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# Adipose Tissue as an Endocrine Organ

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Hannah Xiaoyan Hui and Tianshi Feng

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## Abstract

As one of the largest endocrine organs in the body, adipose tissue secretes a number of bioactive hormones, called adipokines. The expression and secretion of adipokines are tightly controlled and coordinated by physiological and pathophysiological conditions. In multiple physiological conditions, such as obesity, cold adaptation, exercise training, expression and secretion of adipokines are altered accordingly, which in turn modulate the metabolism of the whole body in endocrine, paracrine and autocrine manners. The varied changes in adipose tissues are pivotal mediators that aid the body to adapt to various physiological and pathological conditions, whereas almost all obesity-associated diseases are attributable to dysregulation of adipokines.

**Keywords:** adipokines, obesity, cold adaptation, exercise, inflammation

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## 1. Introduction

For the past two decades, a lot of our knowledge on adipose tissues have been revolutionized by a series of convincing studies using animal models and cell models [1]. In contrast to the classical view that adipose tissue serves as an inert organ for storing excess energy as fat, it is now well acknowledged that adipose tissues are actually one of the largest and most dynamic organs in our body and play pivotal roles in regulation of energy homeostasis [2]. In response to alterations in nutritional status, such as excess calorie intake, fasting, lower temperature exposure, exercise, adipose tissues are among the first organs to respond. In addition to lipolysis and fatty acid synthesis, they also undergo extensive remodeling in various aspects, including in cell size and morphology, angiogenesis, normoxia/hypoxia responses, whitening/browning features, immune reactions. Most importantly, reprogramming of various pathways within adipose tissues eventually leads to substantial changes in

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the expression/secretion patterns of adipose tissues, which expands and perpetuates the local influences systemically.

## **2. The secretory character of the adipose tissue**

The adipose tissue used to be considered a simple organ where lipid is stored. Its main function was thought to be mainly mechanical in that adipose tissue was believed to serve as a cushion in our body to help protect the inner organ from bumping and damaging. In addition, people also believe that the subcutaneous adipose tissue is the insulator that prevents the heat loss of the body. The first groundbreaking discovery indicating that adipose tissue is something beyond cushion and insulator is the work by Dr. GS Hotamisligil and BM Spiegelman, who revealed for the first time that an induction of tumor necrosis factor-alpha (TNF-alpha) messenger RNA was observed in adipose tissue from four different rodent models of obesity and diabetes [3]. In accompany, protein level of TNF-alpha was also found elevated locally and systemically and neutralization of TNF-alpha significantly alleviated glucose intolerance in obese rat models [3]. This study was among the earliest to indicate the potential secretory function of the adipose tissue. But the first direct evidence that led to the realization that adipose tissue is an unneglectable endocrine organ came from the cloning of leptin in 1994 by Friedman and his colleagues [4]. They found that leptin is secreted by fat cells into the bloodstream and acts on the brain to regulate food intake and energy expenditure [5]. Before that, the identity of leptin had been remained mysterious for over four decades with the only knowledge that there existed a circulatory factor in ob/ob mice that causes obesity. Indeed, studies afterwards revealed that leptin is in practice a pleiotropic hormone and its functions extend far wider than appetite and energy balance to encompass a multiplicity of actions, including acting as a signal molecule in reproduction and immunity [6, 7].

In addition to leptin, it is now well recognized that adipose tissue, including the adipocytes and the immune cells within it, are secreting a diverse range of protein factors and signals termed 'adipokines'. These adipokines are involved in overall metabolic regulation and considered key players in maintaining both normal functioning of the body and in pathology of a series of diseases [8].

## **3. The adipokines affected during onset of obesity**

Obesity is now a global epidemic. It is characterized by excessive fat accumulation as a result of a chronic imbalance between energy intake and energy expenditure. In addition as a cosmetic problem, obesity per se poses a substantial health risk to several common diseases including type 2 diabetes, cardiovascular diseases, stroke, arthritis and certain types of cancer [1]. Prospective studies in a cohort of U.S. men found that absolute weight gain throughout adulthood, and waist circumference were good predictors of diabetes [9] and similar conclusion was also obtained in women soon afterwards [10]. Although multiple theories have been

proposed as the underlying mechanisms for obesity-induced metabolic abnormalities, it is generally agreed that dysfunction in the over-expanded adipose tissue, and the dysregulation in adipokines, are key molecular basis for obesity-evoked metabolic pathologies [8].

A number of adipokines have been found altered upon overweight and obesity. In particular, those pro-inflammatory ones are upregulated, including TNF $\alpha$ , resistin, adipocyte fatty acid binding protein (A-FABP), retinol-binding protein 4, monocyte chemoattractant protein 1 (MCP1), interleukin 6 and etc. [11], whereas those with favorable functions are downregulated, such as adiponectin [12].

### 3.1. A-FABP – more than just a lipid chaperon

Fatty acid binding proteins are intracellular lipid chaperones that constitute a group of molecules with molecular weight of 14–15 kDa [13]. They reversibly bind to hydrophobic ligands, such as saturated and unsaturated long-chain fatty acids, eicosanoids and other related compounds (bile acids or retinoids) in their characteristic internal cavity with high affinity to coordinate lipid responses in various cells [14]. As told by its name, A-FABP is most abundantly expressed in mature adipocytes [15], due to the fact that expression of A-FABP is highly regulated during adipogenic differentiation, and its mRNA is transcriptionally controlled by fatty acids, peroxisome proliferator activator receptor gamma (PPAR- $\gamma$ ) agonists and insulin as well [13, 16].

A-FABP is the best characterized member in FABP family due to the striking phenotype observed in A-FABP knockout mice. Mice with a null mutation in *aP2*, the gene encoding A-FABP, were morbidly obese [17]. However, unlike their obese wild-type counterparts, control mice, they were devoid of insulin resistance or diabetes [17]. The protection against insulin resistance was at least partially caused by suppressed inflammation within adipose tissue, since obese A-FABP knockout animals exhibited minimal expression level of TNF $\alpha$  in adipose tissue. The idea that A-FABP works at the crossroad of obesity and metabolic syndrome was further highlighted by the finding that mice deficient of A-FABP were less prone to develop atherosclerotic plaques in apolipoprotein E (ApoE)-deficient mice [18]. Moreover, small molecules targeting A-FABP have been proved efficacious to deter a series of diseases or physiological conditions, including atherosclerosis [19], acute liver injury and non-alcoholic fatty liver disease [20], endothelium dysfunction [21] and etc.

Although cloned in 1983, A-FABP has not been recognized as a secretory protein until one decade ago [22]. During identification of proteins secreted from adipocytes using tandem mass spectrometry-based proteomic analysis, Xu et al. found A-FABP is present at high level in culture medium from differentiated 3T3L1-adipocytes [22]. The presence of A-FABP was further verified in persons as well (121 men and 108 women; age range, 33–72 years). Further analysis demonstrated that age- and sex-adjusted serum A-FABP concentrations correlated positively ( $P < 0.005$ ) with waist circumference, blood pressure, dyslipidemia, fasting insulin, and the homeostasis model assessment insulin resistance index [22]. Moreover, a significant increase in A-FABP concentrations corresponding with increases in the number of components of the metabolic syndrome was also observed. The same group further evaluated the

prospective association of A-FABP with the metabolic syndrome in 495 nondiabetic adults followed up for 5 years, which revealed that subjects with higher baseline A-FABP levels had progressively worse cardiometabolic risk profile and increasing risk of the MetS. A-FABP was the independent predictor of the development of the MetS even after adjustment for each of its individual components [23]. After that, the notion that A-FABP is a circulating biomarker closely associated with obesity and components of the metabolic syndrome has been implicated by a large number of epidemiological studies on different ethnic groups [24]. These studies revealed a close association between serum levels of A-FABP and a cluster of obesity-related cardiometabolic risk factors and complications. In both cross-sectional and prospective studies, plasma levels of A-FABP are positively correlated with several key components of the metabolic syndrome, including adverse lipid profiles, hyperglycemia, hypertension and nonalcoholic fatty liver disease, independently of sex, age, and adiposity [23, 25–27].

The clinical implication and mechanisms of action of A-FABP have been extensively studied. However, much is still left unknown, especially that there are emerging target cell types and organs that are reportedly to respond to A-FABP, with expanding functions. Moreover, the putative receptor of A-FABP is still unknown and thus leaves open whether A-FABP works exclusively in an intracellular manner or also acts via cell surface receptors. Future studies addressing these questions will further enhance the understanding and the therapeutic application of this adipokine.

### **3.2. Hypoadiponectinemia and metabolic syndromes**

Adiponectin is one of the most abundant adipokines in circulation (accounting for 0.01% of total serum protein), and was cloned by three independent groups in 1996 [28–30]. Since its discovery, it has been receiving intense interests, because of its negative association with obesity, which is in sharp contrast to most of the adipokines identified [31]. The monomeric adiponectin is a 30 kDa protein with a C-terminal globular domain and a collagen-like N-terminal domain [32]. However, under physiological settings, adiponectin monomer has never been detected. Instead, its predominant forms in circulation are trimer, hexamer and oligomers (18mers or higher), which are called low-, medium- and high-molecular weight form of adiponectin, accordingly.

Circulating level of adiponectin is tightly controlled at every step, from its transcription, translation, multimer-assembly, and finally to secretion [33]. Therefore, it is not surprising to find that adiponectin is present in blood stream at varied concentrations and multimer ratios as well. Indeed, reduction of adiponectin has been consistently observed in obese adipose tissues at transcriptional levels and in circulation, in both animal models and clinical samples [34]. However, it should also be noted that compared to the total serum level of adiponectin, serum HMW adiponectin values are more relevant to the presence and severity of metabolic syndromes [35]. Multiple clinical studies have reported the inverse association between high-molecular weight (HMW) adiponectin and triglycerides, blood pressure, obesity and fasting glucose, while is positively associated with high density lipoprotein (HDL) cholesterol, the so-called 'good cholesterol' [35–38].

Consistent with its reduced level in obesity and related complications, animal and cell based studies have unequivocally showed that adiponectin indeed exerts a multiplex of favorable functions against almost all the metabolic dysfunctions examined [24]. The protective functions of adiponectin are mainly attributed to its anti-diabetic, anti-inflammation, and vascular-protective functions. It is worthy to note that although adiponectin is exclusively expressed in adipocytes, the receptors for adiponectin [39, 40], the adipoR1, adipoR2 and T cadherin, are widely expressed throughout the body and thereby facilitate the pleiotropic action of this favorable adipokine. Mechanistically, it was shown that phosphorylation and activation of the 5'-AMP-activated protein kinase (AMPK) are stimulated by adiponectin in skeletal muscle and in the liver [41]. In accompany with this, phosphorylation of acetyl coenzyme A carboxylase (ACC), fatty-acid oxidation, glucose uptake and lactate production in myocytes, and phosphorylation of ACC and reduction of molecules involved in gluconeogenesis in the liver were observed, which eventually led to reduction of glucose levels in vivo [41]. Moreover, adiponectin can directly act on inflammatory cells and suppresses reactive oxygen species which in turn stimulates the expression of the anti-inflammatory cytokine IL-10, and suppresses the NF- $\kappa$ B inflammatory signaling pathway, and downregulates the key inflammatory cytokine TNF- $\alpha$  [42, 43]. Protection against cardiovascular diseases by adiponectin is achieved by its actions on various cell types in cardiovascular system, including endothelial cells, macrophages/monocytes, smooth muscle cells, cardiac muscle cells and etc. (reviewed by [34, 44]).

The exact reason in terms of why adiponectin expression is reduced in obese adipose tissue still remains elusive. However, the presence of FGF21 resistance might be a potential mechanism (discussed below).

### **3.3. Fibroblast growth factor 21 (FGF21) resistance in obesity**

The biological function of FGF21 was firstly recognized in a high throughput screening assay for potent stimulator of glucose uptake in mouse 3T3-L1 and primary human adipocytes, during which FGF21 was identified as a positive hit [45]. Further studies revealed that in addition to its glucose-lowering effect, FGF21 is also capable of improving lipid metabolism [46], and is therefore regarded as a new molecule with therapeutic potentials. Although the detailed mechanism is not clear, FGF21 is a potent activator of extracellular signal-regulated kinase (ERK), with a 10-fold higher potency in adipose tissue than in liver, suggesting that FGF21 may preferentially target adipose tissue [47]. Indeed, two back-to-back studies reported that a majority of the biological functions of FGF21 was mediated via its inducing action on adiponectin expression [48, 49]. These studies provide feasible explanation for the previous findings that adiponectin and FGF21 share a plethora of profound benefits on cardiometabolic events, spanning from glucose lowering, lipid lowering to cardiovascular-protective properties, despite of their distinct origin of production and structure. Specifically, FGF21 and adiponectin deficient mice are both more susceptible to high fat diet induced hyperglycemia, insulin resistance, non-alcoholic fatty liver disease and a number of cardiovascular dysfunctions [50]. On the other hand, pharmacological administration of either adiponectin or FGF21 recombinant proteins or analogues was both proved to be efficacious in alleviating a series of metabolic perturbations in diseased rodent models and non-human primates [51–54].

Although a number of pharmacological studies support for the FGF21-adiponectin axis, the correlation between FGF21 and adiponectin is distorted at physiological and pathological conditions. Unlike its downstream effector adiponectin, whose circulating level is found to be reduced in overweight/obesity and metabolic syndromes [34], obesity is accompanied with elevated levels of serum FGF21 in both rodent models and humans [55]. Moreover, positive correlations has been documented between FGF21 and a panel of metabolic syndromes, including insulin resistance, type 2 diabetes, dyslipidemia, non-alcoholic fatty liver disease, coronary heart disease and polycystic ovarian syndrome [56]. Our earlier study only found a weak negative correlation between serum FGF21 and adiponectin and the significance was lost after adjustment for BMI [55]. Likewise, a recent clinical study in patients with metabolic syndrome confirmed the lack of association between FGF21 and adiponectin, although FGF21 was found strongly correlated with A-FABP, another adipokine with unfavorable functions [57].

The dissociation between adiponectin and FGF21 in obese condition can be explained by the state of FGF21 resistance. This is evidenced by the blunted response to FGF21 administration in liver and adipose tissues from obese animals [55, 58]. At the molecular level, the attenuation of FGF21 action in obesity can be attributed to the selective reduction of  $\beta$ -Klotho in white adipose tissue, which is commonly observed in rodent models of obesity and in obese individuals [59].

#### **4. The adipokines affected upon cold adaptation**

Adipose tissue is a highly heterogeneous organ that it can be classified as white adipose tissue (WAT) and brown adipose tissue (BAT), in terms of their function to either store excess energy or to dissipate energy. The latter function is achieved by uncoupling protein-1 (UCP1), which converts the chemical energy into heat [60, 61]. For a long time, the BAT was believed only present in infants; however, the advancement in positron emission tomography (PET) scan technology revealed considerable amount of functional BAT in adult human [62]. Interestingly, a major portion of the functional BAT in adults is “inducible,, upon cold stimulation, which seems to be elicited by both sympathetic nervous system (SNS) dependent and independent mechanisms. Though BAT has great anti-obese potential, animal studies have demonstrated that it possesses systemic metabolic benefits beyond its adiposity-reducing effect, including insulin-sensitizing, lipid-lowering, anti-inflammation and anti-atherosclerosis [63, 64]. Thereafter, it is conceivable that cold-induced adipose browning confers favorable effects at least partially via modulation of its secretory pattern.

##### **4.1. The proinflammatory adipokines in response to cold**

Ten lean, healthy male volunteers were exposed to cold for 2 h and compared with a control group of 10 subjects without exposure to cold [65]. It is found that the plasma concentration of MCP1 was increased by cold temperature while no specific changes were observed for IL-6 and VEGF [65]. The observed alterations appeared to be posttranscriptional because adipokine gene expression was found to be unaltered. Another study in mice also examine

the temporal profile of cold-induced changes in the expression of inflammatory adipokines in adipose tissues or primary adipocytes [66]. To this end, male C57BL/6J mice were exposed to 4°C for 1–5 days. Gene and protein profiling revealed that the inflammatory adipokines were expressed significantly higher in WAT than BAT at baseline [66]. Moreover, it was shown that the browning process alters the inflammatory adipokines expression in adipose tissues, which is dynamically decreased in sWAT whilst increased in eWAT for compensation [66]. In our study, we also found a transient increase of pro-inflammatory cytokines, such as TNF $\alpha$ , MCP-1, in white adipose tissue of mice when they were put to cold environment, especially in subcutaneous adipose tissue [67]. However, longer term cold adaptation led to a remarkable decrease of these proinflammatory cytokines [67], which coincided with the sharp increase of those anti-inflammatory cytokines.

#### **4.2. Type 2 immune cytokines in cold-stimulated white adipose tissue**

It is now known that the classical BAT present in new born baby and those inducible ones scattered in white adipose tissue are fundamentally different, although they are both positive for the brown adipocyte marker UCP-1 [1]. One of the major differences is reliance on type 2 immunity for activation or not [68]. Qiu et al. reported that cold exposure is accompanied by elevation of the Th2 cytokines (mainly interleukin 4 from eosinophils), which can readily engage M2 macrophage activation [68]. The latter one serves as the primary local source of catecholamine for biogenesis of brown-like adipocytes [69]. Later studies found that upon cold challenge, meteorin-like (*Metrn1*) was induced in adipose tissue [70]. More importantly, *Metrn1* stimulates an increase in IL-4 expression in an eosinophil-dependent manner and thereby promotes alternative activation of adipose tissue macrophages. Conversely, blockade of *Metrn1* actions in vivo significantly attenuates chronic cold-exposure-induced alternative macrophage activation and thermogenic reprogramming [70]. Although other studies also suggest that ILC2 cell-derived factors, including interleukin 5 and interleukin 13, act upstream of eosinophil-M2 macrophage cascade during cold-induced adipose browning [71, 72], either the number of ILC2, or its stimulating factor IL33, were not found to be significantly altered by cold stimulation, though they are remarkably decreased in obese conditions [71, 72]. This suggests that there exist other physiological cues that entitle the type 2 immune response during cold adaptation.

#### **4.3. FGF21-adiponectin axis in cold adaptation**

FGF21 has long been known as a pro-browning factor for classical brown adipocytes and was found induced in BAT after cold exposure [73, 74]. Recently it is found that FGF21 expression was also strongly upregulated in white adipocytes under cold-acclimated conditions [75]. By using the adipocyte-specific FGF21 knockout mice, it was further revealed that adipocyte-derived FGF21 acts in an autocrine manner to promote the expression and secretion of CCL11 via activation of ERK1/2 [75]. This event then drives recruitment of eosinophils into subcutaneous WAT, leading to increases in accumulation of M2 macrophages, and proliferation/commitment of adipocyte precursors into beige adipocytes. Neutralization of CCL11 abolished all these events induced by FGF21, and thus demonstrating that the adipose-derived FGF21-CCL11



cascade triggers cold-induced browning and thermogenesis by coupling sympathetic nervous system to activation of type 2 immunity.

On the other hand, considering that adiponectin is induced by and acts downstream of FGF21 at certain conditions as previously reported [48, 49], whether the effect of FGF21 to enhance white adipose browning is partially mediated by adiponectin. However, despite of the fact that transcription of adiponectin was remarkably induced within white adipose tissue upon cold challenge [67], such a change was not abolished adipose-specific deletion of FGF21 or its co-receptor  $\beta$  Klotho [75], indicating that cold-evoked upregulation of adiponectin in adipose tissue was not controlled under FGF21. Moreover, although adiponectin deficient mice were also less sensitive to white adipose browning stimulated by cold [67, 76], it seems that it activates browning remodeling in distinct ways as FGF21. It may on one hand acts on M2 macrophages by promoting their de novo proliferation; while on the other hand promotes mitochondrial biogenesis, insulin signaling, and the AMPK-SIRT1 pathway and up-regulates  $\beta$ 3-adrenergic receptor in BAT [76]. However, it should be notified that opposite findings were also reported [77] and whether the inconsistencies were caused by the different strains of mice used, or gut microbiota in different housing environment, needs to be investigated in future.

## 5. The adipokines changed by exercise

Physical activities are one of the major ways of energy expenditure. Sufficient epidemiological evidences have shown that there exists an inverse association between physical activity and obesity [78]. Exercise has also been demonstrated as an effective non-pharmaceutical therapeutic method to mitigate obesity and obesity-related metabolic syndromes such as type 2 diabetes and cardiovascular diseases [79, 80]. In addition to directly increasing the energy expenditure, exercise also modulates the functions of many organs including muscle, liver, heart and adipose tissue through different pathways to improve the systemic metabolisms [81, 82]. The cross-talk between the muscle and the adipose tissue is also involved in this process and the adipokines secreted from the adipose tissue might play important roles in the effects of exercise.

### 5.1. Adiponectin in exercise

Plenty of clinical study focused on the relationship between exercise and the plasma (or serum) adiponectin levels and the results are largely dependent on the duration and intensity of the exercise [83–85].

In most studies, one single exercise could not show acute influence on the plasma adiponectin level, no matter the duration of exercise or whether the subjects are healthy or obese [84, 86–89]. However, an article published in 2010 reported that both high and low intensity anaerobic exercise could elevate blood adiponectin level in obese men [90], which is similar to the result of another report in 2006 using healthy men with anaerobic exercise [91]. In addition,

not only the total concentration but also the profile (percentage of HMW and LMW/MMW) of adiponectin was reported to be changed by exercise, which shows that the activity and the functions of adiponectin may also be influenced by the exercise [92].

About the chronic effects of training on adiponectin, the results with different training protocols are also conflicting [84]. Kriketos et al. reported in 2004 that with aerobic exercise, the adiponectin level of obese subject will rise from  $7.0 \pm 0.7$  to  $18.2 \pm 1.9$   $\mu\text{g/ml}$ , after about 1 week and remained throughout the 10 weeks of training [93]. This result is similar to Kondo et al.'s work in which they reported that after 7 months training, the plasma level of obese group increased obviously but the control group remains unchanged [94]. However, in some other experiments which were also performed on obese subjects with 2–3 months training, the adiponectin level was not significantly changed [94, 95]. Two systematic review which analyzed the results of numerous experiments both got the conclusion that adiponectin level could be upregulated by the exercise [85, 96]. And, interestingly, Khoo et al. compared dieting and exercise, the two common obesity therapies and found that after 24 weeks of treatment, both methods could effectively lead to weight loss, but adiponectin is upregulated only in the exercise group but not the dieting group [97].

The inconsistency of the results might be caused by the inconsistent factors in these experiments including the type and detailed protocols of exercise (aerobic or anaerobic, duration, intensity, etc.), subjects (gender, race, age, obese or lean, etc.) and diet condition (with or without controlled food intake). This shows that adiponectin level in blood is sensitive to these confounding factors. However, at least in part of the experiments, the beneficial effects of exercise are partially mediated by adiponectin.

## 5.2. Alteration of leptin by exercise training

Similar to adiponectin, the effects of exercise also depend on the duration and intensity of the exercise. Considering that the expression and release of the leptin by the adipose tissue is closely related to the energy homeostasis and low energy state will decrease the leptin level [98], the leptin level shows inverse association with the energy expenditure after a single bout of exercise. In a study which the author compared the leptin level after three kinds of exercise and found that leptin level decreased obviously after ultramarathon race (with about 7000 kcal energy expenditure) and ski-alpinism race (with about 5000 kcal energy expenditure) but not half-marathon run (with about 1400 kcal energy expenditure) [99]. Kraemer et al. summarized the works done by different groups and concluded that >60 min exercise is more likely to induce the decreasing of leptin compared with short-term exercise [100]. Some other groups reported that high intensity of short term (20–30 min) exercise can also down-regulate the blood leptin level [101, 102].

Another study reported that after the first time of 45-min walking, there were no obvious changes in the plasma leptin level. However, after chronic training (>7 times of the same walking exercise), the leptin decreased obviously, which shows that chronic training may be more effective to the decrease of leptin [103]. Bouassida et al. analyzed the 10 previous papers in which the chronic effects of exercise to leptin were studied and found that in all the trainings

that are longer than 3 weeks, the decreasing of leptin was observed no matter the subjects are obese or healthy [85].

Considering the functions of leptin talked in previous parts, the decreasing level of leptin will lead to the increase of appetite and food intake and reduce the energy expenditure, which is the compensatory effects of the weight loss in exercise.

### 5.3. Inflammatory adipokines influenced by exercise

Obesity induced adipose tissue inflammation is closely related to the insulin resistance and adipose tissue dysfunctions. Inflammatory adipokines, such as TNF- $\alpha$ , IL-6 and chemerin, play crucial roles in the chronic inflammation and the recruitment and activation of immune cells.

Nicklas et al. reviewed the previous research and found that there is inverse association between the level of systemic inflammation markers, including TNF- $\alpha$  and IL-6, with the physical activity, which provide epidemiological evidence to the effects of exercise on inflammatory adipokines [104]. For the patients with obesity or diabetes, plenty of studies showed that the long-term training can decrease the level of TNF- $\alpha$  or/and IL-6 [83, 105–108], which demonstrate that the beneficial effects of exercise is partly mediated by decreasing the systemic inflammation.

In addition, in the experiments of Khoo et al., it was found that the long term exercise effectively down-regulated the serum high-sensitivity C-reactive protein (CRP), which is a downstream factor of IL-6, in obese group but not in health group [97]. This indicates that effects of long term exercise might be different for obese subjects and lean subjects, considering their basal levels of adipokines before exercise are also different [109].

In addition to these adipokines that have been repeatedly measured in various experiments, there are increasing number of papers focusing on the relationship of other adipokines and exercise. For example, apelin was found to be upregulated by exercise. Study of the relationship between exercise and the adipokines and the functions of these adipokines may contribute to the understanding of the underlying mechanisms of the beneficial effects of exercise and provides new strategies for developing anti-obesity therapies and exercise mimicking drugs.

## 6. Conclusions

Adipose tissue is gaining increasing interest in the past decade, in both basic research and pharmaceutical industry, owing to the realization that it serves as a commander of the whole-body metabolism. Conceivably, the regulatory function of adipose tissue is almost exclusively mediated by the adipokines, along with other small bioactive molecules (which is not discussed here). Although much progress has been made to decipher the underlying mechanism whereby adipose-derived factors contribute to physiological and pathological conditions, a lot more still remain unanswered. In particular, a number of inconsistencies exist in expression

and mechanisms of the adipokines which hinder the elucidation of their biological functions. However, on the other hand, it is also encouraging that several adipokine-based pharmacological agents have been developed, such as adiponectin receptor agonist [110], PEGylated FGF-21 [111], and neutralizing antibody against IL-1 $\beta$  [112], all of which have shown promising effects against metabolic-related diseases. A better understanding on adipokine biology will further benefit the design and development of novel classes of therapeutics with less side-effects.

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## Conflict of interest

The authors claim no conflict of interest.

## Author details

Hannah Xiaoyan Hui<sup>1\*</sup> and Tianshi Feng<sup>2</sup>

\*Address all correspondence to: [hannahui@hku.hk](mailto:hannahui@hku.hk)

1 Department of Medicine, State Key Laboratory of Pharmaceutical Biotechnology, The University of Hong Kong, Hong Kong

2 Department of Pharmacology and Pharmacy, State Key Laboratory of Pharmaceutical Biotechnology, The University of Hong Kong

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