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REVIEW ARTICLE

Adipokines and Myokines: A Pivotal Role in Metabolic and Cardiovascular Disorders

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Abstract: Obesity induces an imbalance in the expression and secretion of several cytokines, which contributes to the development of metabolic and cardiovascular disorders. On the contrary, skeletal muscle is known to have a role in reversing the detrimental impact of obesity. It has been established that adipose tissue acts as an endocrine organ that secretes proinflammatory and anti-inflammatory adipokines. Similarly, skeletal muscle produces secretory molecules, called myokines, from contracting muscle fibers. Myokines were recently recognized as beneficial modulators of obesity, metabolic syndrome, and type 2 diabetes. Furthermore, adipokines and myokines play a crucial role in the communication between adipose tissue, skeletal muscle and other organs. It could be beneficial to find novel adipokines and myokines, and to explore their signaling pathways to identify targets for the treatment and prevention of cardiometabolic disorders. In this review, we summarize recent studies on cross-talk between skeletal muscle and adipose tissue. In particular, we concentrate on the major action mechanisms of adipokines and myokines, such as adiponectin, adipocyte fatty acid binding protein, C1q/TNF-related proteins, interleukin-6, irisin, and fibroblast growth factor 21.

Keywords: Adipokines, myokines, adiponectin, interleukin-6, irisin, metabolic disease, cardiovascular disease.

1. INTRODUCTION

Cardiometabolic diseases are the main cause of death in the world and have become a global problem [1]. Over the next 2 decades, mortality of ischemic heart disease is predicted to increase by 137% for men and 120% for women in developing countries [1]. With the rising global burden of cardiometabolic disease, it is necessary to identify risk components and to regulate them.

With aging, body composition changes resulting in increased visceral fat and reduced muscle mass. Sarcopenia, age-associated loss of muscle mass and strength, seriously affects the health and life quality of elderly people. We previously reported that sarcopenia is associated with increased risk of type 2 diabetes and non-alcoholic fatty liver disease (NAFLD) [2, 3]. Moreover, albuminuria is independently associated with sarcopenia in patients with type 2 diabetes [4]. In an aging population, the prevalence and crucial consequences of visceral obesity and sarcopenia have rapidly increased and become a significant threat to public health. Both visceral obesity and sarcopenia are important risk factors for cardiometabolic diseases, including hypertension, dyslipidemia, type 2 diabetes, coronary heart disease, and stroke [5]. They influence each other, which may lead to a vicious cycle [5]. Recently, the novel concept of sarcopenic obesity has emerged, indicating a combination of sarcopenia and obesity [6]. The reduction in physical activity due to sarcopenia induces decreased energy expenditure and increases the possibility of obesity [7]. As visceral obesity increases, catabolic inflammatory responses are upregulated and contribute to reduced muscle mass [8]. In fact, we observed that baseline visceral obesity was related to decreasing skeletal muscle mass in a prospective study [9]. Moreover, visceral obesity and sarcopenia share several common

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pathophysiological mechanisms, such as decreased physical activity and increased insulin resistance, inflammation and oxidative stress. Adipose tissue, skeletal muscle and liver communicate with each other and distant target organs through organokines, such as adipokines, myokines and hepatokines, by autocrine, paracrine, and endocrine activities [10].

In this review, we focus on adipokines, including adiponectin, adipocyte fatty acid binding protein (A-FABP), and C1q/TNF-related proteins (CTRPs), and myokines, including interleukin-6 (IL-6), irisin, and fibroblast growth factor 21 (FGF21), as metabolic and cardiovascular regulators.

2. ADIPOKINES

Adipose tissue was recently recognized as an assertive endocrine organ that produces and secretes various adipokines. Adipose tissue has roles in the accumulation of lipids, regulation of inflammation, fat metabolism, insulin sensitivity and energy homeostasis [11]. Adipokines were divided into two groups according to their functions. Some adipokines, known as anti-inflammatory adipokines, possess anti-inflammatory activity and decrease the severity of obesity-linked disorders; these are downregulated by obesity [11]. However, many other adipokines, called proinflammatory adipokines, are upregulated by obesity and cause inflammatory activity and obesity-related complications [11, 12]. This inflammatory activity induces insulin resistance in skeletal muscle, liver and adipose tissue, regarded as an early defect of type 2 diabetes [13]. Here, we highlight anti-inflammatory adipokines (*e.g.* adiponectin and CTRPs) and proinflammatory adipokines (*e.g.* A-FABP) that have effects on metabolic dysfunction, atherosclerosis and cardiovascular disease (CVD) (Table **1**).

2.1. Adiponectin

Adiponectin, the most abundant adipokine in human plasma, is secreted mainly from adipose tissue, although small amounts are also produced by other tissues [14]. Adiponectin is a protein of 244 amino acids containing a C1q-like globular domain at the C-terminus and a collagen-like domain at the N-terminus [14]. Full-length adiponectin is present at high concentrations in healthy humans, mainly as 3 molecular weight isoforms: trimer, hexamer, and a high molecular weight (HMW) complex containing at least 18 monomers [15]. In addition, globular adiponectin, the globular domain produced by proteolysis from full-length adiponectin, also exists in small amounts and has biological activity [16]. In particular, HMW complexes comprise about 50% of total adiponectin and act mostly on metabolic tissues [17]. Adiponectin acts via adiponectin receptors that exist as two isoforms, AdipoR1 and AdipoR2. AdipoR1, the receptor for globular adiponectin, is predominantly expressed in skeletal muscle; AdipoR2, the receptor for full-length adiponectin is predominantly expressed in the liver [18]. Recently, Tanabe *et al.* reported the crystal structures of human AdipoR1 and AdipoR2, which represent a novel class of receptor structure [19]. Adiponectin, mediated via AdipoR1 and AdipoR2, regulates fatty acid oxidation, insulin sensitivity, cytoprotection, and vasodilatation through IRS1/2, AMP-activated protein kinase (AMPK), and p38 mitogen-activated protein kinase (MAPK) pathways [20, 21]. Adiponectin acts directly in vascular endothelium, skeletal muscle, liver, and adipose tissue itself [20]. Iwabu *et al.* reported that PGC-1α and mitochondria are regulated by adiponectin and AdipoR1 through Ca^{2+} and AMPK/SIRT1 pathway [22]. In the cells lacking both adiponectin receptor isoforms, impaired ceramidase activity and elevated ceramide levels were observed [23].

Circulating adiponectin levels are inversely related to risk factors of cardiometabolic disease, such as lipids, blood pressure, body weight, insulin resistance, and atherosclerosis. Ouchi *et al.* reported significant lower adiponectin levels in patients with coronary artery disease (CAD) and found a role of adiponectin as a novel modulator for endothelial adhesion molecules [24]. In the Japanese population, genetic variation in the gene encoding adiponectin resulted in increased risk of type 2 diabetes [25]. In human studies, it has been shown that circulating adiponectin levels are downregulated in obesity, type 2 diabetes and CVD [26]. We previously reported that lower baseline concentrations of adiponectin are significantly correlated with increased risk of type 2 diabetes and metabolic syndrome over a period of 3 years, after adjusting for various confounding factors [27]. In a meta-analysis including 13 prospective studies with a total of 14,598 participants and 2,623 incident cases of type 2 diabetes, lower adiponectin concentrations are consistently associated with an increased risk of type 2 diabetes [28]. Furthermore, we found that circulating adiponectin levels had a significantly negative association with vascular inflammation, as represented by the mean target to background ratio (TBR) values measured using fluorodeoxyglucose positron emission tomography-computed tomography (FDG-PET/CT) [29]. After adjustment for baseline inflammation and glycemic status, increased baseline adiponectin levels were

Table 1. Summary of important studies about several adipokines.

Experimental	Reference	Clinical	Reference
Adiponectin			
Cloning of adiponectin as a adipocyte specific factor	Scherer *et al.* J Biol Chem 1995;270:26746-9 [14]	Endothelial adhesion molecules/CAD	Ouchi *et al.* Circulation 1999;100:2473-2476 [24]
Improvement of insulin resistance associated with both lipoatrophy and obesity	Yamauchi *et al.* Nat Med 2001;7:941-6 [43]	Genetic variation – type 2 diabetes	Hara *et al.* Diabetes 2002;51:536-40 [25]
Cloning of receptors	Yamauchi *et al.* Nature 2003;423;762-9 [18]	Myocardial infarction	Pischon *et al.* JAMA 2004;291:1730-7 [30]
Regulation of PGC-1α by Ca(2+) and AMPK/SIRT1	Iwabu *et al.* Nature 2010;464:1313-1319 [22]	Type 2 diabetes (meta-analysis)	Li *et al.* JAMA 2009;302:179-188 [28]
A small-molecule AdipoR agonist	Okada-Iwabu *et al.* Nautre 2013;503:493-499 [36]		
Ceramidase activity	Holland *et al.* Nat Med 2011;17:55-63 [23]		
Crystal structures of adiponectin receptors	Tanabe *et al.* Nature 2015;420:312-6 [19]		
A-fatty acid binding protein (A-FABP)			
Atherosclerosis	Makowski *et al.* Nat Med 2001;7:699-705 [53]	Obesity, metabolic syndrome	Xu *et al.* Clin Chem 2006;52:405-13 [56]
Glucose and lipid metabolism	Uysal *et al.* Endocrinology 2000;141:3388-96 [52]	Type 2 diabetes	Tso *et al.* Diabetes Care 2007;30:2667-72 [58]
Atherosclerosis and survival	Boord *et al.* Circulation 2004;100:1492-8 [54]	Vulnerable atherosclerotic plaque/cardiovascular events	Peeters *et al.* Eur Heart J 2011;32:1758-68 [59]
Hepatic glucose production	Cao *et al.* Cell Metab 2013;17:768-78 [55]		
C1q/tumor necrosis factor-related proteins (CTRPs)			
Vascular relaxation through AdipoR1/AMPK/eNOS/NO signaling pathway (CTRPs)	Zheng *et al.* Arterioscler Thromb Vasc Biol 2011;31:2616-23 [69]	Type 2 diabetes, metabolic syndrome (CTRP3)	Choi KM *et al.* Diabetes 2012;61:2932-6 [79]
Proangiogenic and cardioprotective adipokine (CTRP3)	Yi *et al.* Circulation 2012;125:3159-69 [78]	Coronary artery disease (CTRP1)	Lu *et al.* Eur Heart J 2016;37:1762-71 [77]
Attenuation of adverse cardiac remodeling after AMI (CTRP9)	Sun *et al.* Circulation 2013;128:S113-20 [71]		
Protection against diabetic cardiomyopathy in rats (CTRP3)	Ma *et al.* Diabetologia 2017;60:1126-37 [81]		

related with a lower risk of myocardial infarction in a prospective study [30].

Several mouse and human studies have demonstrated that adiponectin supplementation modulates anti-inflammatory, insulin-sensitizing, and antiatherogenic effects, as well as weight reduction [31-35]. After injection of recombinant adiponectin (Acrp30), glucose level decreased temporarily without increasing insulin level in animal model [34]. Interestingly, AdipoR agonist (AdipoRon) ameliorated insulin resistance and glucose tolerance in mice [36]. Furthermore, AdipoRon improved diabetes in *db/db* mice and prolonged the shortened lifespan of *db/db* mice on a high-fat diet [36]. Recently many studies proposed that adiponectin also had antineoplastic effect through directly affecting on cancer cell and indirectly modulating inflammatory pathway and tumor angiogenesis [37]. In obese mouse study, L-4F, apolipoprotein mimetic peptide, showed to elevate HMW adiponectin level and to improve insulin sensitivity [38], cardiomyopathy and coronary dysfunc-

tion [39], and multiple myeloma [40]. Additionally, circulating adiponectin levels are elevated with vigorous exercise [41, 42], peroxisome proliferator-activated receptor γ (PPARγ) agonists [43, 44], and L-cysteine [45] in human and/or animal studies. In the future, adiponectin-targeting treatment could provide a potential revolutionary therapeutic strategy for the treatment of obesity, atherosclerosis, type 2 diabetes, cancer and CVD.

2.2. Adipocyte Fatty Acid Binding Protein (A-FABP)

A-FABP (FABP4), belonging to a family of 14–15-kDa proteins, is expressed abundantly in activated macrophages and mature adipocytes [46]. A-FABP plays a direct role in intracellular fatty acid transport and promotes inflammatory processes and metabolic responses [47]. A-FABP modulates signal transduction and gene transcription indirectly by regulating of free fatty acid [48, 49]. It has been discovered that A-FABP works with specific PPARs in regulating the transcriptional activities of their common ligands, consequently supporting the biological functions of PPARs [50].

A-FABP affects lipid metabolism, lipolysis, insulin sensitivity, inflammation, atherosclerosis, and also functions as a major inducer of vulnerable plaque formation [51]. An absence of A-FABP preserved β–cell function and improve dyslipidemia and peripheral insulin resistance in obese mice [52]. Makowski *et al.* demonstrated that mice deficient apolipoprotein E (ApoE) are protected against atherosclerosis by lack of A-FABP [53]. Furthermore, A-FABP deficiency makes lipid metabolism, glucose, and survival better, as well as reduces atherosclerosis in ApoE-/- mice [54]. Cao *et al.* demonstrated A-FABP as an adipokine regulating hepatic glucose production [55].

Many clinical studies have proposed that A-FABP is highly connected with insulin resistance and performs a role as a crucial mediator of the development of metabolic syndrome, type 2 diabetes, and CVD. Serum A-FABP levels were highly associated with components of metabolic syndrome and obesity in a cross-sectional study [56]. In a longitudinal study, we found that A-FABP levels predict the development of adiposity, insulin resistance, and metabolic syndrome in Korean children [57]. Tso *et al.* reported that circulating A-FABP levels were related to dysglycemia and predicted new-onset type 2 diabetes independent of obesity and insulin resistance in a 10-year prospective study [58]. Moreover, Peeters *et al.* showed that A-FABP in carotid atherosclerotic lesions are related to increased cardiovascular risk and vulnerable plaque phenotype [59]. Circulating A-FABP levels increase proportionally to the number of stenotic coronary arteries diagnosed by coronary angiogram [60]. Additionally, we showed that serum A-FABP levels were significantly correlated with vascular inflammation, as detected by maximum TBR values, in Korean men without CVD or diabetes [61]. Kim *et al.* established that circulating A-FABP levels negatively associated with appendicular skeletal muscle mass (ASM)/weight and positively associated with visceral fat area (VFA) in adult [62]. Furthermore, A-FABP significantly associated with sarcopenic obesity, even after adjustment for age, BMI, and VFA in women [62].

In particular, A-FABP, mainly produced during adipocyte differentiation, is controlled by PPARγ agonists, insulin, dexamethasone, and fatty acids, and regulates lipid and glucose metabolism [63]. Recently, many A-FABP inhibitors, such as oxazole derivatives, indole derivatives, imidazole derivatives, thiophene and thiazole derivatives, benzimidazole derivatives, pyrimidine, urea, carbamoyl derivatives, bicyclic pyridine, and quinoxaline derivatives, as well as pyrazole derivatives (BMS309403) have been suggested as treatments for atherosclerosis and diabetes [64]. We need to expend efforts in clinical research to identify attractive therapeutic A-FABP targets for cardiometabolic diseases.

2.3. C1Q/TNF-related Proteins (CTRPs)

Members of the CTRPs family of proteins are considered to be paralogs of adiponectin that have a collagen domain and a C1q-like globular domain [65]. Similar to adiponectin, the CTRP superfamily, a cluster of 15 members, is mainly expressed in adipose tissue and plays potential roles in cardiovascular and metabolic regulation. In particular, CTRP9 contains the most similar amino acids to adiponectin in its C1q-like globular domain [65]. Several studies have revealed that CTRP9 improves metabolic dysfunction and vascular disorders through regulation of insulin resistance, inflammatory response, and vasorelaxation [66-69]. We showed that CTRP9 improved hepatic steatosis through the reduction of endoplasmic reticulum stress by the AMPK-mediated activation of autophagy [70]. Recent studies demonstrated that CTRP9 attenuates ischemic heart disease through anti-apoptotic and anti-inflammatory actions via the cAMP-PKA or AMPK pathways [66, 71-73]. CTRP1 improves local inflammation and the progression of atherosclerosis [74], and protects against acute ischemic heart injury [75, 76]. However, Lu *et al.* reported that CTRP1 levels are

higher in patients with CAD and CTRP1 promotes atherosclerosis in mice [77]. An explanation for this discrepancy is not apparent at the present time. On the other hand, Yi *et al.* found CTRP3 as a novel cardioprotective, antiapoptotic, and proangiogenic adipokine in the ischemic mouse heart [78]. In our previous study, circulating CTRP3 concentrations were associated with components of metabolic syndrome, arterial stiffness, kidney function, and inflammation [79]. We also observed that circulating CTRP3 concentrations reduced in patients with stable angina pectoris or acute coronary syndrome [80]. Recently, Ma *et al.* reported that CTRP3 alleviates inflammation, oxidative stress, and cardiac dysfunction, which result in protection against diabetic cardiomyopathy in rats [81]. Many studies have proposed that CTRP3 and/or CTRP9 are viable therapeutic targets for the treatment of obesity, diabetes, hepatic steatosis, and CVD [75].

3. MYOKINES

Skeletal muscle makes up the largest proportion of tissue, constituting about 40% of the total body weight in adults without obesity [82]. Skeletal muscle mass increases through exercise, nutrients, and hormones, such as growth hormone, insulin like growth factor 1, insulin, testosterone, and progestin [83]. It is well known that aerobic exercise affects on reducing body fat mass via rising oxygen utilization, whereas resistance exercise affects on reinforced muscle strength and increasing muscle mass. Additionally, the benefits of exercise are improved skeletal muscle function and energy balance, and amelioration of chronic diseases such as hypertension, hyperglycemia, and dyslipidemia. Exercise systemically affects other organs, including the brain, heart, liver, and kidney in animal models [84, 85]. Meta-analysis study showed that physical exercise affected positively on cardiovascular health by reducing the risk of stroke and coronary heart disease [86]. Inversely, sarcopenia with/without obesity, induced physical inactivity, influences to organokines and results in development of type 2 diabetes mellitus, cancer, cardiovascular diseases [87]. Nevertheless, little is known about the mechanisms linking exercise training to whole-body metabolism. Several years ago, Pedersen *et al.* suggested that skeletal muscle produces and secretes humoral factors, called myokines, which actively interact with other organs [88]. The verification of novel myokines that regulate inflammation, insulin resistance, and lipid profiles could provide effective approaches for preventing or improving cardiometabolic disease (Table **2**).

3.1. Interleukin-6 (IL-6)

IL-6 has pleiotropic effects in different tissues and organs. IL-6 was originally regarded as a proinflammatory cytokine [89], but later anti-inflammatory effects were also revealed [90]. IL-6 is expressed in vascular endothelial cells, fibroblasts, and stimulated monocytes or macrophages [91]. IL-6 production increases in muscle during exercise, in white adipose tissue upon diabetes and obesity, and in vascular smooth muscle with atherosclerotic plaques [88, 92-94]. The intracellular signaling of IL-6 is connected with glycoprotein 130 dimer binding of IL-6/IL-6 receptor, called as classic signaling, or IL-6/soluble IL-6 receptor, called as trans-signaling [94]. It is suggested that the trans-signaling is related to proinflammatory action and classic signaling is related to anti-inflammatory and metabolic regulation [94]. It helps explain the paradox of the pathophysiological properties of IL-6.

As a myokine, IL-6 is released during skeletal muscle contraction without muscle damage [95]. Acute contraction of skeletal muscle dramatically increases muscle IL-6 mRNA content and plasma IL-6 levels, and these responses are reduced by endurance training or regular exercise training [96]. Opposite IL-6, the IL-6 receptor-α mRNA response in muscle is greater during regular exercise training compared with before training, possibly compensating for the reduction in IL-6 [97].

IL-6 regulates glucose homeostasis and metabolism in other organs, such as adipose tissue, pancreatic ß-cells, neuroendocrine cells, and hepatocytes, as well as in myocytes themselves. Carey *et al.* reported that acute treatment with IL-6 in humans increased insulin-stimulated glucose disposal, proven using a hyperinsulinemic-euglycemic clamp [98]. IL-6 regulates glucose transporter 4 (GLUT4) translocation and fatty acid oxidation via AMPK in adipose tissue and muscle [98, 99]. Moreover, IL-6 increases insulin secretion in beta-cells by upregulating glucagon-like peptide-1 (GLP-1) from intestinal L cells and pancreatic alpha-cells via the classic signaling pathway [100]. Additionally, exercise-induced IL-6 acts on glucose homeostasis in the liver via hepatic glycogenolysis, gluconeogenesis, and glucose release [101]. Exercise-triggered IL-6 attenuated insulin resistance through the suppression of proinflammatory cytokines, including TNF-α and IL-1β, and induction of anti-inflammatory cytokines, including IL-10 [102, 103].

IL-6 -/- mice showed mature-onset obesity, systemic insulin resistance, and hepatic inflammation [104, 105]. In patients with rheumatoid arthritis,

Table 2. Summary of important studies about several myokines.

Experimental	Reference	Clinical	Reference
Interleukin-6 (IL-6)			
IL-6/IL-6 receptor and IL-6/soluble IL-6 receptor	Qu *et al.* Br J Pharmacol 2014;171:3595-603 [94]	Endurance training	Fischer *et al.* Am J Physiol Endocrinol Metab 2004;287:E1189-94 [96]
Glucose uptake by AMPK	Carey *et al.* Diabetes 2006;55:2688-97 [98]	Exercise & IL-6 receptor expression	Keller *et al.* J Appl Physiol 2005;99:2075-9 [97]
Insulin secretion by GLP-1 secretion	Ellingsgaard *et al.* Nat Med 2011;17:1481-9 [100]	Type 2 diabetes	Spranger *et al.* Diabetes 2003;52:812-7 [108]
Mature-onset obesity	Wallenius *et al.* Nat Med 2002;8:75-9 [104]	Vascular complications and mortality	Lowe *et al.* Diabetes 2014;63:1115-23 [109]
Hepatic inflammation and systemic insulin resistance	Matthews *et al.* Diabetologia 2010;53:2431-41 [105]		
Irisin			
PGC1α	Bostrom *et al.* Nature 2012;481:463-8 [113]	Resistance exercise/ endurance exercise	Tsuchiya *et al.* Metabolism 2015;64:1042-50 [117]
White adipose tissue browning via MAPK and ERK	Zhang *et al.* Diabetes 2014;63:514-25 [115]	Circulating Human Irisin	Jedrychowski *et al.* Cell Metab 2015;22:734-40 [121]
Insulin secretion by PKA dependent manner and Beta cell survival by AKT/BCL2	Natalicchio *et al.* Diabetes 2017;66:2849-56 [127]	Sarcopenia and carotid atherosclerosis	Lee *et al.* Atherosclerosis 2015;242:476-82 [125]
Fibroblast Growth Factor 21 (FGF21)			
Adiponectin, hepatic sterol regulatory element-binding protein-2	Lin *e al.* Circulation 2015;131:1861-71 [141]	Hyperinsulinemia	Hojman *et al.* Diabetes 2009;58:2797-801 [133]
PPARgamma activity	Dutchak *et al.* Cell 2012;148:556-67 [144]	Obesity and metabolic syndrome	Zhang *et al.* Diabetes 2008;57:1246-53 [147]
AMPK-SIRT1 pathway	Zhu *et al.* Acta Biochim Biophys Sin 2014;46:1041-8 [146]	Impaired glucose tolerance and type 2 diabetes	Chavez *et al.* Diabetes care 2009;32:1542-6 [149]
Retinoid Fenretinide	Morrice *et al.* Sci Rep 2017;7:43782 [151]	Microvascular disease in patients with type 2 diabetes	Ong *et al.* Diabetologia 2015;58:2035-44 [155]

treatment with tocilizumab, an IL-6 inhibitor, promoted weight gain and dyslipidemia [106, 107]. Some studies reported that circulating IL-6 levels were increased in patients with type 2 diabetes, macrovascular complications, and high-mortality [108, 109]. Recent studies revealed that higher IL-6 levels correlated with higher incidence of coronary heart disease [110, 111]. In prospective study, increasing degree of internal carotid artery stenosis and unfavorable morphology change could be predicted by higher serum IL-6 levels [112]. Considering diverse effects of IL-6 at different stages or cell types, it is not clear that these positive correlations of IL-6 and cardiometabolic disease are attributable to which direct or indirect mechanism. In the future, generation of more evidence is necessary to interpret this paradoxical relationship.

3.2. Irisin

Irisin was recently identified as a PPAR-gamma coactivator-1 alpha (PGC1α)-dependent myokine, induced by cold exposure and exercise. It is produced by cleavage of the extracellular portion of fibronectin type III domain containing protein 5 (FNDC5) [113]. Full-length FNDC5 is a transmembrane protein that includes an extracellular N-terminal portion, proven to have high identity between mice and humans. Irisin stimulates browning and uncoupling protein 1 (UCP1) expression in subcutaneous adipose tissue, resulting in increased energy expenditure and improvement of obesity and glucose homeostasis [113]. In the muscle of PGC1α transgenic mice, the subcutaneous white adipose tissue showed increased browning, UCP1 levels, and cell death-inducing DNA fragmentation factor-α-

like effector A (CIDEA) mRNAs compared to that in controls [113]. In cultured white adipose cells, thermogenic/brown fat programs increased robustly after FNDC5 treatment via PPARα [113]. Transgenic mice with increased PGC1α in muscle showed attenuated age-related obesity and diabetes, and ultimately prolonged life-span [114]. The regulation of obesity and type 2 diabetes suggested by irisin stimulated white adipose tissue browning through MAPK and extracellular signal-related kinase (ERK) signaling pathway [115].

Boström *et al.* showed that circulating irisin levels were significantly elevated in human subjects with supervised endurance exercise training for 10 weeks compared to that in non-exercised subjects [113]. Furthermore, Tsuchiya *et al.* and Huh *et al.* reported that circulating irisin levels increased more after acute resistance exercise than chronic or endurance exercise [116, 117]. However, several studies demonstrated that acute or chronic exercise had no relationship with expression of FNDC5 and irisin in humans [118, 119]. These discrepancies among irisin results may originate from the different exercise regimens, different time of blood sampling after exercise, age, gender, and ethnicity, as well as assays used for measuring irisin. Moreover, Albrecht *et al.* denounced the measurement of circulating irisin in humans using commercial ELISA kits, as it is detected using unspecific cross-reacting proteins, and they claimed it does not exist [120]. Nevertheless, Jedrychowski *et al.* refined the methodology using tandem mass spectrometry and confirmed that human irisin exists and acts as an exercise-induced myokine [121]. Further studies using the highly sensitive mass spectroscopy are necessary to elucidate the inducer and actions of irisin in humans.

Previous human studies showed a relationship between irisin level and obesity or insulin resistance. Serum irisin levels were significantly decreased in subjects with metabolic syndrome or impaired fasting glucose [122]. In obese subjects, increased baseline irisin levels were related with greater improvement of glycemia and hyperinsulinemia after diet-induced weight loss [123]. However, in our previous study, circulating irisin concentrations were not different in subjects with ^{18}FDG-PET-detectable brown adipose tissue (BAT) or subjects with sarcopenia compared to controls [124]. Lee *et al.* reported that serum irisin levels are significantly lower in patients with carotid atherosclerosis or sarcopenia among dialysis patients [125]. Zhang *et al.* also showed that the circulating baseline irisin levels are significantly reduced in patients with type 2 diabetes, and especially in patients with diabetes-related macrovascular complications [126]. Circulating irisin may mediate a protective role in obesity and type 2 diabetes with/without macrovascular complications. Recently, *in vitro* study using human and murine pancreatic islets and *in vivo* study using mouse reported that treatment of recombinant irisin improved beta cell survival through AKT/BCL2 signaling and glucose-stimulated insulin secretion through PKA-dependent mechanism [127]. Although irisin might be regarded as potential therapeutic target, further studies are required.

3.3. Fibroblast Growth Factor 21 (FGF21)

FGF21 is a member of the FGF super family, with major functions in metabolic modulation, that is primarily expressed and secreted by the liver, adipose tissue, skeletal muscle, and pancreas [128-130]. FGF21 is expressed in response to starvation in liver [131], cold exposure, insulin stimulation, and mitochondrial stress in muscle [132-134], as well as thermogenic activation and noradrenergic stimulation in BAT [135]. FGF21 is modulated by various transcription factors, such as retinoic acid rector-β, PPARα, PPARγ, and carbohydrate responsive element-binding protein (ChREBP) [50, 51]. The combination of β-Klotho and FGF receptor isoforms, especially FGF receptor 1 or FGF receptor 2, defines the tissue-specific metabolic activities of FGF19 and FGF21 [136].

In animal and cell culture studies, FGF21 regulates metabolic homeostasis, including glucose and lipid metabolism, and energy balance. FGF21-knockout mice showed impaired glucose homeostasis and weight gain [137]. Furthermore, treatment with FGF21 improved triglyceride and plasma glucose levels to near normal in both *db/db* and *ob/ob* mice [138]. Additionally, FGF21 overexpression in transgenic mice did not lead to hypoglycemia or weight gain [138]. Through PGC-1α, a major transcriptional modulator of energy homeostasis, FGF21 regulates fatty acid and carbohydrate metabolism in the liver during starvation [139], and browning in white adipose tissue during hypothermia as a defense mechanism [140].

Moreover, FGF21 has shown possible antiatherosclerotic actions through lipid profile improvement, protection against oxidative stress, and anti-inflammatory actions. Atherosclerotic plaque formation, dyslipidemia, and hypo-adiponectinemia was aggravated in FGF21/ApoE$^{-/-}$ double knockout mice compared with that in ApoE$^{-/-}$ control mice [141]. Additionally, atherosclerotic plaques were greatly reduced after recombinant FGF21 treatment compared to that

after recombinant adiponectin treatment, suggesting that the antiatherosclerotic effects of FGF21 occur in both adiponectin-dependent and -independent manners [141]. As circulating FGF21 and PPARγ stimulate each other in positive feedback loop [142-144], they increase adiponectin expression geometrically [142]. Lin *et al.* reported that FGF21 decreases total cholesterol level in ApoE knockout mice via the inhibition of sterol regulatory element-binding protein 2 (SREBP2) in an adiponectin-independent manner [141]. In human umbilical vein endothelial cells, FGF21 reduced H_2O_2-induced cell apoptosis and cytotoxic effects through the suppression of caspase 3 and blocking of MAPK signaling cascades [145]. Treatment with FGF21 ameliorated high-fat-diet-induced oxidative stress in atherosclerotic rats [145]. Furthermore, administration of recombinant FGF21 attenuated alcohol-induced injury in HepG2 cells and mouse models through activation of the AMPK-sirtuin 1 pathway [146]

Although FGF21 has beneficial effects on glucose and lipid metabolism, atherosclerosis, and energy balance in cell culture and animal studies, paradoxical increases in circulating FGF21 levels have been observed in humans with cardiometabolic risks, such as obesity [147], dyslipidemia [148], insulin resistance [148, 149], and type 2 diabetes [149]. These increases may be relative to FGF21 resistance or compensatory regulation of metabolic stress [150]. In mice study, treatment with the synthetic retinoid fenretinide normalize FGF21 increased by obese and insulin resistant states as well as improve obesity and hepatic insulin resistance [151]. Increases in FGF21 levels may be used as an early detective biomarker for CVD in humans. In a cross-sectional study, Shen *et al.* reported that elevated FGF21 level was an independent risk factor for coronary artery disease in multiple logistic regression analysis [152]. In a study of 670 Chinese subjects, higher FGF21 levels were significantly associated with greater carotid intima-media thickness, independent of cardiometabolic risk factors [153]. Our study demonstrated that FGF21 levels are positively correlated with brachial-ankle pulse wave velocity, reflecting arterial stiffness as an early risk indicator for CVD [154]. Recently, a longitudinal study reported that elevated baseline FGF21 levels were associated with a higher risk of future microvascular disease, such as nephropathy, neuropathy, and/or microvascular amputation, after adjusting for potential confounding factors in 9,697 patients with type 2 diabetes [155]. In randomized placebo controlled studies, treatment with an analog of FGF21 (LY2405319 or PF-05231023) produced significant increases in adiponectin and improvement of the lipid profiles in obese subjects with type 2 diabetes [40, 156].

CONCLUSION

Adipose tissue and skeletal muscle have been regarded as endocrine organs that synthesize and secrete adipokines and myokines, respectively. Various adipokines play important roles in the regulation of cardiovascular and metabolic homeostasis by their involvement in inflammation, fat distribution, atherosclerosis, impaired insulin sensitivity and endothelial dysfunction. Therefore, upregulated anti-inflammatory adipokines, including adiponectin and CTRPs, and downregulated proinflammatory adipokines, including A-FABP, had positive effect on chronic cardiometabolic disease associated with aging. Similar to the adipokines, myokines, such as IL-6, irisin, and FGF21, have also been reported to have crucial pathogenic roles in the improvement of obesity, insulin sensitivity, substrate oxidation, dyslipidemia and inflammation via inter-organ communication. The identification of clinical significance and elucidation of molecular function may provide important insights for the prevention and treatment of metabolic and cardiovascular disorders.

LIST OF ABBREVIATIONS

AdipoRon	=	AdipoR Agonist
A-FABP	=	Adipocyte Fatty Acid Binding Protein
AMPK	=	AMP-activated Protein Kinase
ASM	=	Appendicular Skeletal Muscle Mass
BAT	=	Brown Adipose Tissue
CAD	=	Coronary Artery Disease
ChREBP	=	Carbohydrate Responsive Element-Binding Protein
CIDEA	=	Cell Death-inducing DNA Fragmentation Factor-α-like Effector A
CTRPs	=	C1q/TNF-related Proteins
CVD	=	Cardiovascular Disease
ERK	=	Extracellular Signal-related Kinase
FDG-PET/CT	=	Fluorodeoxyglucose Positron Emission Tomography-computed Tomography
FGF21	=	Fibroblast Growth Factor 21
FNDC5	=	Fibronectin Type III Domain Containing Protein 5

GLP-1 = Glucagon-like Peptide-1

GLUT4 = Glucose Transporter 4

HMW = High Molecular Weight

IL = Interleukin

MAPK = p38 Mitogen-activated Protein Kinase

NAFLD = Non-alcoholic Fatty Liver Disease

PGC1α = PPAR-gamma Co-activator-1 Alpha

PPARγ = Peroxisome Proliferator-activated Receptor γ

SREBP2 = Sterol Regulatory Element-binding Protein 2

TBR = Target to Background Ratio

UCP1 = Uncoupling Protein 1

VFA = Visceral Fat Area

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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REFERENCES

[1] Yach, D.; Hawkes, C.; Gould, C.L.; Hofman, K.J. The global burden of chronic diseases: Overcoming impediments to prevention and control. *JAMA,* **2004**, *291*(21), 2616-2622.

[2] Kim, T.N.; Park, M.S.; Yang, S.J.; Yoo, H.J.; Kang, H.J.; Song, W.; Seo, J.A.; Kim, S.G.; Kim, N.H.; Baik, S.H.; Choi, D.S.; Choi, K.M. Prevalence and determinant factors of sarcopenia in patients with type 2 diabetes: The Korean Sarcopenic Obesity Study (KSOS). *Diabetes Care,* **2010**, *33*(7), 1497-1499.

[3] Hong, H.C.; Hwang, S.Y.; Choi, H.Y.; Yoo, H.J.; Seo, J.A.; Kim, S.G.; Kim, N.H.; Baik, S.H.; Choi, D.S.; Choi, K.M. Relationship between sarcopenia and nonalcoholic fatty liver disease: The Korean Sarcopenic Obesity Study. *Hepatology,* **2014**, *59*(5), 1772-1778.

[4] Chung, H.S.; Hwang, S.Y.; Choi, J.H.; Lee, H.J.; Yoo, H.J.; Seo, J.A.; Kim, S.G.; Kim, N.H.; Choi, D.S.; Baik, S.H.; Choi, K.M. Effects of low muscle mass on albuminuria and chronic kidney disease in patients with type 2 diabetes: The korean sarcopenic obesity study (KSOS). *J. Gerontol. A Biol. Sci. Med. Sci.,* **2018**, *73*(3), 386-392

[5] Kim, T.N.; Choi, K.M. The implications of sarcopenia and sarcopenic obesity on cardiometabolic disease. *J. Cell. Biochem.,* **2015**, *116*(7), 1171-1178.

[6] Choi, K.M. Sarcopenia and sarcopenic obesity. *Korean J. Intern. Med. (Korean. Assoc. Intern. Med.),* **2016**, *31*(6), 1054-1060.

[7] Zamboni, M.; Mazzali, G.; Fantin, F.; Rossi, A.; Di Francesco, V. Sarcopenic obesity: A new category of obesity in the elderly. *Nutr. Metab. Cardiovasc. Dis.,* **2008**, *18*(5), 388-395.

[8] Gregor, M.F.; Hotamisligil, G.S. Inflammatory mechanisms in obesity. *Annu. Rev. Immunol.,* **2011**, *29*, 415-445.

[9] Kim, T.N.; Park, M.S.; Ryu, J.Y.; Choi, H.Y.; Hong, H.C.; Yoo, H.J.; Kang, H.J.; Song, W.; Park, S.W.; Baik, S.H.; Newman, A.B.; Choi, K.M. Impact of visceral fat on skeletal muscle mass and vice versa in a prospective cohort study: Tthe korean sarcopenic Obesity Study (KSOS). *PLoS One,* **2014**, *9*(12), e115407.

[10] Choi, K.M. The impact of organokines on insulin resistance, inflammation, and atherosclerosis. *Endocrinol. Metab. (Seoul),* **2016**, *31*(1), 1-6.

[11] Ouchi, N.; Parker, J.L.; Lugus, J.J.; Walsh, K. Adipokines in inflammation and metabolic disease. *Nat. Rev. Immunol.,* **2011**, *11*(2), 85-97.

[12] Blüher, M. Clinical relevance of adipokines. *Diabetes Metab. J.,* **2012**, *36*(5), 317-327.

[13] DeFronzo, R.A.; Tripathy, D. Skeletal muscle insulin resistance is the primary defect in type 2 diabetes. *Diabetes Care,* **2009**, *32*(Suppl. 2), S157-S163.

[14] Scherer, P.E.; Williams, S.; Fogliano, M.; Baldini, G.; Lodish, H.F. A novel serum protein similar to C1q, produced exclusively in adipocytes. *J. Biol. Chem.,* **1995**, *270*(45), 26746-26749.

[15] Magkos, F.; Sidossis, L.S. Recent advances in the measurement of adiponectin isoform distribution. *Curr. Opin. Clin. Nutr. Metab. Care,* **2007**, *10*(5), 571-575.

[16] Fruebis, J.; Tsao, T.S.; Javorschi, S.; Ebbets-Reed, D.; Erickson, M.R.; Yen, F.T.; Bihain, B.E.; Lodish, H.F. Proteolytic cleavage product of 30-kDa adipocyte complement-related protein increases fatty acid oxidation in muscle and causes weight loss in mice. *Proc. Natl. Acad. Sci. USA,* **2001**, *98*(4), 2005-2010.

[17] Pajvani, U.B.; Hawkins, M.; Combs, T.P.; Rajala, M.W.; Doebber, T.; Berger, J.P.; Wagner, J.A.; Wu, M.; Knopps, A.; Xiang, A.H.; Utzschneider, K.M.; Kahn, S.E.; Olefsky, J.M.; Buchanan, T.A.; Scherer, P.E. Complex distribution, not absolute amount of adiponectin, correlates with thiazolidinedione-mediated improvement in insulin sensitivity. *J. Biol. Chem.,* **2004**, *279*(13), 12152-12162.

[18] Yamauchi, T.; Kamon, J.; Ito, Y.; Tsuchida, A.; Yokomizo, T.; Kita, S.; Sugiyama, T.; Miyagishi, M.; Hara, K.; Tsunoda, M.; Murakami, K.; Ohteki, T.; Uchida, S.; Takekawa, S.; Waki, H.; Tsuno, N.H.; Shibata, Y.; Terauchi, Y.; Froguel, P.; Tobe, K.; Koyasu, S.; Taira, K.; Kitamura, T.; Shimizu, T.; Nagai, R.; Kadowaki, T. Cloning of adiponectin receptors that mediate antidiabetic metabolic effects. *Nature,* **2003**, *423*(6941), 762-769.

[19] Tanabe, H.; Fujii, Y.; Okada-Iwabu, M.; Iwabu, M.; Nakamura, Y.; Hosaka, T.; Motoyama, K.; Ikeda, M.; Wakiyama, M.; Terada, T.; Ohsawa, N.; Hato, M.; Ogasawara, S.; Hino, T.; Murata, T.; Iwata, S.; Hirata, K.; Kawano, Y.; Yamamoto, M.; Kimura-Someya, T.; Shirouzu, M.; Yamauchi, T.; Kadowaki, T.; Yokoyama, S. Crystal structures of

the human adiponectin receptors. *Nature,* **2015**, *520*(7547), 312-316.

[20] Achari, A.E.; Jain, S.K. Adiponectin, a therapeutic target for obesity, diabetes, and endothelial dysfunction. *Int. J. Mol. Sci.,* **2017**, *18*(6), E1321.

[21] Yamauchi, T.; Kamon, J.; Minokoshi, Y.; Ito, Y.; Waki, H.; Uchida, S.; Yamashita, S.; Noda, M.; Kita, S.; Ueki, K.; Eto, K.; Akanuma, Y.; Froguel, P.; Foufelle, F.; Ferre, P.; Carling, D.; Kimura, S.; Nagai, R.; Kahn, B.B.; Kadowaki, T. Adiponectin stimulates glucose utilization and fatty-acid oxidation by activating AMP-activated protein kinase. *Nat. Med.,* **2002**, *8*(11), 1288-1295.

[22] Iwabu, M.; Yamauchi, T.; Okada-Iwabu, M.; Sato, K.; Nakagawa, T.; Funata, M.; Yamaguchi, M.; Namiki, S.; Nakayama, R.; Tabata, M.; Ogata, H.; Kubota, N.; Takamoto, I.; Hayashi, Y.K.; Yamauchi, N.; Waki, H.; Fukayama, M.; Nishino, I.; Tokuyama, K.; Ueki, K.; Oike, Y.; Ishii, S.; Hirose, K.; Shimizu, T.; Touhara, K.; Kadowaki, T. Adiponectin and AdipoR1 regulate PGC-1alpha and mitochondria by Ca(2+) and AMPK/SIRT1. *Nature,* **2010**, *464*(7293), 1313-1319.

[23] Holland, W.L.; Miller, R.A.; Wang, Z.V.; Sun, K.; Barth, B.M.; Bui, H.H.; Davis, K.E.; Bikman, B.T.; Halberg, N.; Rutkowski, J.M.; Wade, M.R.; Tenorio, V.M.; Kuo, M.S.; Brozinick, J.T.; Zhang, B.B.; Birnbaum, M.J.; Summers, S.A.; Scherer, P.E. Receptor-mediated activation of ceramidase activity initiates the pleiotropic actions of adiponectin. *Nat. Med.,* **2011**, *17*(1), 55-63.

[24] Ouchi, N.; Kihara, S.; Arita, Y.; Maeda, K.; Kuriyama, H.; Okamoto, Y.; Hotta, K.; Nishida, M.; Takahashi, M.; Nakamura, T.; Yamashita, S.; Funahashi, T.; Matsuzawa, Y. Novel modulator for endothelial adhesion molecules: Adipocyte-derived plasma protein adiponectin. *Circulation,* **1999**, *100*(25), 2473-2476.

[25] Hara, K.; Boutin, P.; Mori, Y.; Tobe, K.; Dina, C.; Yasuda, K.; Yamauchi, T.; Otabe, S.; Okada, T.; Eto, K.; Kadowaki, H.; Hagura, R.; Akanuma, Y.; Yazaki, Y.; Nagai, R.; Taniyama, M.; Matsubara, K.; Yoda, M.; Nakano, Y.; Tomita, M.; Kimura, S.; Ito, C.; Froguel, P.; Kadowaki, T. Genetic variation in the gene encoding adiponectin is associated with an increased risk of type 2 diabetes in the Japanese population. *Diabetes,* **2002**, *51*(2), 536-540.

[26] Ouchi, N.; Shibata, R.; Walsh, K. Cardioprotection by adiponectin. *Trends Cardiovasc. Med.,* **2006**, *16*(5), 141-146.

[27] Choi, K.M.; Lee, J.; Lee, K.W.; Seo, J.A.; Oh, J.H.; Kim, S.G.; Kim, N.H.; Choi, D.S.; Baik, S.H. Serum adiponectin concentrations predict the developments of type 2 diabetes and the metabolic syndrome in elderly Koreans. *Clin. Endocrinol. (Oxf.),* **2004**, *61*(1), 75-80.

[28] Li, S.; Shin, H.J.; Ding, E.L.; van Dam, R.M. Adiponectin levels and risk of type 2 diabetes: a systematic review and meta-analysis. *JAMA,* **2009**, *302*(2), 179-188.

[29] Choi, H.Y.; Kim, S.; Yang, S.J.; Yoo, H.J.; Seo, J.A.; Kim, S.G.; Kim, N.H.; Baik, S.H.; Choi, D.S.; Choi, K.M. Association of adiponectin, resistin, and vascular inflammation: Analysis with 18F-fluorodeoxyglucose positron emission tomography. *Arterioscler. Thromb. Vasc. Biol.,* **2011**, *31*(4), 944-949.

[30] Pischon, T.; Girman, C.J.; Hotamisligil, G.S.; Rifai, N.; Hu, F.B.; Rimm, E.B. Plasma adiponectin levels and risk of myocardial infarction in men. *JAMA,* **2004**, *291*(14), 1730-1737.

[31] Kobashi, C.; Urakaze, M.; Kishida, M.; Kibayashi, E.; Kobayashi, H.; Kihara, S.; Funahashi, T.; Takata, M.; Temaru, R.; Sato, A.; Yamazaki, K.; Nakamura, N.; Kobayashi, M. Adiponectin inhibits endothelial synthesis of interleukin-8. *Circ. Res.,* **2005**, *97*(12), 1245-1252.

[32] Ouchi, N.; Kihara, S.; Arita, Y.; Okamoto, Y.; Maeda, K.; Kuriyama, H.; Hotta, K.; Nishida, M.; Takahashi, M.; Muraguchi, M.; Ohmoto, Y.; Nakamura, T.; Yamashita, S.; Funahashi, T.; Matsuzawa, Y. Adiponectin, an adipocyte-derived plasma protein, inhibits endothelial NF-kappaB signaling through a cAMP-dependent pathway. *Circulation,* **2000**, *102*(11), 1296-1301.

[33] Ohashi, K.; Ouchi, N.; Sato, K.; Higuchi, A.; Ishikawa, T.O.; Herschman, H.R.; Kihara, S.; Walsh, K. Adiponectin promotes revascularization of ischemic muscle through a cyclooxygenase 2-dependent mechanism. *Mol. Cell. Biol.,* **2009**, *29*(13), 3487-3499.

[34] Berg, A.H.; Combs, T.P.; Du, X.; Brownlee, M.; Scherer, P.E. The adipocyte-secreted protein Acrp30 enhances hepatic insulin action. *Nat. Med.,* **2001**, *7*(8), 947-953.

[35] Fantuzzi, G. Adipose tissue, adipokines, and inflammation. *J. Allergy Clin. Immunol.,* **2005**, *115*(5), 911-919.

[36] Okada-Iwabu, M.; Yamauchi, T.; Iwabu, M.; Honma, T.; Hamagami, K.; Matsuda, K.; Yamaguchi, M.; Tanabe, H.; Kimura-Someya, T.; Shirouzu, M.; Ogata, H.; Tokuyama, K.; Ueki, K.; Nagano, T.; Tanaka, A.; Yokoyama, S.; Kadowaki, T. A small-molecule AdipoR agonist for type 2 diabetes and short life in obesity. *Nature,* **2013**, *503*(7477), 493-499.

[37] Dalamaga, M.; Diakopoulos, K.N.; Mantzoros, C.S. The role of adiponectin in cancer: A review of current evidence. *Endocr. Rev.,* **2012**, *33*(4), 547-594.

[38] Peterson, S.J.; Drummond, G.; Kim, D.H.; Li, M.; Kruger, A.L.; Ikehara, S.; Abraham, N.G. L-4F treatment reduces adiposity, increases adiponectin levels, and improves insulin sensitivity in obese mice. *J. Lipid Res.,* **2008**, *49*(8), 1658-1669.

[39] Vecoli, C.; Cao, J.; Neglia, D.; Inoue, K.; Sodhi, K.; Vanella, L.; Gabrielson, K.K.; Bedja, D.; Paolocci, N.; L'abbate, A.; Abraham, N.G. Apolipoprotein A-I mimetic peptide L-4F prevents myocardial and coronary dysfunction in diabetic mice. *J. Cell. Biochem.,* **2011**, *112*(9), 2616-2626.

[40] Talukdar, S.; Zhou, Y.; Li, D.; Rossulek, M.; Dong, J.; Somayaji, V.; Weng, Y.; Clark, R.; Lanba, A.; Owen, B.M.; Brenner, M.B.; Trimmer, J.K.; Gropp, K.E.; Chabot, J.R.; Erion, D.M.; Rolph, T.P.; Goodwin, B.; Calle, R.A. A long-acting FGF21 molecule, PF-05231023, decreases body weight and improves lipid profile in non-human primates and type 2 diabetic subjects. *Cell Metab.,* **2016**, *23*(3), 427-440.

[41] Kriketos, A.D.; Gan, S.K.; Poynten, A.M.; Furler, S.M.; Chisholm, D.J.; Campbell, L.V. Exercise increases adiponectin levels and insulin sensitivity in humans. *Diabetes Care,* **2004**, *27*(2), 629-630.

[42] Numao, S.; Katayama, Y.; Hayashi, Y.; Matsuo, T.; Tanaka, K. Influence of acute aerobic exercise on adiponectin oligomer concentrations in middle-aged abdominally obese men. *Metabolism,* **2011**, *60*(2), 186-194.

[43] Yamauchi, T.; Kamon, J.; Waki, H.; Terauchi, Y.; Kubota, N.; Hara, K.; Mori, Y.; Ide, T.; Murakami, K.; Tsuboyama-Kasaoka, N.; Ezaki, O.; Akanuma, Y.; Gavrilova, O.; Vinson, C.; Reitman, M.L.; Kagechika, H.; Shudo, K.; Yoda, M.; Nakano, Y.; Tobe, K.; Nagai, R.; Kimura, S.; Tomita, M.; Froguel, P.; Kadowaki, T. The fat-derived hormone adiponectin reverses insulin resistance associated with both lipoatrophy and obesity. *Nat. Med.,* **2001**, *7*(8), 941-946.

[44] Combs, T.P.; Wagner, J.A.; Berger, J.; Doebber, T.; Wang, W.J.; Zhang, B.B.; Tanen, M.; Berg, A.H.; O'Rahilly, S.;

Savage, D.B.; Chatterjee, K.; Weiss, S.; Larson, P.J.; Gottesdiener, K.M.; Gertz, B.J.; Charron, M.J.; Scherer, P.E.; Moller, D.E. Induction of adipocyte complement-related protein of 30 kilodaltons by PPARgamma agonists: A potential mechanism of insulin sensitization. *Endocrinology,* **2002**, *143*(3), 998-1007.

[45] Achari, A.E.; Jain, S.K. L-Cysteine supplementation increases adiponectin synthesis and secretion, and GLUT4 and glucose utilization by upregulating disulfide bond A-like protein expression mediated by MCP-1 inhibition in 3T3-L1 adipocytes exposed to high glucose. *Mol. Cell. Biochem.,* **2016**, *414*(1-2), 105-113.

[46] Krusinová, E.; Pelikánová, T. Fatty acid binding proteins in adipose tissue: A promising link between metabolic syndrome and atherosclerosis? *Diabetes Res. Clin. Pract.,* **2008**, *82*(Suppl. 2), S127-S134.

[47] Makowski, L.; Hotamisligil, G.S. Fatty acid binding proteins--the evolutionary crossroads of inflammatory and metabolic responses. *J. Nutr.,* **2004**, *134*(9), 2464S-2468S.

[48] Duplus, E.; Glorian, M.; Forest, C. Fatty acid regulation of gene transcription. *J. Biol. Chem.,* **2000**, *275*(40), 30749-30752.

[49] Makowski, L.; Hotamisligil, G.S. The role of fatty acid binding proteins in metabolic syndrome and atherosclerosis. *Curr. Opin. Lipidol.,* **2005**, *16*(5), 543-548.

[50] Tan, N.S.; Shaw, N.S.; Vinckenbosch, N.; Liu, P.; Yasmin, R.; Desvergne, B.; Wahli, W.; Noy, N. Selective cooperation between fatty acid binding proteins and peroxisome proliferator-activated receptors in regulating transcription. *Mol. Cell. Biol.,* **2002**, *22*(14), 5114-5127.

[51] Boord, J.B.; Fazio, S.; Linton, M.F. Cytoplasmic fatty acid-binding proteins: emerging roles in metabolism and atherosclerosis. *Curr. Opin. Lipidol.,* **2002**, *13*(2), 141-147.

[52] Uysal, K.T.; Scheja, L.; Wiesbrock, S.M.; Bonner-Weir, S.; Hotamisligil, G.S. Improved glucose and lipid metabolism in genetically obese mice lacking aP2. *Endocrinology,* **2000**, *141*(9), 3388-3396.

[53] Makowski, L.; Boord, J.B.; Maeda, K.; Babaev, V.R.; Uysal, K.T.; Morgan, M.A.; Parker, R.A.; Suttles, J.; Fazio, S.; Hotamisligil, G.S.; Linton, M.F. Lack of macrophage fatty-acid-binding protein aP2 protects mice deficient in apolipoprotein E against atherosclerosis. *Nat. Med.,* **2001**, *7*(6), 699-705.

[54] Boord, J.B.; Maeda, K.; Makowski, L.; Babaev, V.R.; Fazio, S.; Linton, M.F.; Hotamisligil, G.S. Combined adipocyte-macrophage fatty acid-binding protein deficiency improves metabolism, atherosclerosis, and survival in apolipoprotein E-deficient mice. *Circulation,* **2004**, *110*(11), 1492-1498.

[55] Cao, H.; Sekiya, M.; Ertunc, M.E.; Burak, M.F.; Mayers, J.R.; White, A.; Inouye, K.; Rickey, L.M.; Ercal, B.C.; Furuhashi, M.; Tuncman, G.; Hotamisligil, G.S. Adipocyte lipid chaperone AP2 is a secreted adipokine regulating hepatic glucose production. *Cell Metab.,* **2013**, *17*(5), 768-778.

[56] Xu, A.; Wang, Y.; Xu, J.Y.; Stejskal, D.; Tam, S.; Zhang, J.; Wat, N.M.; Wong, W.K.; Lam, K.S. Adipocyte fatty acid-binding protein is a plasma biomarker closely associated with obesity and metabolic syndrome. *Clin. Chem.,* **2006**, *52*(3), 405-413.

[57] Choi, K.M.; Yannakoulia, M.; Park, M.S.; Cho, G.J.; Kim, J.H.; Lee, S.H.; Hwang, T.G.; Yang, S.J.; Kim, T.N.; Yoo, H.J.; Baik, S.H.; Kim, S.M.; Mantzoros, C.S. Serum adipocyte fatty acid-binding protein, retinol-binding protein 4, and adiponectin concentrations in relation to the development of the metabolic syndrome in Korean boys: a 3-y prospective cohort study. *Am. J. Clin. Nutr.,* **2011**, *93*(1), 19-26.

[58] Tso, A.W.; Xu, A.; Sham, P.C.; Wat, N.M.; Wang, Y.; Fong, C.H.; Cheung, B.M.; Janus, E.D.; Lam, K.S. Serum adipocyte fatty acid binding protein as a new biomarker predicting the development of type 2 diabetes: A 10-year prospective study in a Chinese cohort. *Diabetes Care,* **2007**, *30*(10), 2667-2672.

[59] Peeters, W.; de Kleijn, D.P.; Vink, A.; van de Weg, S.; Schoneveld, A.H.; Sze, S.K.; van der Spek, P.J.; de Vries, J.P.; Moll, F.L.; Pasterkamp, G. Adipocyte fatty acid binding protein in atherosclerotic plaques is associated with local vulnerability and is predictive for the occurrence of adverse cardiovascular events. *Eur. Heart J.,* **2011**, *32*(14), 1758-1768.

[60] Rhee, E.J.; Lee, W.Y.; Park, C.Y.; Oh, K.W.; Kim, B.J.; Sung, K.C.; Kim, B.S. The association of serum adipocyte fatty acid-binding protein with coronary artery disease in Korean adults. *Eur. J. Endocrinol.,* **2009**, *160*(2), 165-172.

[61] Yoo, H.J.; Kim, S.; Park, M.S.; Choi, H.Y.; Yang, S.J.; Seo, J.A.; Kim, S.G.; Kim, N.H.; Baik, S.H.; Choi, D.S.; Choi, K.M. Serum adipocyte fatty acid-binding protein is associated independently with vascular inflammation: analysis with (18)F-fluorodeoxyglucose positron emission tomography. *J. Clin. Endocrinol. Metab.,* **2011**, *96*(3), E488-E492.

[62] Kim, T.N.; Won, J.C.; Kim, Y.J.; Lee, E.J.; Kim, M.K.; Park, M.S.; Lee, S.K.; Kim, J.M.; Ko, K.S.; Rhee, B.D. Serum adipocyte fatty acid-binding protein levels are independently associated with sarcopenic obesity. *Diabetes Res. Clin. Pract.,* **2013**, *101*(2), 210-217.

[63] Furuhashi, M.; Saitoh, S.; Shimamoto, K.; Miura, T. Fatty Acid-Binding Protein 4 (FABP4): Pathophysiological insights and potent clinical biomarker of metabolic and cardiovascular diseases. *Clin. Med. Insights Cardiol.,* **2015**, *8*(Suppl. 3), 23-33.

[64] Floresta, G.; Pistarà, V.; Amata, E.; Dichiara, M.; Marrazzo, A.; Prezzavento, O.; Rescifina, A. Adipocyte fatty acid binding protein 4 (FABP4) inhibitors. A comprehensive systematic review. *Eur. J. Med. Chem.,* **2017**, *138*, 854-873.

[65] Wong, G.W.; Krawczyk, S.A.; Kitidis-Mitrokostas, C.; Ge, G.; Spooner, E.; Hug, C.; Gimeno, R.; Lodish, H.F. Identification and characterization of CTRP9, a novel secreted glycoprotein, from adipose tissue that reduces serum glucose in mice and forms heterotrimers with adiponectin. *FASEB J.,* **2009**, *23*(1), 241-258.

[66] Shibata, R.; Ouchi, N.; Ohashi, K.; Murohara, T. The role of adipokines in cardiovascular disease. *J. Cardiol.,* **2017**, *70*(4), 329-334.

[67] Peterson, J.M.; Wei, Z.; Seldin, M.M.; Byerly, M.S.; Aja, S.; Wong, G.W. CTRP9 transgenic mice are protected from diet-induced obesity and metabolic dysfunction. *Am. J. Physiol. Regul. Integr. Comp. Physiol.,* **2013**, *305*(5), R522-R533.

[68] Wei, Z.; Lei, X.; Petersen, P.S.; Aja, S.; Wong, G.W. Targeted deletion of C1q/TNF-related protein 9 increases food intake, decreases insulin sensitivity, and promotes hepatic steatosis in mice. *Am. J. Physiol. Endocrinol. Metab.,* **2014**, *306*(7), E779-E790.

[69] Zheng, Q.; Yuan, Y.; Yi, W.; Lau, W.B.; Wang, Y.; Wang, X.; Sun, Y.; Lopez, B.L.; Christopher, T.A.; Peterson, J.M.; Wong, G.W.; Yu, S.; Yi, D.; Ma, X.L. C1q/TNF-related proteins, a family of novel adipokines, induce vascular relaxation through the adiponectin receptor-1/AMPK/eNOS/nitric oxide signaling pathway. *Arterioscler. Thromb. Vasc. Biol.,* **2011**, *31*(11), 2616-2623.

[70] Jung, T.W.; Hong, H.C.; Hwang, H.J.; Yoo, H.J.; Baik, S.H.; Choi, K.M. C1q/TNF-Related Protein 9 (CTRP9) attenuates hepatic steatosis via the autophagy-mediated inhibition of endoplasmic reticulum stress. *Mol. Cell. Endocrinol.,* **2015**, *417*, 131-140.

[71] Sun, Y.; Yi, W.; Yuan, Y.; Lau, W.B.; Yi, D.; Wang, X.; Wang, Y.; Su, H.; Wang, X.; Gao, E.; Koch, W.J.; Ma, X.L. C1q/tumor necrosis factor-related protein-9, a novel adipocyte-derived cytokine, attenuates adverse remodeling in the ischemic mouse heart *via* protein kinase A activation. *Circulation,* **2013**, *128*(11)(Suppl. 1), S113-S120.

[72] Kambara, T.; Ohashi, K.; Shibata, R.; Ogura, Y.; Maruyama, S.; Enomoto, T.; Uemura, Y.; Shimizu, Y.; Yuasa, D.; Matsuo, K.; Miyabe, M.; Kataoka, Y.; Murohara, T.; Ouchi, N. CTRP9 protein protects against myocardial injury following ischemia-reperfusion through AMP-activated protein kinase (AMPK)-dependent mechanism. *J. Biol. Chem.,* **2012**, *287*(23), 18965-18973.

[73] Kambara, T.; Shibata, R.; Ohashi, K.; Matsuo, K.; Hiramatsu-Ito, M.; Enomoto, T.; Yuasa, D.; Ito, M.; Hayakawa, S.; Ogawa, H.; Aprahamian, T.; Walsh, K.; Murohara, T.; Ouchi, N. C1q/tumor necrosis factor-related protein 9 protects against acute myocardial injury through an adiponectin receptor I-AMPK-dependent mechanism. *Mol. Cell. Biol.,* **2015**, *35*(12), 2173-2185.

[74] Wang, X.Q.; Liu, Z.H.; Xue, L.; Lu, L.; Gao, J.; Shen, Y.; Yang, K.; Chen, Q.J.; Zhang, R.Y.; Shen, W.F. C1q/TNF-related protein 1 links macrophage lipid metabolism to inflammation and atherosclerosis. *Atherosclerosis,* **2016**, *250*, 38-45.

[75] Yang, Y.; Li, Y.; Ma, Z.; Jiang, S.; Fan, C.; Hu, W.; Wang, D.; Di, S.; Sun, Y.; Yi, W. A brief glimpse at CTRP3 and CTRP9 in lipid metabolism and cardiovascular protection. *Prog. Lipid Res.,* **2016**, *64*, 170-177.

[76] Yuasa, D.; Ohashi, K.; Shibata, R.; Mizutani, N.; Kataoka, Y.; Kambara, T.; Uemura, Y.; Matsuo, K.; Kanemura, N.; Hayakawa, S.; Hiramatsu-Ito, M.; Ito, M.; Ogawa, H.; Murate, T.; Murohara, T.; Ouchi, N. C1q/TNF-related protein-1 functions to protect against acute ischemic injury in the heart. *FASEB J.,* **2016**, *30*(3), 1065-1075.

[77] Lu, L.; Zhang, R.Y.; Wang, X.Q.; Liu, Z.H.; Shen, Y.; Ding, F.H.; Meng, H.; Wang, L.J.; Yan, X.X.; Yang, K.; Wang, H.B.; Pu, L.J.; Zhang, Q.; Chen, Q.J.; De Caterina, R.; Shen, W.F. C1q/TNF-related protein-1: an adipokine marking and promoting atherosclerosis. *Eur. Heart J.,* **2016**, *37*(22), 1762-1771.

[78] Yi, W.; Sun, Y.; Yuan, Y.; Lau, W.B.; Zheng, Q.; Wang, X.; Wang, Y.; Shang, X.; Gao, E.; Koch, W.J.; Ma, X.L. C1q/tumor necrosis factor-related protein-3, a newly identified adipokine, is a novel antiapoptotic, proangiogenic, and cardioprotective molecule in the ischemic mouse heart. *Circulation,* **2012**, *125*(25), 3159-3169.

[79] Choi, K.M.; Hwang, S.Y.; Hong, H.C.; Yang, S.J.; Choi, H.Y.; Yoo, H.J.; Lee, K.W.; Nam, M.S.; Park, Y.S.; Woo, J.T.; Kim, Y.S.; Choi, D.S.; Youn, B.S.; Baik, S.H. C1q/TNF-related protein-3 (CTRP-3) and pigment epithelium-derived factor (PEDF) concentrations in patients with type 2 diabetes and metabolic syndrome. *Diabetes,* **2012**, *61*(11), 2932-2936.

[80] Choi, K.M.; Hwang, S.Y.; Hong, H.C.; Choi, H.Y.; Yoo, H.J.; Youn, B.S.; Baik, S.H.; Seo, H.S. Implications of C1q/TNF-related protein-3 (CTRP-3) and progranulin in patients with acute coronary syndrome and stable angina pectoris. *Cardiovasc. Diabetol.,* **2014**, *13*, 14. doi: 10.1186/1475-2840-13-14.

[81] Ma, Z.G.; Yuan, Y.P.; Xu, S.C.; Wei, W.Y.; Xu, C.R.; Zhang, X.; Wu, Q.Q.; Liao, H.H.; Ni, J.; Tang, Q.Z. CTRP3 attenuates cardiac dysfunction, inflammation, oxidative stress and cell death in diabetic cardiomyopathy in rats. *Diabetologia,* **2017**, *60*(6), 1126-1137.

[82] Janssen, I.; Heymsfield, S.B.; Wang, Z.M.; Ross, R. Skeletal muscle mass and distribution in 468 men and women aged 18-88 yr. *J. Appl. Physiol.,* **2000**, *89*(1), 81-88.

[83] Kimball, S.R. Integration of signals generated by nutrients, hormones, and exercise in skeletal muscle. *Am. J. Clin. Nutr.,* **2014**, *99*(1), 237S-242S.

[84] Colcombe, S.J.; Erickson, K.I.; Raz, N.; Webb, A.G.; Cohen, N.J.; McAuley, E.; Kramer, A.F. Aerobic fitness reduces brain tissue loss in aging humans. *J. Gerontol. A Biol. Sci. Med. Sci.,* **2003**, *58*(2), 176-180.

[85] Brechue, W.F.; Pollock, M.L. Exercise training for coronary artery disease in the elderly. *Clin. Geriatr. Med.,* **1996**, *12*(1), 207-229.

[86] Li, J.; Siegrist, J. Physical activity and risk of cardiovascular disease--a meta-analysis of prospective cohort studies. *Int. J. Environ. Res. Public Health,* **2012**, *9*(2), 391-407.

[87] Pratesi, A.; Tarantini, F.; Di Bari, M. Skeletal muscle: an endocrine organ. *Clin. Cases Miner. Bone Metab.,* **2013**, *10*(1), 11-14.

[88] Pedersen, B.K. Muscles and their myokines. *J. Exp. Biol.,* **2011**, *214*(Pt 2), 337-346.

[89] Hirano, T. Interleukin 6 and its receptor: Ten years later. *Int. Rev. Immunol.,* **1998**, *16*(3-4), 249-284.

[90] Kristiansen, O.P.; Mandrup-Poulsen, T. Interleukin-6 and diabetes: the good, the bad, or the indifferent? *Diabetes,* **2005**, *54*(Suppl. 2), S114-S124.

[91] Akira, S.; Taga, T.; Kishimoto, T. Interleukin-6 in biology and medicine. *Adv. Immunol.,* **1993**, *54*, 1-78.

[92] Ostrowski, K.; Rohde, T.; Zacho, M.; Asp, S.; Pedersen, B.K. Evidence that interleukin-6 is produced in human skeletal muscle during prolonged running. *J. Physiol.,* **1998**, *508*(Pt 3), 949-953.

[93] Steensberg, A.; van Hall, G.; Osada, T.; Sacchetti, M.; Saltin, B.; Klarlund Pedersen, B. Production of interleukin-6 in contracting human skeletal muscles can account for the exercise-induced increase in plasma interleukin-6. *J. Physiol.,* **2000**, *529*(Pt 1), 237-242.

[94] Qu, D.; Liu, J.; Lau, C.W.; Huang, Y. IL-6 in diabetes and cardiovascular complications. *Br. J. Pharmacol.,* **2014**, *171*(15), 3595-3603.

[95] Steinbacher, P.; Eckl, P. Impact of oxidative stress on exercising skeletal muscle. *Biomolecules,* **2015**, *5*(2), 356-377.

[96] Fischer, C.P.; Plomgaard, P.; Hansen, A.K.; Pilegaard, H.; Saltin, B.; Pedersen, B.K. Endurance training reduces the contraction-induced interleukin-6 mRNA expression in human skeletal muscle. *Am. J. Physiol. Endocrinol. Metab.,* **2004**, *287*(6), E1189-E1194.

[97] Keller, C.; Steensberg, A.; Hansen, A.K.; Fischer, C.P.; Plomgaard, P.; Pedersen, B.K. Effect of exercise, training, and glycogen availability on IL-6 receptor expression in human skeletal muscle. *J. Appl. Physiol.,* **2005**, *99*(6), 2075-2079.

[98] Carey, A.L.; Steinberg, G.R.; Macaulay, S.L.; Thomas, W.G.; Holmes, A.G.; Ramm, G.; Prelovsek, O.; Hohnen-Behrens, C.; Watt, M.J.; James, D.E.; Kemp, B.E.; Pedersen, B.K.; Febbraio, M.A. Interleukin-6 increases insulin-stimulated glucose disposal in humans and glucose uptake and fatty acid oxidation *in vitro via* AMP-activated protein kinase. *Diabetes,* **2006**, *55*(10), 2688-2697.

[99] Kelly, M.; Keller, C.; Avilucea, P.R.; Keller, P.; Luo, Z.; Xiang, X.; Giralt, M.; Hidalgo, J.; Saha, A.K.; Pedersen,

B.K.; Ruderman, N.B. AMPK activity is diminished in tissues of IL-6 knockout mice: the effect of exercise. *Biochem. Biophys. Res. Commun.,* **2004**, *320*(2), 449-454.

[100] Ellingsgaard, H.; Hauselmann, I.; Schuler, B.; Habib, A.M.; Baggio, L.L.; Meier, D.T.; Eppler, E.; Bouzakri, K.; Wueest, S.; Muller, Y.D.; Hansen, A.M.; Reinecke, M.; Konrad, D.; Gassmann, M.; Reimann, F.; Halban, P.A.; Gromada, J.; Drucker, D.J.; Gribble, F.M.; Ehses, J.A.; Donath, M.Y. Interleukin-6 enhances insulin secretion by increasing glucagon-like peptide-1 secretion from L cells and alpha cells. *Nat. Med.,* **2011**, *17*(11), 1481-1489.

[101] Gleeson, M. Interleukins and exercise. *J. Physiol.,* **2000**, *529*(Pt 1), 1. doi: 10.1111/j.1469-7793.2000.00001.x

[102] Pedersen, B.K. IL-6 signalling in exercise and disease. *Biochem. Soc. Trans.,* **2007**, *35*(Pt 5), 1295-1297.

[103] Xing, Z.; Gauldie, J.; Cox, G.; Baumann, H.; Jordana, M.; Lei, X.F.; Achong, M.K. IL-6 is an antiinflammatory cytokine required for controlling local or systemic acute inflammatory responses. *J. Clin. Invest.,* **1998**, *101*(2), 311-320.

[104] Wallenius, V.; Wallenius, K.; Ahrén, B.; Rudling, M.; Carlsten, H.; Dickson, S.L.; Ohlsson, C.; Jansson, J.O. Interleukin-6-deficient mice develop mature-onset obesity. *Nat. Med.,* **2002**, *8*(1), 75-79.

[105] Matthews, V.B.; Allen, T.L.; Risis, S.; Chan, M.H.; Henstridge, D.C.; Watson, N.; Zaffino, L.A.; Babb, J.R.; Boon, J.; Meikle, P.J.; Jowett, J.B.; Watt, M.J.; Jansson, J.O.; Bruce, C.R.; Febbraio, M.A. Interleukin-6-deficient mice develop hepatic inflammation and systemic insulin resistance. *Diabetologia,* **2010**, *53*(11), 2431-2441.

[106] Richez, C.; Barnetche, T.; Khoryati, L.; Duffau, P.; Kostine, M.; Contin-Bordes, C.; Blanco, P.; Schaeverbeke, T. Tocilizumab treatment decreases circulating myeloid dendritic cells and monocytes, 2 components of the myeloid lineage. *J. Rheumatol.,* **2012**, *39*(6), 1192-1197.

[107] Md Yusof, M.Y.; Emery, P. Targeting interleukin-6 in rheumatoid arthritis. *Drugs,* **2013**, *73*(4), 341-356.

[108] Spranger, J.; Kroke, A.; Möhlig, M.; Hoffmann, K.; Bergmann, M.M.; Ristow, M.; Boeing, H.; Pfeiffer, A.F. Inflammatory cytokines and the risk to develop type 2 diabetes: Results of the prospective population-based European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam Study. *Diabetes,* **2003**, *52*(3), 812-817.

[109] Lowe, G.; Woodward, M.; Hillis, G.; Rumley, A.; Li, Q.; Harrap, S.; Marre, M.; Hamet, P.; Patel, A.; Poulter, N.; Chalmers, J. Circulating inflammatory markers and the risk of vascular complications and mortality in people with type 2 diabetes and cardiovascular disease or risk factors: the ADVANCE study. *Diabetes,* **2014**, *63*(3), 1115-1123.

[110] Tehrani, D.M.; Gardin, J.M.; Yanez, D.; Hirsch, C.H.; Lloyd-Jones, D.M.; Stein, P.K.; Wong, N.D. Impact of inflammatory biomarkers on relation of high density lipoprotein-cholesterol with incident coronary heart disease: Cardiovascular Health Study. *Atherosclerosis,* **2013**, *231*(2), 246-251.

[111] Saremi, A.; Anderson, R.J.; Luo, P.; Moritz, T.E.; Schwenke, D.C.; Allison, M.; Reaven, P.D. Association between IL-6 and the extent of coronary atherosclerosis in the veterans affairs diabetes trial (VADT). *Atherosclerosis,* **2009**, *203*(2), 610-614.

[112] Puz, P.; Lasek-Bal, A. Repeated measurements of serum concentrations of TNF-alpha, interleukin-6 and interleukin-10 in the evaluation of internal carotid artery stenosis progression. *Atherosclerosis,* **2017**, *263*, 97-103.

[113] Boström, P.; Wu, J.; Jedrychowski, M.P.; Korde, A.; Ye, L.; Lo, J.C.; Rasbach, K.A.; Boström, E.A.; Choi, J.H.; Long, J.Z.; Kajimura, S.; Zingaretti, M.C.; Vind, B.F.; Tu, H.; Cinti, S.; Højlund, K.; Gygi, S.P.; Spiegelman, B.M. A PGC1-α-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. *Nature,* **2012**, *481*(7382), 463-468.

[114] Wenz, T.; Rossi, S.G.; Rotundo, R.L.; Spiegelman, B.M.; Moraes, C.T. Increased muscle PGC-1alpha expression protects from sarcopenia and metabolic disease during aging. *Proc. Natl. Acad. Sci. USA,* **2009**, *106*(48), 20405-20410.

[115] Zhang, Y.; Li, R.; Meng, Y.; Li, S.; Donelan, W.; Zhao, Y.; Qi, L.; Zhang, M.; Wang, X.; Cui, T.; Yang, L.J.; Tang, D. Irisin stimulates browning of white adipocytes through mitogen-activated protein kinase p38 MAP kinase and ERK MAP kinase signaling. *Diabetes,* **2014**, *63*(2), 514-525.

[116] Huh, J.Y.; Panagiotou, G.; Mougios, V.; Brinkoetter, M.; Vamvini, M.T.; Schneider, B.E.; Mantzoros, C.S. FNDC5 and irisin in humans: I. Predictors of circulating concentrations in serum and plasma and II. mRNA expression and circulating concentrations in response to weight loss and exercise. *Metabolism,* **2012**, *61*(12), 1725-1738.

[117] Tsuchiya, Y.; Ando, D.; Takamatsu, K.; Goto, K. Resistance exercise induces a greater irisin response than endurance exercise. *Metabolism,* **2015**, *64*(9), 1042-1050.

[118] Hecksteden, A.; Wegmann, M.; Steffen, A.; Kraushaar, J.; Morsch, A.; Ruppenthal, S.; Kaestner, L.; Meyer, T. Irisin and exercise training in humans - results from a randomized controlled training trial. *BMC Med.,* **2013**, *11*, 235.

[119] Norheim, F.; Langleite, T.M.; Hjorth, M.; Holen, T.; Kielland, A.; Stadheim, H.K.; Gulseth, H.L.; Birkeland, K.I.; Jensen, J.; Drevon, C.A. The effects of acute and chronic exercise on PGC-1α, irisin and browning of subcutaneous adipose tissue in humans. *FEBS J.,* **2014**, *281*(3), 739-749.

[120] Albrecht, E.; Norheim, F.; Thiede, B.; Holen, T.; Ohashi, T.; Schering, L.; Lee, S.; Brenmoehl, J.; Thomas, S.; Drevon, C.A.; Erickson, H.P.; Maak, S. Irisin - a myth rather than an exercise-inducible myokine. *Sci. Rep.,* **2015**, *5*, 8889.

[121] Jedrychowski, M.P.; Wrann, C.D.; Paulo, J.A.; Gerber, K.K.; Szpyt, J.; Robinson, M.M.; Nair, K.S.; Gygi, S.P.; Spiegelman, B.M. Detection and quantitation of circulating human irisin by tandem mass spectrometry. *Cell Metab.,* **2015**, *22*(4), 734-740.

[122] Yan, B.; Shi, X.; Zhang, H.; Pan, L.; Ma, Z.; Liu, S.; Liu, Y.; Li, X.; Yang, S.; Li, Z. Association of serum irisin with metabolic syndrome in obese Chinese adults. *PLoS One,* **2014**, *9*(4), e94235.

[123] Lopez-Legarrea, P.; de la Iglesia, R.; Crujeiras, A.B.; Pardo, M.; Casanueva, F.F.; Zulet, M.A.; Martinez, J.A. Higher baseline irisin concentrations are associated with greater reductions in glycemia and insulinemia after weight loss in obese subjects. *Nutr. Diabetes,* **2014**, *4*, e110.

[124] Choi, H.Y.; Kim, S.; Park, J.W.; Lee, N.S.; Hwang, S.Y.; Huh, J.Y.; Hong, H.C.; Yoo, H.J.; Baik, S.H.; Youn, B.S.; Mantzoros, C.S.; Choi, K.M. Implication of circulating irisin levels with brown adipose tissue and sarcopenia in humans. *J. Clin. Endocrinol. Metab.,* **2014**, *99*(8), 2778-2785.

[125] Lee, M.J.; Lee, S.A.; Nam, B.Y.; Park, S.; Lee, S.H.; Ryu, H.J.; Kwon, Y.E.; Kim, Y.L.; Park, K.S.; Oh, H.J.; Park, J.T.; Han, S.H.; Ryu, D.R.; Kang, S.W.; Yoo, T.H. Irisin, a novel myokine is an independent predictor for sarcopenia and carotid atherosclerosis in dialysis patients. *Atherosclerosis,* **2015**, *242*(2), 476-482.

[126] Zhang, M.; Chen, P.; Chen, S.; Sun, Q.; Zeng, Q.C.; Chen, J.Y.; Liu, Y.X.; Cao, X.H.; Ren, M.; Wang, J.K. The association of new inflammatory markers with type 2 diabetes

mellitus and macrovascular complications: a preliminary study. *Eur. Rev. Med. Pharmacol. Sci.,* **2014**, *18*(11), 1567-1572.

[127] Natalicchio, A.; Marrano, N.; Biondi, G.; Spagnuolo, R.; Labarbuta, R.; Porreca, I.; Cignarelli, A.; Bugliani, M.; Marchetti, P.; Perrini, S.; Laviola, L.; Giorgino, F. The myokine irisin is released in response to saturated fatty acids and promotes pancreatic beta-cell survival and insulin secretion. *Diabetes,* **2017**, *66*(11), 2849-2856.

[128] Kharitonenkov, A. FGFs and metabolism. *Curr. Opin. Pharmacol.,* **2009**, *9*(6), 805-810.

[129] Nishimura, T.; Nakatake, Y.; Konishi, M.; Itoh, N. Identification of a novel FGF, FGF-21, preferentially expressed in the liver. *Biochim. Biophys. Acta,* **2000**, *1492*(1), 203-206.

[130] Fon Tacer, K.; Bookout, A.L.; Ding, X.; Kurosu, H.; John, G.B.; Wang, L.; Goetz, R.; Mohammadi, M.; Kuro-o, M.; Mangelsdorf, D.J.; Kliewer, S.A. Research resource: Comprehensive expression atlas of the fibroblast growth factor system in adult mouse. *Mol. Endocrinol.,* **2010**, *24*(10), 2050-2064.

[131] Badman, M.K.; Pissios, P.; Kennedy, A.R.; Koukos, G.; Flier, J.S.; Maratos-Flier, E. Hepatic fibroblast growth factor 21 is regulated by PPARalpha and is a key mediator of hepatic lipid metabolism in ketotic states. *Cell Metab.,* **2007**, *5*(6), 426-437.

[132] Lee, P.; Linderman, J.D.; Smith, S.; Brychta, R.J.; Wang, J.; Idelson, C.; Perron, R.M.; Werner, C.D.; Phan, G.Q.; Kammula, U.S.; Kebebew, E.; Pacak, K.; Chen, K.Y.; Celi, F.S. Irisin and FGF21 are cold-induced endocrine activators of brown fat function in humans. *Cell Metab.,* **2014**, *19*(2), 302-309.

[133] Hojman, P.; Pedersen, M.; Nielsen, A.R.; Krogh-Madsen, R.; Yfanti, C.; Akerstrom, T.; Nielsen, S.; Pedersen, B.K. Fibroblast growth factor-21 is induced in human skeletal muscles by hyperinsulinemia. *Diabetes,* **2009**, *58*(12), 2797-2801.

[134] Tyynismaa, H.; Carroll, C.J.; Raimundo, N.; Ahola-Erkkilä, S.; Wenz, T.; Ruhanen, H.; Guse, K.; Hemminki, A.; Peltola-Mjøsund, K.E.; Tulkki, V.; Oresic, M.; Moraes, C.T.; Pietiläinen, K.; Hovatta, I.; Suomalainen, A. Mitochondrial myopathy induces a starvation-like response. *Hum. Mol. Genet.,* **2010**, *19*(20), 3948-3958.

[135] Hondares, E.; Iglesias, R.; Giralt, A.; Gonzalez, F.J.; Giralt, M.; Mampel, T.; Villarroya, F. Thermogenic activation induces FGF21 expression and release in brown adipose tissue. *J. Biol. Chem.,* **2011**, *286*(15), 12983-12990.

[136] Kurosu, H.; Choi, M.; Ogawa, Y.; Dickson, A.S.; Goetz, R.; Eliseenkova, A.V.; Mohammadi, M.; Rosenblatt, K.P.; Kliewer, S.A.; Kuro-o, M. Tissue-specific expression of betaKlotho and fibroblast growth factor (FGF) receptor isoforms determines metabolic activity of FGF19 and FGF21. *J. Biol. Chem.,* **2007**, *282*(37), 26687-26695.

[137] Badman, M.K.; Koester, A.; Flier, J.S.; Kharitonenkov, A.; Maratos-Flier, E. Fibroblast growth factor 21-deficient mice demonstrate impaired adaptation to ketosis. *Endocrinology,* **2009**, *150*(11), 4931-4940.

[138] Kharitonenkov, A.; Shiyanova, T.L.; Koester, A.; Ford, A.M.; Micanovic, R.; Galbreath, E.J.; Sandusky, G.E.; Hammond, L.J.; Moyers, J.S.; Owens, R.A.; Gromada, J.; Brozinick, J.T.; Hawkins, E.D.; Wroblewski, V.J.; Li, D.S.; Mehrbod, F.; Jaskunas, S.R.; Shanafelt, A.B. FGF-21 as a novel metabolic regulator. *J. Clin. Invest.,* **2005**, *115*(6), 1627-1635.

[139] Potthoff, M.J.; Inagaki, T.; Satapati, S.; Ding, X.; He, T.; Goetz, R.; Mohammadi, M.; Finck, B.N.; Mangelsdorf, D.J.; Kliewer, S.A.; Burgess, S.C. FGF21 induces PGC-1alpha and regulates carbohydrate and fatty acid metabolism during the adaptive starvation response. *Proc. Natl. Acad. Sci. USA,* **2009**, *106*(26), 10853-10858.

[140] Fisher, F.M.; Kleiner, S.; Douris, N.; Fox, E.C.; Mepani, R.J.; Verdeguer, F.; Wu, J.; Kharitonenkov, A.; Flier, J.S.; Maratos-Flier, E.; Spiegelman, B.M. FGF21 regulates PGC-1α and browning of white adipose tissues in adaptive thermogenesis. *Genes Dev.,* **2012**, *26*(3), 271-281.

[141] Lin, Z.; Pan, X.; Wu, F.; Ye, D.; Zhang, Y.; Wang, Y.; Jin, L.; Lian, Q.; Huang, Y.; Ding, H.; Triggle, C.; Wang, K.; Li, X.; Xu, A. Fibroblast growth factor 21 prevents atherosclerosis by suppression of hepatic sterol regulatory element-binding protein-2 and induction of adiponectin in mice. *Circulation,* **2015**, *131*(21), 1861-1871.

[142] Lin, Z.; Tian, H.; Lam, K.S.; Lin, S.; Hoo, R.C.; Konishi, M.; Itoh, N.; Wang, Y.; Bornstein, S.R.; Xu, A.; Li, X. Adiponectin mediates the metabolic effects of FGF21 on glucose homeostasis and insulin sensitivity in mice. *Cell Metab.,* **2013**, *17*(5), 779-789.

[143] Muise, E.S.; Azzolina, B.; Kuo, D.W.; El-Sherbeini, M.; Tan, Y.; Yuan, X.; Mu, J.; Thompson, J.R.; Berger, J.P.; Wong, K.K. Adipose fibroblast growth factor 21 is up-regulated by peroxisome proliferator-activated receptor gamma and altered metabolic states. *Mol. Pharmacol.,* **2008**, *74*(2), 403-412.

[144] Dutchak, P.A.; Katafuchi, T.; Bookout, A.L.; Choi, J.H.; Yu, R.T.; Mangelsdorf, D.J.; Kliewer, S.A. Fibroblast growth factor-21 regulates PPARγ activity and the antidiabetic actions of thiazolidinediones. *Cell,* **2012**, *148*(3), 556-567.

[145] Zhu, W.; Wang, C.; Liu, L.; Li, Y.; Li, X.; Cai, J.; Wang, H. Effects of fibroblast growth factor 21 on cell damage *in vitro* and atherosclerosis *in vivo*. *Can. J. Physiol. Pharmacol.,* **2014**, *92*(11), 927-935.

[146] Zhu, S.; Ma, L.; Wu, Y.; Ye, X.; Zhang, T.; Zhang, Q.; Rasoul, L.M.; Liu, Y.; Guo, M.; Zhou, B.; Ren, G.; Li, D. FGF21 treatment ameliorates alcoholic fatty liver through activation of AMPK-SIRT1 pathway. *Acta Biochim. Biophys. Sin. (Shanghai),* **2014**, *46*(12), 1041-1048.

[147] Zhang, X.; Yeung, D.C.; Karpisek, M.; Stejskal, D.; Zhou, Z.G.; Liu, F.; Wong, R.L.; Chow, W.S.; Tso, A.W.; Lam, K.S.; Xu, A. Serum FGF21 levels are increased in obesity and are independently associated with the metabolic syndrome in humans. *Diabetes,* **2008**, *57*(5), 1246-1253.

[148] Domingo, P.; Gallego-Escuredo, J.M.; Domingo, J.C.; Gutiérrez, Mdel.M.; Mateo, M.G.; Fernández, I.; Vidal, F.; Giralt, M.; Villarroya, F. Serum FGF21 levels are elevated in association with lipodystrophy, insulin resistance and biomarkers of liver injury in HIV-1-infected patients. *AIDS,* **2010**, *24*(17), 2629-2637.

[149] Chavez, A.O.; Molina-Carrion, M.; Abdul-Ghani, M.A.; Folli, F.; Defronzo, R.A.; Tripathy, D. Circulating fibroblast growth factor-21 is elevated in impaired glucose tolerance and type 2 diabetes and correlates with muscle and hepatic insulin resistance. *Diabetes Care,* **2009**, *32*(8), 1542-1546.

[150] Woo, Y.C.; Xu, A.; Wang, Y.; Lam, K.S. Fibroblast growth factor 21 as an emerging metabolic regulator: clinical perspectives. *Clin. Endocrinol. (Oxf.),* **2013**, *78*(4), 489-496.

[151] Morrice, N.; Mcilroy, G.D.; Tammireddy, S.R.; Reekie, J.; Shearer, K.D.; Doherty, M.K.; Delibegović, M.; Whitfield, P.D.; Mody, N. Elevated Fibroblast growth factor 21 (FGF21) in obese, insulin resistant states is normalised by the synthetic retinoid Fenretinide in mice. *Sci. Rep.,* **2017**, *7*, 43782. doi: 10.1038/srep43782.

[152] Shen, Y.; Ma, X.; Zhou, J.; Pan, X.; Hao, Y.; Zhou, M.; Lu, Z.; Gao, M.; Bao, Y.; Jia, W. Additive relationship between serum fibroblast growth factor 21 level and coronary artery disease. *Cardiovasc. Diabetol.,* **2013**, *12*, 124. doi: 10.1186/1475-2840-12-124.

[153] Chow, W.S.; Xu, A.; Woo, Y.C.; Tso, A.W.; Cheung, S.C.; Fong, C.H.; Tse, H.F.; Chau, M.T.; Cheung, B.M.; Lam, K.S. Serum fibroblast growth factor-21 levels are associated with carotid atherosclerosis independent of established cardiovascular risk factors. *Arterioscler. Thromb. Vasc. Biol.,* **2013**, *33*(10), 2454-2459.

[154] Yang, S.J.; Hong, H.C.; Choi, H.Y.; Yoo, H.J.; Cho, G.J.; Hwang, T.G.; Baik, S.H.; Choi, D.S.; Kim, S.M.; Choi, K.M. Effects of a three-month combined exercise programme on fibroblast growth factor 21 and fetuin-A levels and arterial stiffness in obese women. *Clin. Endocrinol. (Oxf.),* **2011**, *75*(4), 464-469.

[155] Ong, K.L.; Januszewski, A.S.; O'Connell, R.; Buizen, L.; Jenkins, A.J.; Xu, A.; Sullivan, D.R.; Barter, P.J.; Scott, R.S.; Taskinen, M.R.; Rye, K.A.; Keech, A.C. Relationship of fibroblast growth factor 21 with baseline and new on-study microvascular disease in the fenofibrate intervention and event lowering in diabetes study. *Diabetologia,* **2015**, *58*(9), 2035-2044.

[156] Gaich, G.; Chien, J.Y.; Fu, H.; Glass, L.C.; Deeg, M.A.; Holland, W.L.; Kharitonenkov, A.; Bumol, T.; Schilske, H.K.; Moller, D.E. The effects of LY2405319, an FGF21 analog, in obese human subjects with type 2 diabetes. *Cell Metab.,* **2013**, *18*(3), 333-340.