed mutagenesis, one N-glycosylation site can be removed from the glycosylated molecule and showed that the elimination led to a notable decrease in the stability of FNDC5, with a half-life of approximately 7 hours instead of the 12-hours duration typically observed for the fully glycosylated protein. The FNDC5 protein without glycosylation does not adopt its usual spatial structure and is not integrated into the cell membrane, leads to a notable reduction in the release of irisin into the bloodstream.(28,29) Irisin also possesses two N-glycosylation sites located at Asn-7 and Asn-52. Removing the sugar groups from irisin reduces its molecular weight to 12 kDa or 15 kDa. Both N-glycans are likely significant in increasing the mass of one or two sugar chains after inclusion of some chains to 22 kDa or 25 kDa, respectively and these changes might alter irisin's stability and its halflife. Role of irisin in the browning of adipocytes is indicated by the up-regulation of mitochondria UCP1 expression and its transcriptional factor peroxisome, which is likely important for this function, as (Figure 1).(30,31)

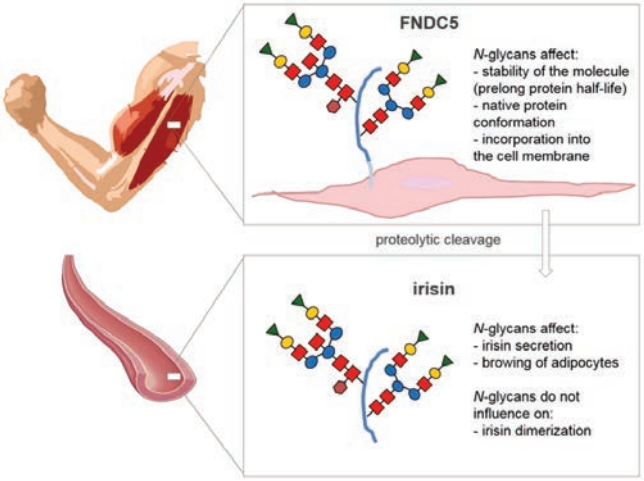

Figure 1. The role of N-glycans attached to FNDC5 and irisin proteins affecting its weight molecules and the stability.(31) (Adapted with permission from MDPI Basel).

Despite of many doubts about the presence of circulating human irisin, stemmed from two main reasons: firstly, human FNDC5 has a non-standard ATA translation start, and secondly, there are accusations that numerous human irisin antibodies used in commercial enzyme-linked immunosorbent assay (ELISA) kits do not possess the necessary specificity, recent studies has discovered and measured human irisin in plasma using mass spectrometry. This was done by employing control peptides that were enriched with heavy stable isotopes as internal standards. This advanced approach demonstrates that human irisin is mostly produced from its non-standard start codon and circulates at approximately 3.6 ng/mL in inactive persons. This level is elevated to around 4.3 ng/mL in those participating in aerobic interval training. This research clearly shows that human irisin is present, circulates, and is influenced by exercise.(32)

The Biology of Irisin

Several *in vitro* experiments, primarily using r-irisin on various cell types, have been published. Different signaling pathways was suggested to be influenced by irisin or involved in the regulation of irisin. The evidence suggesting that irisin primarily exerts its biological effects through mitogen-activated protein kinase (MAPKs) has been shown.(33) Besides the suggested impacts of irisin on fat tissue, bones, and the brain, many studies showed that irisin is important for energy metabolism and impact various function including anti-inflammatory and antimetastatic properties, enhanced glucose absorption in muscle cells, promoted the growth of endothelial cells, reduced blood pressure, and improved cardiac hypertrophy.

FNDC5 plays important role in the process of neuronal development, and FNDC5 expression increases following retinoic acid (RA) treatment of mouse embryonic stem cells (mESCs) and promote brain-derived neurotrophic factor (BDNF) transcript levels during brain development. RA attaches to its nuclear receptor, RA receptor (RAR), and then functions as a transcription factor to influence RA-responsive genes, such as the activation of the genes encoding MAPKs (ERK1/2, JNK, p38). Consistently, the decrease in ERK1/2 function greatly reduced the expression of FNDC5 and BDNF during the process of neuronal development.(34)

BDNF expression in the hippocampus can be influenced by FNDC5/irisin and contributes to its role in learning and memory function, protecting against brain illnesses like Alzheimer's disease (AD).(1) cAMP response element-binding protein (CREB) is a cellular transcription factor that is widely known for its involvement in neural plasticity and the creation of long-term memory in the brain. Recent research has shown that recombinant irisin activates the cAMP/PKA/CREB pathway in both human cortical slices and mouse hippocampus slices. The significance of irisin in neurogenic regulation has been determined since irisin promotes cell proliferation in mouse H19-7 HN cells through signal transducer and activator of transcription 3 (STAT3), but not AMPK and/or ERK. However, irisin does not have a dose-dependent impact on neurite outgrowth and synaptogenesis in these cells.(35)

Irisin triggers the browning of WAT through p38 and ERK elevating signaling. Irisin increased the expression of UCP1 in this process, a reaction that was hindered by medications that suppress p38 or ERK.(5) A recently discovered hormone called betatrophin has been found to play a role in the regeneration of pancreatic β-cells and particularly leads to an increase in β-cell mass in mice then improve insulin resistance. Irisin not only stimulates UCP1 expression via MAPK pathways (p38 and ERK), but also enhances the expression of betatrophin through same pathways.(36) It appears that irisin could activate MAPK signaling pathways, which play a role in cellular energy expenditure, cell proliferation, and differentiation in various cell and tissue types. The physiological coordination between the metabolic rate of tissues and organs is critically influenced by the activity of irisin.

Irisin can also function as a sort of adipokine, in addition to its myokine activity. Additionally, in addition

to its primary function of promoting the browning of WAT, irisin also prevents the lipids accumulation by increasing the expression of adipose triglyceride lipase (ATGL) and decreasing the expression of fatty acid synthase (FAS). (37) The peroxisome proliferator activated receptor-gamma (PPARγ), C/EBPa, and fatty acid-binding protein (FABP)4 axis, controlled by Wnt signaling, mediate this modulatory impact. Irisin increases the expression of Wnt6, Wnt10a, and Wnt10b, which inhibits adipocyte differentiation. (38) The role of irisin in Wnt signaling complements the browning of WAT, which is regulated by MAPK signaling pathways to reduce body fat percentage (BFP) in humans. Thus, it can be inferred that the primary factor influencing the release of irisin in the muscles is the regulation of body fat levels, which in turn affects the metabolic rate of adipose tissue.

Irisin might possibly have the potential to be used as a therapy to counteract heart fibrosis caused by angiotensin II. In skeletal muscle cells, ADAM-10 is accountable for splitting FNDC5 into irisin. This process leads to irisin-induced cardiac autophagy by activating the AMPK-mammalian target of rapamycin complex (mTOR) pathway. Given that FNDC5 expression is notably reduced in ischemic cardiomyopathy, in mice with severe chronic heart failure, the use of irisin could potentially be advantageous as a new therapeutic method for treating heart disease. Recent research has shown that Irisin also possesses qualities that can help combat cancer, depression, hypertension, and heart hypertrophy.(10)

Physical Activity and Muscle: Organ Crosstalk

In 2012, a novel chemical that is released by myocytes and subcutaneous fat was announced. The chemical was capable of causing alterations in adipose tissue and triggering thermogenesis.(6) In addition, it was suggested that this molecule serves as a connection between the muscles and other body tissues. The recently identified protein has been named "irisin," which is derived from the Greek goddess *Iris*.(39) Since then, irisin has been extensively studied, which has allowed researchers to acquire insight into its diverse features.(31)

Exercise can trigger various impact in molecular levels due to skeletal muscle plasticity. The myokines released by contracted muscle play an important role in the communication between skeletal muscles and other tissues, as well as maintaining overall body balance.(40) Exercise quickly induces significant alterations at the organismal level based on many criteria, such as kind, duration, and intensity.(41) In order to optimize myofibers contractions, the functioning of the circulatory, respiratory, metabolic, and neuroendocrine systems can be adjusted. To some extent, these changes are triggered by muscle tissue, such as the release of nitric oxide (NO), adenosine triphosphate (ATP), or reactive oxygen species (ROS) by myofibers. (42) Additional modifications are facilitated by hormonal communication, such as glucagon, catecholamines, or growth hormones. For instance, the production of glucose in the liver and the breakdown of fats in adipose tissue are increased to make sure that enough energy is provided to the contracting muscle fibers.(43)

Exercise also increases the expression of PGC-1α, a protein that helps the body adapt to exercise by promoting the growth of mitochondria, improving insulin sensitivity, increasing energy expenditure, and enhancing the formation of new blood vessels. PGC-1α in muscle can initiate a breakdown of FNDC5 (a protein found in the membrane) to generate irisin, which is then released into the bloodstream. Irisin is also produced in the hippocampus after exercise in a PGC-1α-dependent manner, leading to the activation of many neuroprotective genes. After exercising, several substances such as lactate, pyruvate, glycerol, alanine, glutamine, and β-hydroxybutyrate (BOHB) are present in increased amounts in the bloodstream. Certain metabolites, such as lactate and BOHB, can serve as energy sources for CNS when glucose is scarce, and also operate as signalling molecules at the central level by binding to hydroxycarboxylic acid receptors (HCARs).(44) BOHB and lactate transport are facilitated by monocarboxylate transporters (MCTs) at the blood-brain barrier (BBB) (45), which also be altered by physical activity in rat hippocampus (46). Lactate affects the activity of neurons, the signalling of calcium, the myelination of axons, the construction of new blood vessels, and the creation of memories. Glutamine, which is the most plentiful free amino acid in the human body, is important for providing energy and creating proteins. It also has a strong influence on several pathways that are associated with inflammation, cell health, and metabolism. Interestingly, glutamine levels increased in the rat hippocampus, striatum, and cerebellum after endurance exercise.(47) However, because the brain independently produces glutamine and the BBB is somewhat impermeable to this amino acid, it is doubtful that there would be a redistribution from skeletal muscle in this situation.(48) Lastly, it is crucial to emphasize the metabolic connection between neuronal and glial cells. Prolonged exercise reduces brain glycogen, which is

primarily stored in astrocytes and provides lactate to nearby neurons. The transfer of lactate from astrocytes to neurons has been linked to the establishment of long-term memory and has been found to affect endurance ability.(49)

Immunohistochemical research revealed that lower quantities of irisin are also generated in visceral adipose tissues, testes, liver, pancreas, brain, spleen, heart, and stomach. Irisin concentration was discovered to be greater in physically active individuals compared to those who are sedentary (p=0.006). Additionally, the level of irisin is influenced by the activities carried out at home, as it was observed that serum levels were significantly higher in rural individuals compared to urban residents (p<0.0001). (50) The kind of physical activity has an impact, as irisin upregulation was shown after high-intensity exercise (51) and after resistance training, but not after the endurance exercise (52). The level of irisin in the blood was discovered to be approximately 3.6 ng/mL in inactive individuals and increases to 4.3 ng/mL in active individuals. Whole-body vibration exercise also helps increasing the level of irisin concentration.(53) In addition to physical activity, food and hormonal balance also impact the levels of irisin.(54) Reduced levels of irisin were found in metabolic diseases including obesity, T2DM, chronic renal failure, and persistent hypothyroidism.(33)

So far, a particular receptor for irisin has not been identified and recent findings showed that since irisin shares a great homolog with integrin ligands, irisin might exerts almost all of its effects via binding to the members of the αV integrin family, particularly αVβ5 as its main receptor. (55) Muscle extracellular Hsp90α (eHsp90α) level is elevated by exercise. In mice, eHsp90α acts as co-factor that mediates irisin binding to integrin αVβ5 with high affinity. (56) Integrins are extensively present transmembrane receptors that attach to extracellular matrix ligands (cell-matrix interactions), membrane proteins of adjacent cells (intercellular interactions), and identify soluble ligands (57) for the attachment, movement, and clustering of cells both from cells to cells or to the extracellular matrix (31). Therefore, integrins mediates cells physiology and pathophysiology.(68)

Exercise acts by inducing stress both during and after its performance, and it has the potential to induce inflammation.(59) Interestingly, though, regular physical exercise training will act as a persistent anti-inflammatory treatment, once the initial acute inflammatory activities have been resolved.(60) In addition, the acute pro-inflammatory processes that occur initially after exercise, may play a crucial role in the long-term adaptive responses to exercise training by releasing cytokines. Inflammation is necessary to induce repair processes, that result from exercise and training.(61)

Short periods of high-intensity training start a series of complicated inflammatory processes which are influenced by factors such as the type, intensity, duration, and familiarity of the exercise, age and clinical condition of the participants. Exercise can impact various measurable immunological parameters, including alterations in the numbers of peripheral blood cells, activity of granulocytes, cytotoxic activity of natural killer (NK) cells, proliferation of lymphocytes, and levels of cytokines in plasma, among other factors.(62)

Cytokines are soluble proteins or glycoproteins that are created and released during inflammation. They have a role in facilitating communication between immune and non-immune cells and regulating several biological processes. The production of cytokines can be increased quickly in response to inflammatory signals, and this response might be short-lived or long-lasting. The inflammatory cytokines (TNF-α, IL-1β, and IL-6) are released following physical exercise of enough intensity, followed by the release of anti-inflammatory or regulatory cytokines (IL-4, IL-10, IL-1RA, and IL-13) that reduce that reaction.(63)

Many proteins are influenced by inflammatory processes. Proteins that experience an increase in concentration are known as positive acute-phase proteins. C-reactive protein (CRP) is a protein produced by the liver in response to acute inflammation. It is used as a marker to indicate the presence of inflammation throughout the body and is also linked to the risk of CVD. In addition, its levels have been associated with weakness, illness, and death.(64) CRP levels are lower in individuals who engage in moderate exercise as compared to those who are inactive. Creatine kinase (CK) is a protein involved in muscle metabolism, and its quantity is typically regarded as an indicator of physical stress.(65) The release of CK into the plasma is considered a semi-quantitative measure of damage in muscle fiber.(66) CK levels are different based on sex and race, and the type of exercise. Eccentric exercise results in more muscle damage compared to concentric contractions of similar intensity. Figure 2 describes how exercise activates the secretion of many factors from the muscle including PGC-1α, and many proinflammatory factors that induce BDNF in neurons, while preventing the accumulation of kynurenines (KYN) in the brain. Increased BDNF level then improve cerebral vascularization and plasticity.(67)

WAT and BAT were different on its morphology, namely the fat cells' structure and function. WAT mostly

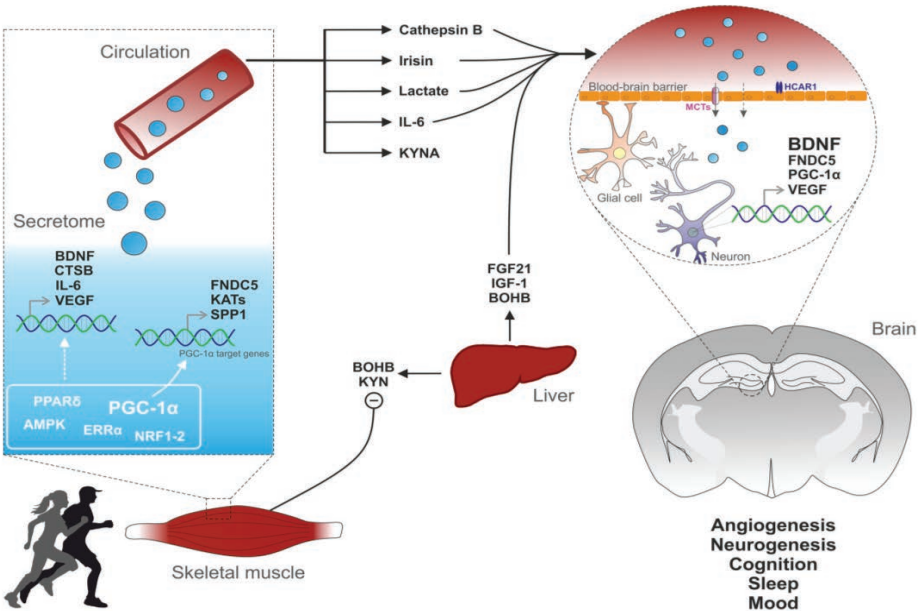

Figure 2. Muscle-brain crosstalk. Physical exercise activates specific cellular pathways in muscle cells. (67) (Adapted with permission from Frontiers Media SA).

consist of mature white fat cells with peripheral nucleus and contain a large lipid droplet, and function by storing extra energy as triglycerides, shielding organs from physical harm, and producing adipokines that control different biological processes, such as inflammatory responses. Thermogenesis occurs in BAT and is important for maintaining body temperature. BAT on the other side, consists of several tiny lipid droplets, a nucleus on the centre, and a high quantity of mitochondria. The lipids in BAT are mostly utilized for oxidative phosphorylation and production of heat facilitated by UPC1 or also known as thermogenin in the mitochondrial membrane.(68-70)

Increased PGC-1α during exercise is accompanied by a rise in the production of new mitochondria. PGC-1α controls gluconeogenesis and has an impact on heme biosynthesis. Irisin also impacts the functioning of WAT, and the effects of its actions vary according on the degree of cell differentiation. In BAT, PGC-1α, together with irisin, regulates the expression of UCP1 and thermogenesis. Consequently, there is an increase in energy consumption, then lipids and glucose metabolism is stimulated. Irisin also result in browning, or a transformation of the cell's characteristics from WAT to BAT. In browning, a third variety of adipose tissue known as beige adipocyte tissue may be created. The browning process was controlled by irisin-induced activation of MAPKs, including ERK and p38 protein. The application of irisin to WAT preadipocytes did not lead to their browning, but instead inhibit adipogenesis and significantly decreased the generation of new adipocytes. Moreover, irisin improves insulin sensitivity by promoting glycogenesis and decreasing gluconeogenesis. Because of these characteristics, irisin could potentially be considered as a choice for preventing and managing obesity and diabetes.(71)

Hippocampus is the important part of the brain for memory and learning. Regular exercise has a positive impact in improving hippocampus, and cognitive performance (72) by enhancing the growth and specialization of mouse neurons, extended their lifespan, and promoted movement (73). FNDC5 is found in Purkinje cells of the cerebellum (74) and in rodent hippocampus (1). Insufficient FNDC5 expression hindered the process of mouse embryonic stem cells transforming into neurons and disrupted the development of astrocytes.(75) Aplication of a higher dosages of irisin (50-100 nM) promoted the growth of mouse H19-7 hippocampus neuronal cells.(35) Oppositely, irisin decreased neuronal damage caused by oxidative stress by blocking the release of proinflammatory cytokines, like TNF-α and IL-6, through the Akt/ERK1/2 signaling pathway in a mouse model of cerebral ischemia (MCAO) (76), probably linked to the stimulation of the PGC-1α/BDNF pathway. Physical activities enhance mood, and more recently they have also been seen as having antidepressant effects. Besides serotonin, irisin might possibly play a role in this effect, as lower levels of this myokine are linked to changes in mood.

Physical activity also a powerful motivator for promoting the growth of bones. Regular exercise has a positive impact on bone mineral density (BMD), improves mineral content, and lowers the incidence of fractures. Therefore, it can help prevent bone loss that occurs with aging. Irisin greatly enhanced the size and power of the

cortical bones and made positive changes to their shape by reducing the production of substances that inhibit osteoblasts and triggering the activation of activating transcription factor 4 (ATF4) and runt-related transcription factor 2 (Runx2). This, in turn, led to the activation of genes specific to bone formation, such as Osx (which encodes osterix) and Col1a1 (which encodes collagen type I α1), as well as an increase in the activity of cells involved in bone formation cells.(77) An *in vitro* study has also demonstrated that irisin promotes the process of osteoblast development by activating the aerobic glycolysis pathway. The MAPK signaling pathway was proposed to have a significant function in irisin-induced osteogenesis.(77,78)

Contradictive results were shown in obese individuals. It was proposed that a condition of irisin resistance, similar to leptin resistance, may be observed throughout the progression of obesity. This could perhaps account for the higher levels of irisin found in these individuals.(79) A study reported an increase of fat mass by 1 kg can result in a doubling of irisin level, while two other studies showed that weight loss in obese individuals leads to a decrease in serum irisin levels.(80,81)

Recent data has indicated that adipocytes are sensitive to irisin.(82) Adipocyte in inflammatory condition generated and released significantly lower levels of pro-inflammatory cytokines when they were cultured with irisin. Irisin also lowered monocyte chemoattractant protein-1 (MCP-1) expression, which in turn reduced the migration of macrophages. In addition, irisin hindered the expression and release of leptin, a kind of adipokine linked to pro-inflammatory activation, and increased the level of adiponectin, an anti-inflammatory cytokine.(82) Leptin function is strongly linked to insulin resistance and the onset of metabolic syndrome. Leptin is found to be involved in the expression of FNDC5 in adipose tissue.(83) Adiponectin, a substance that reduces inflammation in fat cells, enhances the cell's response to insulin. Insulin levels are known to drop with obesity, and may be linked to the development of insulin resistance.(84) Irisin, through the heme oxygenase 1 (HO-1)/adiponectin pathway, enhances the function of perivascular adipose tissue (PVAT) in mice with diet-induced obesity and thus decrease TNF-α. This might be the protective pathway of irisin. Additionally, it reduces the anti-contraction effect of PVAT.(85) Irisin also enhanced endothelial function in overweight individuals by activating the AMPK-eNOS pathway. Given the beneficial anti-inflammatory effects of irisin on both adipocytes and macrophages, it becomes logical to search for variables that enhance sensitivity to irisin.(86)

Control of Satellite Cell Function in Muscle Regeneration and Disruption in Aging

Skeletal muscles, make up the largest amount of tissue in a healthy-weight person (40-50% of total mass), serve multiple important functions in the human body. They are responsible for controlling movement, as well as essential processes such as breathing, eating, energy expenditure, and maintaining balance in glucose, amino acids, and lipids. Ultimately, skeletal muscles play a crucial role in maintaining a good quality of life (QoL). Typically, the metabolic changes happening in skeletal muscles are believed to affect health and disease, and the quality of muscle mass is a significant predictor of death. Skeletal muscle is composed of organized groups of myofibers (which are muscle cells that have many nuclei, are striated, and can contract) and a complex system of blood vessels, nerves, and the extracellular matrix (ECM). Skeletal and cardiac muscle cells are unique because their cytoplasm contains contractile proteins that are surrounded by organelles, particularly mitochondria and endoplasmic reticulum. Unlike other types of cells, the cytosol of contractile proteins and organelles is densely packed, leaving no vacant space. This structured arrangement suggests that the turnover of proteins and organelles significantly affects the size and function of myofibers.

When exercising or experiencing anabolic hormone stimulation, muscles increase in size due to the accumulation of new proteins and organelles in the cytosol, which leads to an increase in cellular volume. This process is known as hypertrophy. On the other hand, catabolic situations including cancer, infections, diabetes, organ failure, or inactivity/disuse lead to a decrease in proteins, organelles, and cytoplasm, resulting in a reduction in cellular volume known as atrophy. Thus, the equilibrium between biogenesis/biosynthesis and removal/destruction determines the size and function of muscle cells. The pathways that regulate the balance between synthesis and degradation are controlled by signals that come from both autologous and non-autologous signals such as from the cells that surround muscle fibers, such as muscle stem cells or known as satellite cells.(87) Satellite cells located beneath the basal lamina and next to the plasma membrane of myofibers in certain microenvironments. Satellite cells make it possible for healthy adult muscle to completely restore its structure and ability to contract after both normal daily use and sudden injury.(88,89)

In homeostatic muscle, satellite cells are often in a condition of quiescence, which means they remain quiescent and temporarily unable to go through the cell cycle. When there are muscle injuries, which can be either small (like strains, stretching or exercising) or serious (like trauma or degenerative muscular disorders), signals from the changed environment activate satellite cells and encourage their muscle-building activities. Activated satellite cells (ASCs) experience significant changes in energy usage to increase their ability to create new molecules and multiply, resulting in enough offspring to aid in regeneration. After going through multiple rounds of multiplication, these cells stop dividing and either transform and merge at the injury site to fix the damaged fibres or renew themselves and replenish the quiescent satellite cell (QSC) group to prepare for future instances of muscle damage and repair. Satellite cells also become active and multiply in response to an increase in muscular load, like the kind caused by physical exercise, and help in the effective growth of adult muscle fibres.

The long-term presence of satellite cells in the body makes them especially susceptible to the accumulation of damage inside the cells, which ultimately results in a decrease in the number and effectiveness of satellite cells. These changes hinder the effective regrowth of skeletal muscle in older individuals. In the process of aging, the ability of satellite cells to regenerate is gradually diminished in hereditary muscle wasting disorders. One such disorder is Duchenne muscular dystrophy, which is the most common and severe muscle disorder found in infants. This disorder is caused by the absence of dystrophin, a large protein that is involved in the contraction of muscle fibres and the division of satellite cells.

Not all stem cells are the same, even within the same tissue. This diversity has been suggested as an advantageous characteristic of stem cells, enabling them to quickly adapt to the evolving needs of their surrounding tissue by retaining a range of functional capabilities.(88) The transcriptional programs that determine satellite cells depend on the paired box protein (PAX)7 transcription factors PAX3 and PAX7. PAX3 plays a more significant role in the early embryo, whereas PAX7 becomes more important from mid-embryogenesis onwards. The myogenic regulatory factors (MRFs), namely MyoD, myogenic factor 5 (MYF5), myogenin, and MRF4 have a role in determining the identity of myogenic cells, as well as in the differentiation and development of muscle fibres in the embryo. They also contribute to the production of new fibres during muscle regeneration in postnatal life.(90,91)

Updated data recognized different subgroups of satellite cells can be distinguished based on gene activity, epigenetic signals, characteristics of the cell surface, and functional properties like as division rates, ability to self-renew, and resilience to stress. While another study divides satellite cells based on their association with a particular myofibre type or embryological origin, For instance, satellite cells derived from extraocular muscles, which are responsible for eye movement, demonstrate higher rates of proliferation and fusion. They also respond differently to the effects of aging and are even preserved in muscular diseases, unlike satellite cells from other muscles.(92,93)

Quiescence is the state when a subset of tissue-specific adult stem cells are arrested in the G0 phase of the cell cycle, for extended periods of time. These cells have the ability to re-enter the cell cycle and become active adult stem cells in response to physiological injury. Disruption of quiescence frequently leads to an uneven distribution of progeny cells, which ultimately causes a decrease in stem cells and has a negative impact on the balance and renewal of tissues. Satellite cells have a role in both the creation of new myofibers following injury (regeneration) and the effective growth of existing adult myofibers in response to increased load (hypertrophy). After QSCs are activated, each next stage of the regeneration process (proliferation, differentiation, and fusion to produce myofibers) is precisely controlled by specific elements that are inherent to satellite cells (which will be detailed later) and variables from the surrounding and overall environment.

Age-related issues in the activation and growth of satellite cells were initially explained as outcomes of altered systemic environment. The main cause of reduced regenerative ability of satellite cells is their ability to exit from the cell cycle. This can be impacted by the epigenetic activation of the *p16Ink4a* gene and the development of a pre-senescent state, which can eventually lead to full senescence when subjected to regenerative stress. Upstream driving factors such as the accumulation of ROS was caused by damaged mitochondria due to impaired autophagy, long-term activation of p38α/β MAPKs, and reduced expression of the transcriptional repressor Slug. Impairments in autophagy and mitochondrial processes can further restrict the activation of satellite cells by reducing cellular energy production.(94)

Interactions with the microenvironment signals control all aspects of satellite cell function, guaranteeing successful regeneration. Recent research further suggests that satellite cells are not solely passive recipients of niche signals, but they also play an active role in signalling to

regulate neighbouring cell types.(88) Satellite cell numbers in inactive muscle decrease with age, and have diminished repair capacity. The elevated production of fibroblast growth factor (FGF)2 by elderly myofibers is accountable for the reduction of satellite cell quiescence in normal conditions, causing a continuous state of activation that depletes the satellite cell pool and increases cell death. Increased expression of sprouty RTK signaling antagonist 1 (SPRY1), a suppressor of tyrosine kinase growth factors, helps to counteract the increased FGF2 signalling and provides greater resistance to maintain quiescence in older satellite cells. In addition, the long-term activation of mTORC1 due to ageing or repeated activation of satellite cells, which leads to continuous proliferation and differentiation of ASCs, may cause depletion of the stem cell pool by promoting stem cell differentiation.(95) Therefore, therapies that decrease mTORC1 activation in mice can maintain satellite cell populations in old age. In addition, forkhead box protein O (FOXO) signalling is required to keep true QSCs in a quiescence state by controlling gene expression, such as Cd34 and MyoG. Since AKT signalling may both activate mTORC1 and inhibit FOXO, an increase in AKT activity, which is regulated by several growth factors such as insulin and IGF given by the aging niche, could significantly contribute to the depletion of satellite cells.(96) Perhaps by understanding the satellite cells character in aging, we can dig more appropriate strategy to maintain the skeletal muscle. On the other side, irisin inhibit the act of myostatin, and together with FGF21 activate mTOR pathway for muscle protein synthesis, while insulin-like growth factor (IGF)-1 stimulates satellite cells and induce their proliferation.(97)

Irisin in Metabolic Disease

Obesity is a health issue that exists in both developed and underdeveloped countries. Most obesity develops into insulin resistance which serves as the connection between obesity and chronic degenerative illnesses including T2DM and CVD. In the last ten years, the majority of research on metabolic illnesses has concentrated on adipose tissue and its involvement in chronic inflammation. In recent times, the role of muscle function or dysfunction has gained importance in maintaining metabolic balance. Skeletal muscle, like the gut and adipose tissue, has also been suggested to function as an endocrine organ. It can secrete hormones known as myokines, which play a significant role in postprandial glucose uptake and lipid metabolism, and to communicate with other tissues, such as adipose tissue, liver, and bone. The release of myokines can be influenced by the type and intensity of physical activity. This discovery has led to the theory that some of the positive effects of exercise on metabolic illnesses may be connected to myokines and how they interact with other systems.(98)

Originally classified as a myokine, modest quantities of irisin are also produced and released from the liver or adipose tissue. Irisin is produced in response to exercise in both mice and humans, and suggested to promote the browning of WAT leads to an increase in energy expenditure.(99) Irisin stimulates the expression of several genes related to muscle development and the reaction to exercise in muscle cells. When injected into mice, it leads to noticeable muscle growth by activating satellite cells and promoting protein synthesis. This suggests that irisin acts as a myogenic agent. The WAT is regarded as the second most significant irisin source following the skeletal.(100) In mice, FNDC5/irisin is largely released by adipocytes in the subcutaneous adipose tissue (SAT) and to a lesser extent by adipocytes in the visceral adipose tissue (VAT).(26) The WAT-derived FNDC5/irisin might make up around 30% of its circulating levels and, like skeletal muscle, its production is enhanced during endurance exercise training. In humans, WAT has a limited role in the levels of circulating irisin. After being released into the body during exercise or exposure to cold temperatures, irisin encourages the production of UCP1 and the browning of WAT. This leads to a rise in overall energy expenditure in the body through increased UCP1-mediated thermogenesis.(101) In human preadipocytes from subcutaneous adipose tissue, irisin prevents the process of maturation into fully developed adipocytes. Somehow, it does not promote browning and instead reduces genes associated with browning like irisin does in fully developed human fat cells. In addition, irisin promotes glycolysis as shown by an increase in lactate production.(40)

Irisin shows varying effects based on the species (rodents, humans), type of fat cells (immature or mature fat cells), and location/type of the fat tissue (SAT, VAT, BAT). In mice with obesity, the levels of irisin in the bloodstream increase when they are injected with adenoviral particles that produce FNDC5 or when they are given recombinant human irisin through the abdomen. Moreover, treatment with irisin either *in vitro* or *in vivo* promotes basal and isoproterenol-induced breakdown of fats, enhances lipid metabolism, and reduces lipid production in mice. Interesting how recent data indicates that irisin may have an appetite-suppressing effect in fish, and its actions may be influenced by several elements that govern hunger, including as cocaine and amphetamine-regulated mRNA, orexins, UCP2, and brain

agents such BDNF.(102) The effect of natural irisin on food consumption is probably influenced by its interactions with other metabolic peptides; unchanged natural irisin is necessary to regulate food intake in zebrafish.(103) In humans, the decrease in irisin levels with higher energy intake aligns with the negative metabolic consequences of overeating.(104)

Many research have found that circulating irisin is generally linked to body mass index (BMI) and weight. Individuals diagnosed with anorexia nervosa have a 15% decrease in circulating irisin levels when compared to those of normal weight, and a 30% decrease when compared to individuals who are severely obese. Higher levels of irisin were found to have a positive correlation with the circulating endothelial progenitor cells.(105) In addition, irisin levels are said to have a positive correlation with leptin (106) and a negative correlation with adiponectin. It seems unlikely that there is a direct connection between leptin and irisin, as giving leptin to humans does not change the levels of irisin in the bloodstream. In conclusion, losing weight decreases irisin levels, which are then replenished when recovering the lost weight.(107)

Irisin has the potential to have several positive impacts on glucose regulation and insulin sensitivity by increasing energy expenditure, glucose uptake, and glycogenolysis, while also lowering gluconeogenesis, adipogenesis, and lipid accumulation. Moreover, it could enhance the survival of pancreatic beta-cells and enhance insulin production in response to glucose in lipotoxic circumstances by inhibiting apoptosis triggered by either high glucose or high saturated fatty acids. Irisin level appear to higher in individual with type 1 diabetes mellitus (T1DM), but lower in T2DM compared to controls. Ethnicity also play a role, as the link between T2DM and irisin was stronger in Asian populations compared to European populations. This could clarify the conflicting results regarding slightly elevated irisin levels in Caucasian (108) and Saudi Arabian (109) T2DM patients. Likewise, there have been reports of reduced irisin levels in populations with pre-diabetes and in drug-naive patients with T2DM.

Irisin levels have also been linked to diabetic macro- and microvascular problems. In a group of 100 recently diagnosed, non-obese, and drug-naive patients with T2DM, there was a negative correlation between blood irisin levels and urinary albumin excretion. T2DM individuals with macroalbuminuria exhibit notably reduced levels of irisin compared to normo-albuminuria/microalbuminuria T2DM and healthy individuals. A greater decrease in irisin levels is observed in stage 5 chronic kidney disease (CKD) (110), while the decrease in muscle mass and/or the severe decrease in renal function may impact irisin levels. CKD patients commonly experience weight loss, and progressive muscle and fat loss. Resistance training in hemodialysis patients can increase the muscle mass but does not impact the resistin level. This might be because the uremic toxin upregulating autophagy and directly inhibiting irisin precursor (FNDC5) expression and blocking the PGC-1α signaling pathway.(111) It appears that there is a decline in the level of irisin in the blood serum of individuals with T2DM, and an even more significant decrease in patients with diabetic nephropathy.(112) Therefore, irisin can be an independent contributor for CKD comorbidities including sarcopenia, mineral and bone disorder, and CVD.(111)

Irisin could potentially be investigated for the future treatment of T2DM. Metformin was demonstrated to enhance FDNC5 mRNA/protein expression and irisin levels in diabetic mice, independent from adenosine monophosphate AMPK (113), shows its beneficial in metabolic effects. New data suggests that β-arrestin-2 has an important role in irisin-induced glucose metabolism in T2DM by controlling the p38 MAPK signalling, and could potentially be a new target for treating diabetes. The β-arrestin-2 enhances glucose utilization in diabetes by increasing glucose uptake and insulin sensitivity, as demonstrated in mice with higher levels of β-arrestin-2.(114)

Hepatic production of irisin can be stimulated, at least partially, by the constitutive androstane receptor, a nuclear receptor that is able to directly promote FNDC5 expression in the liver to increase irisin levels in the bloodstream of mice. (115) Irisin has been found to play a role in the regulation of glucose and lipid metabolism in liver cells and animal models. In HepG2 cells, of human primary hepatocytes, and in diabetic mice, irisin decreased hepatic gluconeogenesis and enhanced glycogenesis, leading to an improvement in glucose homeostasis. These effects were accomplished via PI3K/Akt and AMPK pathways. Regarding lipid metabolism, it was first demonstrated that irisin treatment prevented lipids accumulation induced by palmitic acid in mice liver cells (AML12 and primary hepatocytes). This was achieved by inhibiting two key regulators of lipogenesis, namely liver X receptor-α and sterol regulatory element-binding protein (SREBP)1c.(116) Later on, irisin treatment was found to decrease the amount of cholesterol in mouse primary hepatocytes and in obese mice fed a high fat diet (HFD) (117), or the amount of triglycerides in human HepG2 cells (118), human primary hepatocytes, and ob/ob mice by activating AMPK and subsequently inhibiting SREBP2 and other lipogenic enzymes.

Irisin might also have an impact on oxidative stress and the survival of liver cells, which are closely linked to the development of non-alcoholic fatty liver disease (NAFLD). The ROS levels caused by hydrogen peroxide in mouse liver cells were somewhat decreased following irisin therapy. The liver (as well as the lung) was harmed by breathing in formaldehyde, also caused a decrease in irisin levels. However, after giving carnosine supplements to Sprague Dawley rats, the irisin levels were recovered.(119) In addition, irisin therapy reduced the oxidative stress caused by palmitic acid in mouse liver cells and primary hepatocytes.(116) Several investigations have indicated that irisin supports cell viability in HepG2 cells through an AMPK-dependent mechanism.(118) Recent results suggest that increased irisin levels may play a protective role in liver cancer cells by partially activating the PI3K/Akt pathway. This activation could potentially promote hepatocellular carcinoma (HCC) and reduce the susceptibility to chemotherapy. It is worth mentioning that NAFLD is a significant risk factor for the development of HCC.(120)

The myocardium, which is one of the largest muscles in the human body, also releases irisin. Its impact on the levels of circulating irisin is significant, at least in animals. Ischemic heart diseases, such as coronary artery disease (CAD) and the comorbidity, myocardial infarction (MI), alter the secretion of irisin. This impact can directly result from cardiomyocytes stress or damage, or indirectly by the poor lipid profile associated with these situations. Regarding the direct impact of CAD/MI on irisin secretion, it was once believed that the injured heart muscle cells would lead to higher levels of irisin after a heart attack. However, in rats, the expression of irisin in tissues and circulation are lower in cases of isoproterenol-induced MI and have a negative correlation with well-known indicators of cardiac injury, such as troponin and creatine phosphokinase-myocardial band iso-enzyme (CK-MB). The lower irisin level in individuals with T2DM who had macrovascular disease have been linked to endothelial dysfunction.(121) These results suggest that irisin is not released passively due to cardiomyocyte injury, like CK-MB, but is actively secreted as a reflection of the adequacy of blood supply and the functional capacity of the heart muscle. In another study, it has been suggested that when there is a decrease in blood and oxygen flow, the myocardium might release less irisin to limit the metabolic needs of the heart in order to compensate for the reduced energy. This idea is backed by studies indicating that the expression of FNDC5 is regulated by oxidative stress, and that irisin plays a crucial role in maintaining energy balance and promoting the growth and function of cardiomyoblasts.(122)

Polycystic ovary syndrome (PCOS) has been strongly associated with obesity and other metabolic symptoms of insulin resistance (IR) syndrome, such as NAFLD.(123) Several research have found that irisin levels are generally greater in women with PCOS compared to controls. However, there are also other studies that have observed similar or lower levels of circulating irisin in women with PCOS compared to controls. Irisin levels were shown to be higher in overweight/obese women with PCOS compared to those with normal weight in certain research.(124) Irisin can affect the metabolism through autocrine or paracrine manner (Figure 3).(125)

Bone tissue could produce FNDC5 and/or irisin during exercise as studied in 5-week-old mice. The expression of FNDC5 protein and irisin rose by a factor of 6 in bone tissue and to a lesser extent in articular cartilage following exercise. Furthermore, the osteogenic potential of irisin has been confirmed by studying its impact on undifferentiated bone marrow stromal cells and was showed that irisin enhance the differentiation of osteoblasts through the Wnt/β-catenin pathway.(126) In a more recent study, irisin was shown to activate the p38 MAPK and ERK, leading to the proliferation, differentiation, alkaline phosphatase activity, and mineralization of cultured osteoblasts.(78) Moreover, the suppression of p38 MAPK or pERK eliminated the stimulatory and enhancing effects of irisin, validating its direct impact on osteoblasts via these mechanisms.(127)

Irisin and The Bone

Bone tissue is characterized by its intricate composition and wide range of cell types. Bone is made up of inorganic ions (30%) and collagenous and non-collagenous proteins (70%). It also acts as a storage place for minerals like calcium, phosphorus, magnesium, sodium, and bicarbonate. In addition to strict restrictions from hormones like Vitamin D (cholecalciferol), parathyroid hormone (PTH), and calcitonin, and with the help of many organ systems, these minerals are kept in balance. The minerals in the bone compartment are maintained in perfect balance by different cells. These cells may have changed functions due to genetic alterations associated with primary osteoporosis, hormonal changes such as the loss of estrogen in post-menopausal women and the loss of androgens in men, natural aging, or pathological changes caused by disease or treatment. These factors can result in various forms of osteoporosis.(128)

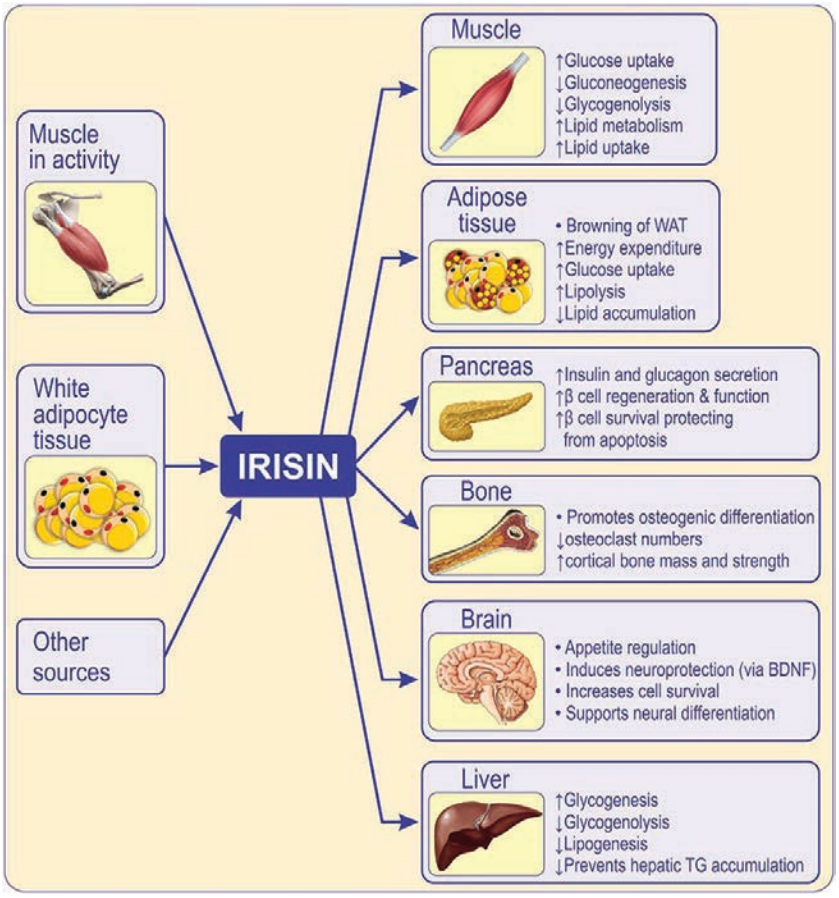

Figure 3. Irisin can act locally, in autocrine or paracrine manner to effect the metabolism.(125) (Adapted with permission from Frontiers).

There are many human and animal studies observed the involvement of irisin in promoting bone formation. *In vivo*, irisin was found to enhance the differentiation of osteoblasts through the Wnt/β-catenin pathway. (126) It also stimulated the growth, differentiation, alkaline phosphatase activity, and mineralization of cultured osteoblasts by activating p38 MAPK and ERK. (78) Additionally, in RAW264.7 cells, irisin inhibited the development of osteoclasts by suppressing the receptor activator of NF-κB ligand (RANKL).(129) In addition, the administration of irisin within the peritoneal cavity led to an increase in the thickness of both trabecular and cortical bone, as well as the number of osteoblasts. Likewise, in male mice, the introduction of recombinant irisin increased the activity of genes related to bone formation, such as Runx2, Osterix, low-density lipoprotein-related protein 5, β-catenin, alkaline phosphatase, and type I collagen, in bone marrow stromal cells. This led to an increase in bone formation and a decrease in the number of osteoclasts, resulting in higher cortical bone mass and strength. (77) Ultimately, in mice with hind-limb suspension, the administration of recombinant irisin maintained the density of both cortical and trabecular bone, and also avoided the expected reduction in trabecular bone volume caused by immobility.(130) In human studies, the levels of irisin were negatively correlated with the levels of sclerostin, which is a substance that inhibits osteoblastic activity, and was positively associated with BMD and strength in young athletes, as well as with bone mineral status assessed using quantitative ultrasound (QUS) in healthy children. In addition, the levels of irisin in circulation were found to have a negative correlation with past osteoporotic fractures in postmenopausal women. This correlation was independent of other parameters related to bone fragility, such as BMD and bone turnover indicators.(131)

Age-related functional deterioration in osteoblasts is caused by increased apoptosis, decreased proliferation, impaired osteoblast differentiation, increased osteoblast senescence, and defective osteoprogenitors. This ultimately leads to a preference for marrow adipogenesis as the pathway of choice.(132) The decrease in bone mass as people get older is related to the formation of bone marrow adipose tissue (BMAT) in an opposite way. BMAT is also observed in post-menopausal women, as a result of immobility caused by spinal cord injury and steroid therapies. Age become an additional factor that contributes

to this. Inherited alterations in many genes have been linked to the development of idiopathic osteoporosis and skeletal aging.(133) For example is the different level of expression in various genes related to bone formation, including Wnt10b, Runx2, RANKL, osterix, osteocalcin (OCN), osteoprotegerin (OPG), and sclerostin (SOST) in individuals with male idiopathic osteoporosis. This condition is characterized by reduced bone volume and a decrease in the number of trabeculae, and lower expression of the genes Wnt10Bb, Runx2, RANKL, and SOST.(134)

Higher mechanical stimuli, such as those experienced during exercise, reduce the generation of sclerostin, hence promoting canonical Wnt/β-catenin signaling and the development and activity of osteoblasts.(135) The administration of irisin resulted in the stimulation of sclerostin production by osteocyte-like cells in a laboratory setting, as well as in mice bones that were enriched with osteocytes, in a manner that was dependent on the dosage. This also led to an increase in the levels of circulating sclerostin. These alterations suggest a decrease in osteoblast activity, which is different from the previously reported relationship between circulating irisin and sclerostin levels in humans (136), as well as the positive effects of irisin on bone formation shown in prior research. In addition, the study also found that FNDC5 knock-out mice had lower levels of RANKL, which is a key factor in the development, function, and survival of osteoclasts.(55) In addition, the knock-out animals exhibited higher femoral trabecular bone mass and greater connection density, perhaps as a result of the subsequent decrease in bone resorption, and interestingly were resistant to bone loss caused by ovariectomy. The second one was ascribed to the inactivation of both bone resorption by osteoclasts and bone breakdown by osteocytes. Osteocytes, in addition to indirectly stimulating bone resorption by increasing RANKL synthesis, can also directly resorb bone during times of high calcium demand. This is known as osteocytic osteolysis.(137)

The negative impacts of irisin on bone are challenging to reconcile with its supposed positive effects on many metabolic issues. To clarify the distinctions between earlier research and this recent one, the PTH paradigm was employed.(55) This paradigm involves a chemical that has both anabolic and catabolic impacts on the skeleton. The specific effects depend on whether the molecule is administered intermittently or whether its levels are consistently elevated. In a similar situation, consistently high levels of irisin could contribute to the breakdown of bone. Conversely, consistently low or non-existent levels of irisin, as seen in mice lacking FNDC, may be advantageous for bone health. Other than irisin, integrin αV/β5 also has specific affinity for other ligands, for example osteopontin, bone sialoproteins and vitronectin. Some studies showed that high level of irisin can induce bone catabolism, while lower level of irisin might exert anabolic effect on bone through the stimulation of osteoblast formation and function, and reduce PTH.(138) Thus, an intermittent irisin pulse as occurs in exercise may induce the intermittent bone remodeling and have an overall positive effect on the skeletal system. If confirmed, this apparent double function of irisin in the skeletal system will redefine its potential for treating osteoporosis. However, irisin appears to be a promising new factor in metabolism and a possible target for treating metabolic bone illnesses, but further research is needed to fully understand its specific impact on bone metabolism.(139)

The Beneficial Effects of Exercise on The Brain and in Neurodegenerative Diseases

Sedentary lifestyle has emerged as a risk factor for numerous illnesses, such as CVD, metabolic disorders, cancer, and neurological diseases. In the past several years, it has been suggested that engaging in regular physical activity, such as aerobic exercise, anaerobic exercise, or resistance training, is important for maintaining a healthy lifestyle. Engaging in suitable physical activity helps to sculpt a fit physique and enhances the body's resting metabolic rate (RMR).(140) Physical activity also has an important impact on brain health, particularly in avoiding and reducing the loss of cognitive function and the emergence of certain neurodegenerative illnesses. Because of the significant effects of brain health and the advantages of physical exercise for physical fitness, there have been systematic reviews and meta-analyses that aim to summarize the potential links. These studies provide us with valuable conclusions supported by quantitative evidence.(141,142)

In normal brain conditions, basic cognitive abilities support the more advanced brain skills including language proficiency, learning strategies, problem-solving abilities, and logical thinking, which are crucial for the growth and advancement of human society. Cognitive decline is commonly seen in rapidly aging populations, and in many instances, it can develop into moderate cognitive impairment or dementia with the diagnosis of neurodegenerative diseases like AD and Parkinson's disease (PD). As a result, discussions about cognitive decline and neurodegenerative

illnesses throughout both typical and atypical brain aging have emerged as significant health concerns.(143-145)

Exercise delivers its benefit for the brain by two main categories: the neurotrophins which are produced by the brain itself, and myokines which are produced in the skeletal muscle and released to the circulation, for example the FNDC5 or irisin. Neurotrophins have a significant impact on the growth and development of neurons, including synaptic plasticity and survival. One of these growth agents is BDNF, which is significantly regulated by FNDC5. BDNF has been demonstrated to improve the survival of neurons, their migration, and the formation of dendrites. Moreover, it controls synaptic plasticity and cognitive function. Therefore, BDNF is an important controller of the positive effects of exercise in the brain. When the tropomyosin receptor kinase B (TrkB), which is the BDNF receptor, is blocked using anti-TrkB antibodies, there is a reduction in the levels of crucial synaptic proteins results in a decrease in performance in spatial learning tasks, both of which have been previously associated with the positive effects of exercise on the brain.(146,147)

The detection of irisin in the cerebral fluid of humans was confirmed using Western blot and mass spectrometry. (143) During the development of primary mouse embryonic cortical neuron cultures or the formation of human embryonic stem cell-derived neural cells into neurons as observed by mature neuronal markers (Map2, b-tubulinIII and Neurocan), astrocyte marker (glial fibrillary acidic protein/GFAP) and BDNF level, FNDC5 levels are increasing.(1,148,149) Irisin, as dissected from FNDC5, was mediated by PGC-1α and passed through the BBB and activate the sirtuin (SIRT)/ PGC-1α/FNDC5 pathway increase the hippocampal BDNF expression to enhance learning, memory, and mood.(150) Inducing higher levels of FNDC5 during the development of neuronal precursors from a population of mouse embryonic stem cells resulted in elevated levels of BDNF, GFAP, as well as Map2, b-tubulinIII, and Neurocan, all of which are markers indicating the maturation of neurons. Suppression of FNDC5 in neural precursor cells oppositely has been demonstrated to impair the development of neurons and astrocytes.(75) Increasing the expression of FNDC5 *in vivo* in primary cortical neurons enhanced cell survival in culture, while reducing the expression of FNDC5 decreased cell survival. These findings indicate that FNDC5/irisin have a role in controlling the process of neuronal differentiation and maturation during development.(1)

Brain aging is a natural condition, differ with the neurodegeneration which is pathologic. However, the two phenomena are connected since most older persons would eventually experience neurodegeneration, and in the other side neurodegeneration is the result of faster aging. (151) During the process of natural brain aging, cognitive function steadily decreases. The decline in cognitive function is not the only problem in neurodegeneration. The gradual impairment in learning and memory, which may ultimately result in dementia were also included. Moreover, neuronal apoptosis is an inherent physiological process that facilitates regulated cell death. As a result, to a certain degree, the two illnesses share parallels in symptoms and manifestations (such as memory and learning problems) and the main pathological characteristics (such as neuronal death).(145,152)

There is a large amount of data showing the positive effects of exercise on neurodegenerative disorders, such as AD, PD, and Huntington's disease (HD).(153) As mentioned before, the neurotrophin BDNF has a significant role in the regulation in maintaining the neurons, especially in terms of synaptic plasticity and neurogenesis. Lower levels of BDNF have been found in the blood serum, as well as in samples taken from the hippocampus and cortex of patients with AD and PD.(164-166) The serum levels of BDNF, irisin, and molecules from the kynurenine pathway was examined to identify new blood-based biomarkers for cognitive decline and dementia in older persons who are at risk of developing dementia. Studies showed that exercise or cognitive training can promote BDNF and irisin blood levels and global cognition scores and memory (157), as well as giving recombinant BDNF to animal models with AD and HD. Exercise had a positive effect on the cognitive abilities of AD mice via promoting the growth of new neurons in the adult hippocampus, as well as increasing the levels of BDNF and FNDC5. Genetic and pharmacological stimulation to adult hippocampal neurogenesis (AHN) also increasing BDNF levels, or by delivering FNDC5 adenovirus either through intracerebroventricular injection or tail vein injection.(158)

As mentioned before, aerobic exercise has been found to have the most significant effect on cognitive performance in older adults and those with neurodegenerative disorders. While further research is needed to establish if the FNDC5/ irisin protein can enhance cognitive performance in animals, our previous experiments indicate that a hormone supplied externally could produce similar effects on the brain as endurance exercise. The outlook for FNDC5/ irisin is quite promising, and we are eager to explore the potential therapeutic applications of this myokine and physical activity in improving cognitive impairments linked to neurodegenerative conditions.(159)

The Role of Exercise in The Interplay between Myokine, Adipokine, Hepatokine and Osteokine

Exercise has been noted as an important approach to treat obesity and the cardiometabolic comorbidities. It can promote body fat mass reduction, conversion WAT to BAT, redistributes energy sources, improves overall energy expenditure, improve brain-related appetite regulation, reduce inflammation, and improve insulin resistance. It is believed that was because of certain substances produced during exercise, such as myokines, hepatokines, osteokines, immunological cytokines, and adipokines which help regulate metabolic pathways and communication between different tissues through autocrine, paracrine, and endocrine effects.(160)

Some myokines including irisin, IL-6, IL-15, meteorin-like (METRNL), and β-aminoisobutyric acid (BAIBA) have been regularly seen to be secreted by skeletal muscle in response to exercise. The physiological and metabolic effects not only in skeletal muscle itself but also in far off tissues such WAT, bone, liver, the CNS, and the immune system to induce a systemic anti-inflammatory and insulin-sensitive state, allowing for optimization of total-body energy expenditure. Similarly, hepatokines including FGF21, angiopoietin-like 4 (ANGPTL4), and follistatin, which are released during and after exercise, could impact the metabolism of WAT, and skeletal muscle in a way that promotes the transfer of lipid-derived metabolic fuel towards catabolic pathways.(161) However, the harmful hepatokines fetuin A and selenoprotein P, which are elevated in insulin resistance, may reduce the positive effects of exercise-related variables. Exercise can reduce the levels of those hepatokines and reverse the development of hepatic steatosis in obesity.(162) In addition, the protein OCN is released by bone after exercise and works together with myokines to enhance the use of free fatty Acids (FFA) in many tissues.(163) The collective effects of these factors, whether through direct or indirect means, probably lead to a reduction in the accumulation of triglycerides in visceral fat stores and an increase in the mobilization and oxidation of fatty acids in the liver and skeletal muscle.

Acute exercise triggers the activation of many neuroendocrine pathways that lead to both short-term and long-term metabolic changes throughout the body. Short term breakdown of ATP and phosphocreatine in the active skeletal muscle results in anaerobic glycolysis. The sympathetic nervous system (SNS) regulates for higher metabolic demand including the breakdown of fat in WAT, which relies on the activation of hormone sensitive lipase (HSL) by catecholamines. Additionally, the release of hepatic glycogen stores and the inhibition of insulin's anabolic effects are also mediated by the SNS. This leads to an increased release of cortisol and growth hormone (164), which promotes the breakdown of triglycerides in WAT. The overall outcome is a higher amount of glucose and FFAs that are accessible for the active skeletal muscle.(165)

Through chronic aerobic exercise (such as daily training), the cellular processes responsible for oxidative metabolism in skeletal muscle are enhanced over time. However, these processes return to their original state once exercise is stopped. Certainly, skeletal muscle experiences various adaptive mechanisms, such as enhanced production of mitochondria, expression of fatty acid transporters, activity of oxidative enzymes and those activities involved in the electron transport chain within the mitochondria, as well as the skeletal muscle hypertrophy.(166) Therefore, physical activity can promote the redistribution of energetic substrates to skeletal muscle, where they are used, rather than to WAT, where they are stored. This helps to maintain normal levels of body fat mass. The post-exercise time seems to be important for the reported decrease of VAT that occurs with exercise, regardless of the mechanism.

Irisin breakdown is likely to include ADAM family proteases.(167) Favorable effect of irisin was achieved by increasing the expression of UCP1 in mice that overexpressed PGC-1α and were subjected to exercise (168), including fat breakdown, glucose and FFA uptake and oxidation, promoted M2 polarization, and also reversing the established M1-polarized proinflammatory state (169).

Elevated levels of IL-6, produced by fat cells and immune cells and activated by a specific biological mechanism, have traditionally been linked to inflammatory reactions and reduced sensitivity to insulin in individuals with obesity. Skeletal muscle release IL-6 during exercise in reaction to activation of the MAPK/JNK/AP-1 pathway. IL-6 has been demonstrated to have an anti-inflammatory and insulin-sensitizing effect. The levels of IL-6 in the blood have been found to rise after periods of aerobic exercise, and the length of the exercise is the key factor that determines the extent of the increase. For example, the levels can increase by 5 times after 30 minutes of running at 75% of the maximum oxygen consumption (VO_2 max), and by 100 times during a marathon run.(170)

IL-15 is generated by skeletal muscle as a reaction to exercise, and it functions through autocrine mechanisms. IL-15 enhances the absorption of glucose in skeletal muscle

by enhancing the process of transcription and the movement of glucose transporter type 4 (GLUT4) to the membrane through JAK3/STAT3 signaling. It also enhances the activity of PPARδ and PGC-1α, which promotes the creation of new mitochondria and the oxidation of fatty acids. It reduces fat mass by encouraging the flow of energy sources to skeletal muscle, which restricts the accumulation of FFA in visceral adipose tissue and adipocytes. The worldwide impact of IL-15 on fat accumulation seems to be noteworthy, as demonstrated in a mouse model that had an excess of IL-15. In this model, the proportion of visceral fat mass, evaluated by dual x-ray absorptiometry (DEXA), was around half compared to the control group.(171)

In skeletal muscle, METRNL is increased by activation of the PGC-1α isoform. Research has demonstrated that it can stimulate PPARγ activity in WAT, leading to an increase in preadipocyte differentiation and insulin sensitivity.(172) It was discovered to encourage M2 polarization (173), improve oxidative metabolism in skeletal muscle and WAT browning (174), boost fatty acid oxidation (FAO), and reduce FFA-induced inflammation and IR in skeletal muscle through the activation of AMPK and PPARδ. A favorable connection between METRNL and irisin levels in patients with T2DM was also reported.(175)

BAIBA, first discovered in the culture supernatant of mouse skeletal muscle cells and in the blood of chronically exercised mice. It has been found to promote the browning of WAT and enhance hepatic β-oxidation through PPARα-dependent mechanisms. BAIBA facilitated the reduction of weight gain and accumulation of fat in extremely obese mice due to a HFD.(176) This effect was linked to the restoration of hypothalamic neuronal activity and potentially an increased response to hormones that suppress appetite. BAIBA stimulates enhanced VAT lipolysis, increased FAO, and glucose absorption in skeletal muscle.(177,178)

Myostatin was the initial muscle-secreted factor that has been found to promote skeletal muscular atrophy.(179) It is the only myokine that is known to be decreased by both acute and chronic endurance- and resistance-type exercise in both mice and humans.(179) The expression of this gene is higher in cases of human obesity and is closely linked to insulin resistance by reducing the production of GLUT4 and decreasing the phosphorylation of insulin receptor substrate (IRS)1. Blocking myostatin increases oxidative metabolism in skeletal muscle. The lack of Mstn in $Mstn^{-/-}$ mice leads to higher expression of genes related to lipolysis, mitochondrial FAO, and WAT browning, along with a reduction in VAT mass.(180) It helps stimulate the production of PGC-1α, FNDC5, and irisin in skeletal muscle. An inter-myokine axis involving irisin and interaction with follistatin may potentially serve as a mechanism by which exercise reduces myostatin levels. In short, when you exercise, it can reduce the activity of myostatin, which helps to increase the size of your skeletal muscles and improve your body's ability to use oxygen. It can also encourage the breakdown of VAT and the conversion of WAT into BAT. This can help to shift the use of fatty acids from being stored as fat to being used as fuel for your metabolism.(181)

Hepatokines are new hormone-like substances that are released from the liver. Clinical research has indicated that physical activity affects the amounts and function of FGF21, follistatin, ANGPTL4, and fetuin A, which together may reduce levels of body fat. Moreover, selenoprotein P (SeP), while not directly influenced by exercise, might attenuate the skeletal muscle adaptation response to exercise. In addition, hepatokines can influence the effects of other factors that are induced by exercise, thereby preventing the accumulation of fat. This supports the adaptation of skeletal muscles to exercise and creates an environment that reduces inflammation and promotes the loss of fat, improvement of liver health, and reduction of insulin resistance.

High levels of SeP have been seen in humans with metabolic disorders and are able to reduce insulin sensitivity seen in animal and laboratory studies. Although exercise does not seem to regulate its levels, this could be because the exercise intensity or duration is not enough.(182) SeP has been linked to the concept of exercise resistance, which suggests that not everyone experiences the same positive effects from exercise. In animal models, overweight mice lacking SeP showed improved ability to perform aerobic exercise along with increased production and function of mitochondria in skeletal muscle. This effect was associated with higher levels of ROS and activation of AMPK, as well as increased activity of PGC-1α.(183) In humans, elevated pre-training levels of SeP were associated with reduced aerobic exercise capacity, as measured by VO_2max. This indicates that the FFA released by VAT lipolysis during and after exercise are not efficiently utilized by skeletal muscle. Instead, they are preferentially reabsorbed into VAT through very low-density lipoproteins (VLDL). A possible reduction in irisin, METRNL, and BAIBA also weakens the exercise-induced reduction in fat mass. These mechanisms may partly account for why overweight individuals, who have greater baseline levels of SeP, seem to need a longer time of exercise to effectively lose weight compared to healthy individuals.(184)

Fetuin A interacts with toll-like receptor (TLR-4) in adipocytes and M2 to stimulate proinflammatory activation,

along with FFAs. Fetuin A has been demonstrated to directly cause insulin resistance, inhibit the generation of adiponectin by adipocytes, and cause damage to pancreatic β-cells. It is significantly elevates in obesity, particularly in relation to NAFLD, and are indicative of the likelihood of developing T2DM.(185) It was also found to be higher in elderly VAT mass. In relation to physical activity, a recent study combining the results of multiple studies found that fetuin A levels decreased after completing different aerobic exercise programs with varying lengths (ranging from 1 to 12 weeks), frequencies (3 to 5 sessions per week), durations (40 to 70 minutes per session), and intensities (60 to 85% of maximum heart rate). However, this decrease was not observed in patients with T2DM, indicating that the effect of exercise on fetuin A levels may be influenced by the individual's metabolic condition.(186)

Exercise intensity affects the amount of FGF21 released by the liver. The levels of FGF21 have been observed to be noticeably greater during the recovery period compared to immediately after exercising. Elevated FGF21 levels were seen one hour after a 30-minute treadmill exercise at 80% VO_2max compared to 50% VO_2max in sedentary healthy individuals. In the liver, FGF21 increases β-oxidation and decreases lipogenesis. In WAT, it promotes the breakdown of fats and the conversion of white fat cells to brown fat cells, probably via increasing the expression of PGC-1α. In the CNS, FGF21 activates the SNS, which leads to an increase in BAT activity. Weight loss is expected to happen by reducing VAT, as shown by a 15% average decrease in abdominal fat content, in obese monkeys. Interestingly, a new study indicates that FGF21 might play a role in controlling the preference for certain foods. More specifically, it helps decrease the desire for sugary foods. (187) To sum up, exercise-induced FGF21 may help reduce visceral fat mass by boosting the breakdown of fat and increasing heat production in WAT (thus shifting energy sources to skeletal muscle), by reducing the consumption of sugary foods (which limits the liver's production of new fat), and by decreasing the accumulation of fat in WAT through VLDL.

The liver predominantly regulates the secretion of ANGPTL4 during exercise. This occurs after 3 hours of ergometer cycling at 50% VO_2max, in response to an elevated glucagon-to-insulin ratio. It is postulated that ANGPTL4 plays an endocrine role. In WAT, it was demonstrated to promote the breakdown of fats by activating adipose triglyceride lipase and reducing the activity of lipoprotein lipase (LPL). It has also been demonstrated to hinder pancreatic lipase, reducing the absorption of dietary fat. (188) Anptl$^{4-/-}$ animals showed increased levels of visceral fat mass, visceral LPL activity, and WAT inflammation (189), indicating the involvement of ANGPTL4 in the redistribution of lipoprotein-derived FFAs. While Skeletal muscle shows increased expression of ANGPTL4 mRNA after aerobic or resistance exercise, it is interesting to note that the inactive portion of skeletal muscle actually exhibits an even higher degree of ANGPTL4 mRNA expression compared to the active skeletal muscle. This suggests that there is a mechanism in place to redistribute the delivery of FFA from the unexercised skeletal muscle to the exercised one.

In humans, the liver is the main source of circulating follistatin. It increases in response to a higher glucagon-to-insulin ratio in conditions like fasting and exercise, including high-intensity interval training (HIIT), continuous aerobic, and resistance training.(100,190) Human studies has discovered follistatin as a substance produced by the liver in response to exercise. It temporarily increases during the recovery phase following physical activity. As anticipated, similar to FGF21, individuals with insulin resistance caused by obesity have higher levels of follistatin at rest, while the liver's release of follistatin during exercise is reduced. Follistatin may potentially increase the growth of skeletal muscle by binding to and neutralizing myostatin. This can lead to an increase in the amount of skeletal muscle available for the uptake and oxidation of glucose and FFA.(191,192)

OCN is a hormone produced by osteoblasts and activated by osteoclasts during bone resorption. Ocn$^{-/-}$ mice showed higher levels of overall body fat and inflammation in the liver and adipose tissue, as well as reduced insulin sensitivity and total energy expenditure.(193) Meta analysis studies demonstrated negative associations between OCN levels and BMI, insulin resistance, the inflammatory marker CRP, body fat mass, and visceral fat mass, evaluated by radiologic imaging investigations. Significantly, OCN was found to have an independent association with visceral fat area, suggesting its role in regulating VAT. OCN enhanced the survival and activity of pancreatic β-cells and boosted insulin secretion, whereas insulin itself triggered the production of OCN. OCN may also have its positive effects by promoting the production of adiponectin and IL-10, by reducing TNF-α in fat cells, and by increasing the expression of thermogenic genes in adipose tissue and the formation of mitochondria in skeletal muscle.(194)

Levels of adipokines fluctuate in response to long-term exercise rather than short-term episodes of exercise, especially when changes in body composition occur. This is in line with the observation that exercise lowers VAT

regardless of weight loss. Therefore, exercise sessions cause temporary alterations in other exercise-responsive variables that could potentially facilitate metabolic changes and lead to a reduction in WAT mass, thereby altering the adipokine profile as described in Figure 4. Sudden reductions in leptin levels have been observed in response to sudden episodes of aerobic and resistance exercise.(195) However, in cases of obesity where the hypothalamic set point is altered, this could potentially result in excessive eating and a decrease in metabolic rate, which can hinder weight loss. It seems that continuous exercise is necessary to re-establish the physiological effects of leptin. Studies combining data from multiple sources have shown that long-term aerobic, resistance, and mixed exercise have been found to lead to a decrease in fat mass, along with lower levels of leptin hormone. In addition to its traditional role in increasing SNS drive to promote global energy expenditure, restored leptin sensitivity in peripheral organs could also support the maintenance of reduced body fat. This is because leptin is known to enhance the uptake and oxidation of glucose and FFA by skeletal muscle, and to decrease the amount of lipid in the liver by promoting FAO.(196) Therefore, leptin may also play a role in the transfer of resources away from WAT, which aligns with its function as an adipostat that closely controls the size of adipocytes in normal settings.

Regarding physical activity, certain studies have found higher levels of adiponectin throughout the period of recuperation after intense aerobic and strength training sessions.(197) Consideration must be given to the upregulation caused by other substances that increase significantly during or shortly after exercise and have been shown in preclinical investigations to enhance the production of adiponectin. These factors include irisin, IL-15, FGF21, and OCN. Regarding regular exercise, studies combining data from multiple studies have shown that levels of adiponectin, a hormone involved in metabolism, tend to increase, particularly with long-term aerobic exercise programs, in individuals with a range of BMI values, from those who are overweight to those with T2DM. The higher levels of adiponectin caused by physical activity are probably due to a reduction in visceral fat, improved metabolic state of WAT, and a general decrease in inflammation throughout the body.(198)

There are some controversies about the benefit of exercise in managing obesity, including the chronic inflammation and metabolic comorbidities. Somehow, the physiological reactions of exercise still continue after the workout end. For example, following the initial rise, the lipolysis remains higher for up to 24 hours after exercise (199), while the elevated basal metabolic rate (BMR) may continue for up to 48 hours. The consequences after exercising are believed to be influenced by alterations in the levels and/or activity of several variables that are induced by exercise. Significantly, several hormones that are triggered by exercise have also been demonstrated to directly increase insulin sensitivity in certain tissues, regardless of their impact on inflammation (Figure 4). These factors include irisin, IL-6, IL-15, METRNL, BAIBA, and FGF21. At the same time, other substances that are caused by exercise, such as irisin follistatin and OCN, directly shield β-cells from harm, so enhancing their positive metabolic characteristics. (200) Overall, the reduction in insulin resistance and the decrease in stress on β-cells caused by exercise-related factors could lead to a decrease in hyperinsulinemia and the amount of material available for fat production. This, in turn, could reduce the expansion of WAT. Therefore, it can be stated that regular exercise sessions have a cumulative impact on inflammation and metabolism, while long-term

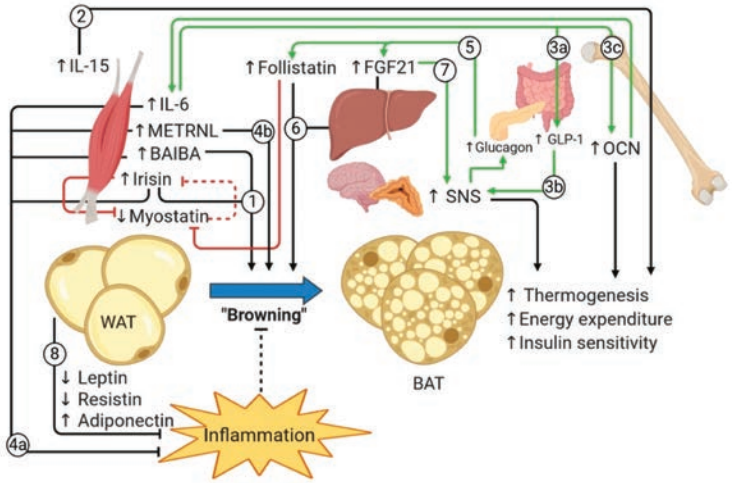

Figure 4. Effects of exercise-inducible factors on WAT browning.(195) (Adapted with permission from MDPI).

exercise helps to maintain a state of reduced inflammation and increased insulin sensitivity, which promotes the maintenance of a healthy fat mass.

In general, the majority of clinical evidence indicates that exercise more useful to avoiding overweight and obesity than reversing them (201), since exercises show benefit in decrease VAT deposits but not always reducing total body weight which is more affected by calories reduction. Actually, weight loss is not a suitable and accurate measure of the effectiveness of an exercise program. It can be deceiving since exercise not only leads to a reduction in VAT, but it can also result in an increase in fat-free mass, which can balance out the overall weight. Therefore, the significance of physical activity should not be underestimated, even if it does not lead to overall weight reduction.(202)

The Therapeutic Potential of Irisin and Exercise Mimetics for Obesity and Metabolic Diseases

Among all, irisin shows potential in managing obesity by browning the WAT and reducing the fat accumulation in the body. Many studies have proved the association between irisin and chronic diseases such as T2DM, NAFLD, CKD, psoriasis, osteoporosis, hypertension, atherosclerosis, and cancer, even the telomere length which is a well-known genetic marker of aging.(203) It is well known that obesity is a chronic inflammation condition with increasing pro-inflammatory cytokines include TNF-α, IL-6, MIP-1α, MCP-1, macrophage 1 antigen (MAC-1), and ADAM8, thus impair the insulin sensitivity.(204) Exposure to high levels of glucose causes cell death and results in reduced beta cell activity and insulin sensitivity.(205,206) However, irisin has been demonstrated to decrease the presence of apoptotic markers generated by glucose, such as Bad, Bax, Caspase-9, and Caspase-3, while simultaneously boosting the levels of anti-apoptotic proteins like Bcl-2 and Bcl-xl. Studies have shown that lower levels of irisin in the bloodstream may be linked to metabolic issues such T2DM.(207)

ROS trigger a series of pathways that promote inflammation, resulting in damage to small blood vessels and consequent malfunction.(208,209) In this context, antioxidants have been found to reduce the negative impacts of free radicals and prevent issues related to diabetes.(210) Irisin has been demonstrated to alleviate oxidative/nitrative stresses caused by diabetes by decreasing the production of superoxide and peroxynitrite, inducible nitric oxide synthase (iNOS), and the heme binding subunit of the superoxide-generating nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (gp91phox). Additionally, it increases the production of antioxidant enzymes such as glutathione peroxidase (GPX-1), catalase (CAT), and superoxide dismutase (SOD). Irisin seems to be a hopeful chemical for treating vascular problems caused by diabetes. The findings of another study demonstrated that irisin reduces oxidative stress caused by high sugar/high fat in human umbilical vein endothelial cells. This is achieved via suppressing the activation of Protein kinase C (PKC)-β/NADPH oxidase and NF-κB/iNOS signaling pathways.(205)

NAFLD is a prevalent source of long-term liver damage. The spectrum of this condition varies from mild hepatic steatosis (accumulation of fat) to more severe forms such as nonalcoholic steatohepatitis (NASH), which is characterized by hepatic steatosis, inflammation, and oxidative damage. Liver fat accumulation leads to cell death and the consequent release of danger signals, which can activate sterile inflammatory pathways. Besides stress-induced inflammation, there is additional evidence showing the involvement of pro-inflammatory substances before the onset of steatosis. Oxidative stress has been suggested as a pathogenic process linked to the advancement of liver damage.(211,212)

The atherogenic diets induce the inner layer of the arteries to produce certain molecules that help attract and attach specific types of white blood cells, especially T-lymphocytes and monocytes. Moreover, excessive migration and multiplication of smooth muscle cells and leukocytes result in the excessive breakdown of extracellular matrix, which is a crucial feature of advanced atherosclerotic plaque. Considering that programmed cell death of endothelial cells is a crucial factor in the development of atherosclerosis the pathogenesis of atherosclerosis is primarily attributed to the apoptosis of vascular endothelial cells produced by oxidized low-density lipoprotein (ox-LDL). Oxidative stress results from elevated FFA also play a role in the development of atherosclerosis and myocardial ischemia injury. FFAs could contribute to endothelial dysfunction in obese patients. Thus, exercise can have beneficial effects on liver and heart.(213)

Cancer starts with a single cell mutation, which is often linked to genetic abnormalities, smoking, diet (such as greasy foods and red meat), alcohol intake, sun exposure, environmental pollution, infections, stress, obesity, and lack of physical activity. Imbalance in the regulation of cell death pathways results in the development of cancerous cells and the spread of tumors. It has been shown that reducing the activity of p53 promotes the formation of tumors and is

believed to be significant in many types of human cancers. A study showed that the stimulation of the PI3K-Akt pathway can delay p53-induced cell death. Moreover, there is a reciprocal link between cancer and inflammation. The several chemicals that cause inflammation and contribute to the formation and progression of cancer include transcription factors (such as NF-κB, hypoxia-inducible factor 1α (HIF1α), and STAT3) and pro-inflammatory cytokines (such as TNF-α and IL-6, IL-23, and IL-1β). Besides their involvement in leukocyte recruitment, chemokines such as chemokine C–X–C motif ligand (CXCL) and macrophage pro-inflammatory chemokine (MIP) also support tumor cell growth and survival, matrix modification, blood vessel formation, and spread to other parts of the body. (214) Oxidative stress might have a significant impact on the start and advancement of cancer. In addition, cancer development and advancement have been linked to oxidative stress through an elevation in DNA damage, cell growth, and genomic instability.(215) The potential anti-oxidant impact of irisin on cancer has not yet been investigated. Possible future research might be conducted to investigate the antioxidant pathways present in cancer cells that could potentially be affected by irisin.

Degenerative diseases are a group of conditions that entail the decline of tissues and organs function over time, leading to potentially lasting harm. These illnesses usually become more common as people become older and can impact many areas of the body, like muscles, bones, the brain, and the nervous system. Examples of common degenerative disorders include muscle wasting, bone loss, amyotrophic lateral sclerosis (ALS), AD and PD. There are no cure for majority of degenerative diseases, and the usual approach to treatment is focused around symptom management and enhancing quality of life. Irisin therefore can act as the myokine biomarker to monitor the treatment efficacy.(31)

Irisin has been discovered to have a crucial role in the process of tissue regeneration, especially related to aging and injury. Irisin not only has anti-inflammatory and anti-apoptotic properties, but it also helps coordinate the activities of different cell types in damaged tissues.(216) The medical community has long been trying to develop active substances that can mimic or enhance the genetic effects of exercise, considering the various health benefits associated with exercise. Although achieving this goal has been difficult, studies have demonstrated that natural extracts such as resveratrol can improve the endurance.(217) PGC-1α activation as an important regulator of the body's response to exercise. It helps facilitate communication between muscle regeneration caused by exercise and the creation of new mitochondria. The aerobic advantages of resveratrol are believed to rely on the stimulation of the AMPK/SIRT1/PGC-1α pathway in skeletal muscle.(217) AMPK and PPARs agonists have been suggested as potential exercise mimetics. Another biosynthetic agents, such as adipokine (adiponectin), cytokine (IL-6), and myokine (irisin), also imitate the effects of exercise. While the possible protective and regenerative benefits of biosynthetic agents during exercise are still being studied, the discovery of irisin as a new target has attracted a lot of attention because of its apparent role in several illnesses and metabolic disorders via PGC-1α and by increasing the expression of UCP1. This mechanism has received considerable interest for its presumed capacity to control conditions including obesity and diabetes. In the meanwhile, several studies have emphasized the potential of irisin as a possible option for preventing, intervening, or treating degenerative disorders. (218,219)

Exercise mimetics agents aims to enhance or imitate the positive impacts of physical exercise for both preventive and therapeutic uses, including in the area of CNS diseases. Recent comprehensive reviews and analyses have examined the impact of physical activity on various neurological conditions, including AD, other forms of dementia, PD, stroke, multiple sclerosis, and ALS. Additionally, these reviews have also explored the effects of exercise on cognitive function during both development and aging, as well as its potential benefits for individuals with schizophrenia and depression. Although there are limitations in certain studies and the need for more well-powered randomized controlled trials, the current data indicates that exercise can be a safe and effective intervention and may work well with other treatments, such as medication. Significantly, in addition to the healing properties of exercise on the results of individual illnesses, the notable positive effects of exercise on cognitive improvement across many conditions indicate potential overall advantages of physical activity.(220)

Exercise mimetics have been suggested as a new type of treatments to imitate or boost the positive impacts of physical exercise, given that physical activity has been proven to have beneficial effects on various human conditions, such as neurological and psychiatric disorders, cardiovascular, metabolic, inflammatory, and oncological diseases. At a basic level, exercise can be broadly defined as any form of physical activity that does not entail sedentary behavior. Physical activity can take many different forms and last for varying amounts of time. The exercise intensity can greatly impact heart rate and affect

metabolic and physiological processes. Exercises can take the form of aerobic or anaerobic exercise, and can be either acute or chronic. The impact of exercise on an individual is influenced by genetics, epigenetics, and other processes at the molecular, cellular, and systems levels. Moreover, in order to create exercise mimetics, it is necessary to comprehend the molecular and cellular processes that facilitate the therapeutic effects brought about by exercise. More study is necessary to methodically examine molecules that play a causal role in facilitating the positive impacts of physical activity. Undoubtedly, numerous new categories of molecular targets will be discovered for the possible development of prospective exercise mimetics. The possible pharmacological options are not limited and can include small-molecule medicines, peptides, antibodies, noncoding RNAs, antisense oligonucleotides, and epigenetic editing structures.(221)

Considering the established impact of mental stimulation and physical activity on the brain, some of exercise mimetics are suggested to be cognitive enhancers. An exercise mimetic technique has the potential to stimulate a reaction in the peripheral using a therapeutic substance that does not pass the BBB. This would prevent possible negative effects mediated by the CNS, while molecules that are increased in the peripheral region by the therapeutic medication might still pass through the blood-brain barrier and provide positive benefits. Therefore, exercise mimetics may be suitable for therapeutic applications that integrate precision medicine.

The Irisin System in Pharmacological and Nutraceutical Perspective

Since it was first found, the production of irisin has been strongly linked to physical activity and being exposed to cold temperatures. In recent times, researchers have also studied the potential to adjust irisin levels by making changes to one's diet and taking natural chemicals as supplements. In more recent times, certain investigations have demonstrated that certain medicines often used in clinical practice for diverse purposes have an effect on this signaling system. This additional mechanism can somewhat impact the overall effects of these medications and their therapeutic results.(15)

A pharmaceutical approach, assessed in preclinical investigations, to stimulate the irisin pathway involves the use of r-irisin. R-Irisin has been demonstrated to have positive effects on osteoporosis and to provide protection to cardiomyocytes after MI. The relationship between sitagliptin and irisin as well as its metabolic pathway was studied, and it was found that sitagliptin is a type of medication used to treat diabetes. It is taken orally and belongs to a group of drugs called dipeptidyl-peptidase 4 inhibitors. Treatment to HFD-diet and T2DM induced rats indicated that the levels of PGC-1α, AMPK, and irisin were noticeably increased in both groups treated with sitagliptin 5 and 10 mg/kg, with a particularly larger increase observed in the high-dose treatment group. Similarly, the levels of mRNA for PGC-1α and FNDC5 were significantly elevated in both groups receiving sitagliptin treatment, with the highest increase observed in the group treated with 10 mg/kg of sitagliptin.(222)

All-trans retinoic acid (ATRA or tretinoin) is derived from vitamin A by replacing the end alcoholic group with a carboxylic group. ATRA, similar to other retinoids, has been utilized for many years in the prevention and treatment of cancer. Additionally, it is recognized for its advantageous impacts on obesity and metabolic syndrome. The relationship between ATRA and skeletal muscle metabolism as well as the secretion of key myokines and components related to the FAO process was examined in a study. The findings of the study demonstrated the immediate impacts of ATRA on the promotion of FAO, the generation of irisin in skeletal muscle cells (C2C12 myocytes), and the elevation of irisin levels in the bloodstream and FNDC5 transcription in an animal model (NMRI male mice). Immunohistochemistry examination of FNDC5 indicated that ATRA administration enhanced the secretion of FNDC5/irisin from skeletal muscle and its buildup in interscapular BAT and inguinal WAT.(223)

Follistatin, sometimes called activin-binding protein, is a glycoprotein that is produced in almost all organs of higher animals that has role to bind and neutralize members of the TGF-β superfamily. Follistatin is known to induce irisin encoded FNDC5 gene in mouse muscle cells. Giving follistatin to HFD obese mice boosted their energy expenditure by promoting the browning of SAT. Follistatin also stimulated the release of irisin, via the AMPK/PGC-1α pathway, which is responsible for activating browning mechanisms and enhancing insulin sensitivity. In addition to studying how exercise and exposure to low temperatures affect the irisin pathway, many studies have also looked into the potential impact of diet and natural substances on this pathway. This research has emphasized the potential nutraceutical and phytotherapeutic implications.(15)

A number of studies have examined the potential link between irisin expression and diet quality. Irisin had

a positive correlation with a healthy diet known as the Dietary Approaches to Stop Hypertension (DASH). On the other hand, other inflammatory biomarkers like leptin, soluble intercellular adhesion molecule-1 (slCAM-1), and CRP showed an inverse relationship with a healthy diet and a direct association with a western diet model. The rise in fruit eating and the decrease in meat consumption were associated with elevated levels of circulating irisin.(224)

There was a study examining the scientific literature in the field of pharmacology and nutrition to explore the effect of certain types of polyphenols in treating obesity. The focus of the study was on how these polyphenols can stimulate the browning process by activating irisin pathway via the PGC-1α/UCP1 pathway. The chemicals examined were: Flavan-3-ols, Resveratrol, Capsaicin, Curcumin, Thymol, Chrysin, Magnolol, Honokiol, Quercetin. The findings from preclinical and clinical research indicated that some phytochemical components found in food may be associated with a thermogenic mechanism that is closely linked to the irisin pathway. Recent research indicates that some of the impacts of icariin may be due to a strong association with irisin. Icariin is a type of flavonoid that is found in significant quantities in plants belonging to the Epimedium genus, which are commonly found in Asia. It is considered to be a crucial bioactive compound in Chinese Herbal Medicine. A study examined the effect of icariin administration to mouse skeletal muscle cells, specifically myocytes C2C12. The results showed that icariin increased the gene expression of FNDC5 and PGC-1α, and it also led to the phosphorylation of AMPK in a manner that depended on the dosage. The findings were validated in living organisms, where an elevation in the levels of PGC-1α and FNDC5, as well as the activation of AMPK, were accompanied by a conversion of inguinal adipose tissue to a brown-like state and an excessive production of UCP1. Certain polyphenols, such isoflavones such as genistein, are believed to enhance the expression of browning indicators. Consuming genistein has been demonstrated to decrease weight gain and enhance glucose tolerance and blood cholesterol levels.(225)

Resveratrol, a polyphenolic molecule naturally found in grape skins, has the ability to affect the gene expression of FNDC5 and UCP1/UCP2. UCP1 interacts with BAT as well as ROS. As a result, beverages that contain resveratrol, including red wine and grape juice, may have the ability to enhance the expression of UCP1, and consequently, irisin, which can boost energy expenditure. This effect may still occur even when consumed as part of a HFD. Further research has shown that resveratrol has a significant impact on the process of thermogenesis and browning of adipocytes. This leads to a reduction in fat formation and an increase in the expression of markers associated with thermogenesis, such as UCP1 and bone morphogenetic protein 7 (BMP7). The study demonstrated that HFD led to a decrease in FNDC5, but resveratrol supplementation enhanced its expression. This suggests that resveratrol plays a significant role in the regulation of FNDC5 expression. Resveratrol has the ability to stimulate FNDC5 and subsequently irisin, as well as genes linked to the thermogenesis process. This contributes to an elevation in the overall energy expenditure of the body. It was also verified that resveratrol was capable of enhancing the FNDC5 expression in the skeletal muscle of mice by an unidentified mechanism, which is definitely not associated with DNA methylation.(226) The expression of FNDC5 increased in the muscles of Wistar rats treated with resveratrol and grape juice. This suggests that grape juice, like resveratrol, may be effective in regulating the FNDC5/UCP2 system by increasing the expression of these genes.(227)

Citrus flavonoids, such as naringenin and nobiletin, have been linked to the prevention of metabolic diseases. Giving mice immature *Citrus reticulata* extract by mouth at a concentration of 1% for a duration of 11 weeks resulted in notable decreases in body weight, epididymal fat, fasting glucose, triglyceride, and total cholesterol levels. The primary chemical compounds found in young *Citrus reticulata*, extracted using water and evaluated using high-performance liquid chromatography (HPLC), including synephrine, narirutin, hesperidin, nobiletin, and tangeretin. The cause of these effects has been linked to an increased expression of UCP1 and the genes involved in thermogenesis. Hesperidin, another flavanone found in citrus fruits, has recently been discovered to regulate lipid and glucose metabolism via activating the AMPK/PPAR pathway.(228)

Green tea is made by brewing the fresh leaves of the Camellia sinensis plant and it has a high concentration of flavan-3-ol monomers. In addition to (–)-epicatechin and (+)-catechin, green tea also contains distinctive components such epigallocatechin and 3-O-galloylated flavan-3-ols. Male rats who were overweight and administered green tea for around 2 weeks demonstrated a reduction in the amount of fat they gained, as well as an increase in the amount of energy they burned and the quantity of BAT protein. On the other hand, the concomitant use of propranolol (β-AR antagonist) eliminated these effects, suggesting that SNS activation was involved.(229,230)

Capsaicin and its non-spicy counterparts, capsinoids, are a group of dietary components that stimulate BAT.

Capsaicin is often regarded as the primary spicy element in hot red peppers. The proteomic study on obese mice WAT treated with capsaicin indicated significant changes in proteins related to thermogenesis and lipid metabolism. These findings suggest that capsaicin consumption could be a beneficial phytochemical for preventing obesity by increasing expression of PGC-1α to increase FNDC5. This will increase energy expenditure, thermogenesis, and fat burning were seen in small rats and humans when capsaicin and capsinoids were given in high amounts.(231,232)

Curcumin, a polyphenolic flavonoid that occurs naturally in turmeric, a spice commonly used in South Asian cooking, is one of the extensively researched medicinal plants. The weight-reducing properties of curcumin have been extensively studied. Importantly, a study using random assignment and control groups found that overweight individuals who consumed a bioavailable version of curcumin for 30 days saw weight loss throughout a 30-day diet and lifestyle intervention. Many studies showed that the use of curcumin was well-tolerated and resulted in weight loss, as well as reduced fat mass and waist and hip circumference. Curcumin caused browning effects in WAT, which has generated significant interest. The study investigated the activation of beige phenotype in 3T3-L1 and mouse primary white adipocytes using curcumin. Later on, it was demonstrated that curcumin increases the expression of brown-specific markers such UCP1, PGC-1α, and PR domain containing 16 (PRDM16), and also decreases lipids in these cells via activating AMPK. Consistently, changes in the proteins of cultured white fat cells taken from the rat's inguinal WAT when treated with curcumin revealed a strong association between hormone-sensitive lipase and markers specific to brown fat.(233) It is also known that polyphenolic nutraceuticals are responsible for WAT browning and their cellular targets (Figure 5).(234)

Quercetin, also known as 3,3′,4′,5,7-pentahydroxyflav one, is a polyphenolic chemical and flavonoid that is present in significant amounts in onions, broccoli, apples, berries, asparagus, and leafy vegetables. Quercetin has been found to have positive effects on obesity, as well as beneficial effects on the cardiovascular system and lipid metabolism. It is worth mentioning that HFD-induced mice treated with quercetin were shown to be protected against obesity caused by the diet. This protection was achieved by increasing energy expenditure and reducing inflammation. Previous studies have examined the benefits of consuming quercetin in mice that were given a HFD. These studies found that quercetin helped with weight reduction and lowered levels of triglycerides and plasma cholesterol due to better metabolic functions. Quercetin was also found to help obese mice recover from dyslipidemia and metabolic problems. Treating mature white adipocytes with an extract rich in quercetin resulted in a decrease in the formation of new fat cells, as well as a reduction in the accumulation of fats and cell death. Mice that were given a diet supplemented with quercetin have been found to have higher levels of UCP1 expression and thermogenesis. Quercetin operates through an AMPK/SIRT1-mediated pathway. Since SIRT1 and AMPK have a recognized involvement in energy expenditure. it is feasible that quercetin can potentially promote browning of WAT. It is worth mentioning that quercetin has been found to be involved in the transformation of white adipocytes into brown-like adipocytes. While research conducted on cells and animals has yielded more information on the impact of quercetin on adiposity and obesity, additional studies are required to establish conclusive evidence on the direct effects of quercetin on the transformation of white adipocytes.(235)

Berberine, a polyphenolic component and plant alkaloid obtained from several herbs including *Coptis*

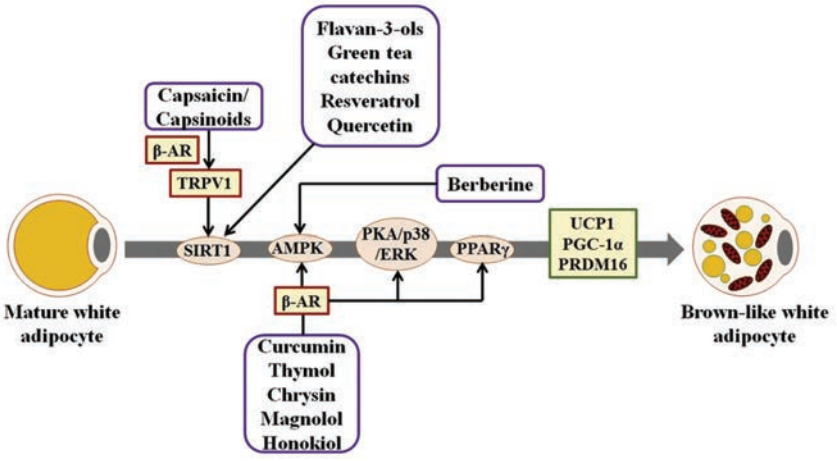

Figure 5. The polyphenolic nutraceuticals (violet squares) are responsible for WAT browning and their cellular targets (brown circles).(235) (Adapted with permission from Elsevier Inc).

chinensis (Chinese goldthread) and *Hydrastis canadensis* (goldenseal), shields rodents from weight gain and fat accumulation. Berberine administration also results in decreased weight gain in rats treated with olanzapine and mice with a deletion of the leptin receptor. In mice with genetically induced diabetes, berberine reduced weight growth and lipid buildup, suggesting that it controls the mobilization of fat and has antiobesity properties. In addition, berberine has been demonstrated to control adaptive thermogenesis. Treatment of db/db mice with berberine increased overall energy expenditure, indicating that berberine affects the metabolism of energy fuel through fatty acid oxidation. In addition, berberine influenced BAT by reducing lipid accumulation and increasing mitochondrial content, thermogenic markers (such as PGC-1α, cell death-inducing DNA fragmentation factor-like effector A (CIDEA), and UCP1), and BAT activity. It also increased cold tolerance.(236)

Modifying one's diet and exercise level are particularly crucial in preventing and controlling obesity. Increasing data indicates that nutrition has a significant role in managing weight. Although calorie restriction is widely recognized as the most effective method to combat obesity, bioactive or functional food components, such as polyphenols, have the ability to exert anti-obesity effects. Activating irisin pathway and increasing brown fat mass is important for regulating energy in the body and can be targeted to help with weight loss and enhance metabolic health in humans.(234)

Despite of the great value of irisin, it is now still too early for irisin as a biomarker and therapeutic target. Many issues still need to be resolved, including the inconsistency results of irisin measurements due to its half-life, sampling time, individual differences, etc. Therefore, it becomes tricky to determine the dose of irisin as drug for therapy. Based on current knowledges, the better strategy is to utilize the irisin signaling pathways to control human metabolic problems, for example by utilizing the nutraceuticals. However, irisin holds a great potency for future therapeutic target and more studies need to be done on elucidating the molecular mechanism of irisin on metabolism.

Conclusion

The scientific community has been interested in identifying new factors and pathways that are engaged in the complex network responsible for regulating metabolic homeostasis and the development of metabolic dysregulation. This medical problem affects not only the fat tissue in the abdomen, but also causes other types of hidden harm to other parts of the body, including the cardiovascular system, liver, muscles, brain, and bones. The identification of irisin offers a fresh potential basis for kinesitherapy, and irisin shows promise as a therapeutic target due to its various biological activities. While there is ongoing debate about whether irisin has a role in improving health through exercise, several animal studies indicate that administering irisin directly can be beneficial for both metabolic and non-metabolic disorders. The experimental evidence regarding irisin, a myokine linked to an increase in energy expenditure, shows that this metabolic pathway can be beneficial for preventive/therapeutic approaches. This myokine is possible to regulate through changes in dietary habits, the use of natural substances, and also through various drugs that are already accessible in the market and can interact with this signaling pathway.

Authors Contribution

IRD and AW proposed the topic of the manuscript. IRD and AM drafted the original manuscript. AM and NMD edited and revised the manuscript. AW supervised and gave critical correction to the manuscript. All author have agreed with the final revision of the manuscript.

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