Review

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Adiponectin: friend or foe in obesity and inflammation

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Abstract: Adiponectin is an adipokine predominantly produced by fat cells, circulates and exerts insulin-sensitizing, cardioprotective and anti-inflammatory effects. Dysregulation of adiponectin and/or adiponectin signaling is implicated in a number of metabolic diseases such as obesity, insulin resistance, diabetes, and cardiovascular diseases. However, while the insulin-sensitizing and cardioprotective effects of adiponectin have been widely appreciated in the field, the obesogenic and anti-inflammatory effects of adiponectin are still of much debate. Understanding the physiological function of adiponectin is critical for adiponectin-based therapeutics for the treatment of metabolic diseases.

Keywords: adipogenesis; adiponectin; inflammation; insulin sensitivity; obesity.

Introduction

Adipose tissue plays a central role in the maintenance of whole-body energy and metabolic homeostasis at both organ and system levels [1], by serving as a passive fuel reservoir, an endocrine organ and thermogenic effector. Adiponectin, the most representative adipokine, is a 30 kDa protein predominantly secreted by adipocytes and targets a variety of cell types or tissue/organs by binding to its own receptors, protecting against obesity [2–5], insulin resistance [6, 7], and inflammation-related diseases [5, 8]. As a circulating protein, adiponectin accumulates in heart, vasculature, and skeletal muscles through interaction with T-cadherin, which is essential for adiponectin-mediated cardiovascular protection [9–11]. Since obesity increases the risk of developing serious health problems including metabolic diseases [12, 13], there is an urgent need for the advanced understanding of the physiological function of adiponectin for the therapeutic purpose [14].

Despite well-accepted beneficial effects in metabolism, adiponectin-based treatment is still challenging given its high abundance in circulation and the potential adverse effects, including increased food intake, elevated adipogenesis, decreased energy expenditure, and substantial adiposity [15–18].

In this review, we have discussed the physiological roles of adiponectin, not only its beneficial properties but also the unfavorable effects related to its therapeutic potential for the treatment of obesity and its related diseases. We also summarized the advances in the understanding of adiponectin action in the regulation of metabolism and inflammation, highlighting the obesogenic and pro-inflammatory effects of adiponectin.

Adiponectin and adiponectin signaling

Adiponectin was discovered as an adipocyte-enriched protein highly induced during adipogenesis [2, 3, 5, 19] and cloned in 1995 [5]. The full-length adiponectin protein contains a signal peptide, a variable region, a collagen-like domain, and a C-terminal globular domain [20, 21]. Adiponectin circulates in multiple forms: low-molecular weight (LMW) trimers, medium-molecular weight (MMW) hexamers, and high-molecular weight (HMW) multimers [22–25], and globular adiponectin (gAd) which is a proteolytic adiponectin globular domain at very low concentrations in human plasma [26, 27]. Each form exerts distinct biological effects due to their divergent affinity to their receptors and various cellular targets [20, 28–30]. The

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HMW form presents most biological effects of adiponectin [24, 25, 30–32]. However, it is still a challenge to measure the levels of individual isoform of adiponectin and enrich a particular isoform *in vivo* [33].

The pleiotropic actions of adiponectin are mediated by its receptors including AdipoRs (AdipoR1 and AdipoR2) and T-cadherin [34]. Adiponectin receptors present in metabolically active cell types such as adipocytes, hepatocytes, and muscle cells as well as immune cells and neuronal cells in the different brain regions [18, 35–38]. AdipoR1 is abundantly expressed in skeletal muscle, while AdipoR2 is enriched in liver. Adiponectin binds to AdipoRs and exerts antidiabetic effect through activation of two critical downstream factors: 5′-adenosine monophosphate-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor α (PPARα) [37, 39–41]. APPL1 binds to AdipoRs and mediates adiponectin signaling and its downstream events, promoting glucose uptake and insulin receptor substrate-1 (IRS-1) action to sensitize insulin signaling [42, 43]. Adiponectin homolog osmotin activates AdipoR1/R2 to suppress abdominal fat accumulation in mice on high-fat diet (HFD) [44, 45], and prevents obesity-caused NAFLD by upregulating AdipoRs/APPL1/PPAR-α/AMPK/SIRT1 pathway [46]. The additional downstream pathways of adiponectin, including MAPK, mTOR, STAT3, PI3K/Akt and NF-κB pathways, are tissue- and cell-specific [47–50]. However, while the recombinant globular adiponectin has been wide used to study its action in various cells, HMW multimer of adiponectin has been considered as most biologically active form [24, 25, 30–32]. Whereas the mechanism underlying the binding of HMW adiponectin to its receptor and subsequent signaling transduction are poorly defined. One of existing challenge is that HMW form 16–18mer is over 400 kDa, about 10 times larger than the receptors themselves. The structural analysis using current state-of-the-art-technology may provide information on how HMW multimer works.

Furthermore, ceramidase-activating effect of AdipoRs is critical for the clearance of cellular ceramides which was considered an important mechanism by which adiponectin improves glucose and lipid metabolism [51–56]. AdipoRs are also required for adiponectin to suppress macrophage lipid accumulation and foam cell formation via an APPL1-dependent mechanism [57]. In an AdipoR2-dependent manner, adiponectin promotes M2 macrophage polarization [58, 59], whereas the anti-inflammatory effects of gAd in brain are mediated by AdipoR1 to limit the M1 activation state of microglia [60]. Moreover, Smad1/5/8 acts as a novel intracellular partner of adiponectin/AdipoR1 signaling in osteoblasts and mesenchymal progenitor cells that is parallel to APPL1 [61]. In addition, the physiological role of AdipoRs beyond adiponectin signaling have been recognized. For instance, the insulin sensitiving effects of adiponectin are partially mediated by AdipoR1 and AdipoR2 in mice [34, 62–64]. In adiponectin deficient mice, pioglitazone is able to improve insulin sensitivity by stimulation of AdipoR2 pathway in skeletal muscle [65].

T-cadherin is a glycosylphosphatidylinositol-anchored (GPI-anchored) cadherin without the intracellular or transmembrane domain required for intracellular signaling. It selectively binds to MMW and HMW adiponectin and impacts circulating adiponectin by regulating its binding to cardiovascular tissues, and adiponectin positively regulates T-cadherin abundance on endothelial cells via attenuating phosphatidylinositol-specific phospholipase C-mediated T-cadherin release from the cell surface [66, 67]. Furthermore, adiponectin was reported to be endocytosed into multivesicular bodies with T-cadherin and enhances exosome biogenesis and release dependently on T-cadherin, leading to reduction of cellular ceramides in endothelial cells [68]. Single nucleotide polymorphism of T-cadherin strongly correlates with plasma adiponectin level and cardiovascular diseases in human [69–74]. It has been demonstrated that adiponectin/T-cadherin axis protects against vascular injury related to atherosclerosis and cardiac stress [9, 10, 75]. Besides, T-cadherin is also required for tethering of adiponectin to M2 macrophages during cold-induced browning in subcutaneous white adipose tissue (WAT) [76]. Later, adiponectin was shown to be accumulated in CD63-positive endosomes of regenerating myotubes and promote muscle regeneration in a T-cadherin-dependent manner [77]. This ability of T-cadherin in adiponectin sequestration to cell surface is responsible for adiponectin signal transduction pathway, and could be disrupted by an increased specific phospholipase D (GPI-PLD)-mediated cleavage of T-cadherin during diet-induced obesity or insulin resistance [78], ultimately leading to a state of adiponectin resistance in metabolic diseases [79]. Taken together, these findings supported adiponectin/T-cadherin interaction interprets the cardioprotective effects of adiponectin.

Insulin sensitizing effect of adiponectin

Adiponectin is an insulin-sensitizing hormone. The circulating levels of adiponectin are inversely correlated with obesity, and such downregulation has been considered as a mechanism mediating obesity-induced insulin resistance and diabetes in mice and humans [41, 80–84]. Congenital deletion of adiponectin led to insulin resistance in mice fed a high calorie diet [40, 85], and acute depletion of

adiponectin resulted in more severe systemic insulin resistance, hyperlipidemia and dramatic reduction in survival rate in obese mice [86]. Conversely, enhanced adiponectin expression improves insulin resistance and other metabolic parameters in ob/ob mice [16]. Administration of adiponectin or pharmaceutically enhancing adiponectin signaling ameliorates insulin resistance and hyperglycemia in several mouse models [16, 34, 39, 40, 65, 84, 87, 88]. Furthermore, adiponectin has been shown to mediate insulin sensitizing effects of FGF21 on maintaining a "healthy-obese" status, a factor that contributes to prolonged healthspan and lifespan [89–91].

Suppressing gluconeogenesis has been suggested as a primary mechanism by which adiponetin enhances insulin sensitivity in liver [92, 93]. In addition, other mechanisms include stimulating fatty acid oxidation via AdipoRs-mediated activation of AMPK and PPAR-α in the liver and skeletal muscle [7, 34, 84, 94, 95], and suppressing hepatic SREBP1c, the master regulator in fatty acid synthesis, through the AdipoR1/LKB1/AMPK pathway [96]. Moreover, adiponectin via signal transducer and activator of transcription-3 (STAT3) upregulates hepatic IRS-2 and enhances insulin signaling, which is linked to adiponectin-increased NFκB activity and subsequently macrophage IL-6 production [97]. Ceramideslowing effect of adiponectin and the ceramidase activity of AdipoRs provide new insight into insulin sensitizing effects of adiponectin [52, 55, 56]. Adiponectin stimulates the ceramidase activity of AdipoRs to improve insulin action by disruption of ceramide accumulation and decrease apoptosis via formation of sphingosine-1-phosphate (S1P) which does not require AMPK [53]. Overexpression of AdipoRs in adipocyte or hepatocyte enhances ceramidase activity and results in adiponectin-dependent improvement of insulin sensitivity and hepatic steatosis [54]. In line with this, an FGF21--adiponectin-ceramide axis was shown to exert its glycemic and insulin sensitizing effects in mice [89]. The adiponectin-increased S1P secretion attenuated insulin resistance in HFD mice or palmitate-induced cardiomyocyte lipotoxicity model, another mechanism mediating insulin sensitizing and cardioprotective effects of adiponectin [51]. Contradictory to this, a recent study showed that the total ceramide content may not reflect the insulin-sensitizing effect of adiponectin in liver and muscle under obesity conditions [98].

More recently, skeletal muscle has been identified as a source of adiponectin [99, 100], fueling interest in the role of adiponectin as both a circulating adipokine and a locally expressed paracrine/autocrine factor [101, 102]. Within skeletal muscle, adiponectin stimulates phosphorylation of IRS1 at Ser 636/639 and activates of Akt by inhibiting mTOR signaling [100]. It also improves insulin signal transduction by decreasing fatty-acid transporter CD36 and subsequent triglyceride accumulation in muscle and liver [84]. In addition, adiponectin regulates mitochondrial biogenesis and insulin sensitivity via AdipoR1-mediated CaMKKβ/AMPK/SIRT1 pathway to induce PGC-1α deacetylation and further regulating the expression of mitochondrial-derived peptide MOTS-c [103, 104]. What's more, adiponectin activates skeletal muscle autophagy and reduces oxidative stress by which enhances insulin sensitivity in HFD-feeding mice [105, 106]. Along this line, suppressing endoplasmic reticulum (ER) stress mediates adiponectin-induced autophagy in skeletal muscle cells [107]. Consistently, syringin improve HFD-induced insulin resistance through adiponectin-mediated attenuation of ER stress in skeletal muscle [108]. Interestingly, adiponectin and its signaling are improved in skeletal muscle and may explain the beneficial effects of exercise [109–112]. Characterization of the role of exercise-activated adiponectin signaling in muscle or system metabolism may provide mechanistic insights into how exercise promotes metabolic health and improves physical fitness.

By targeting adipocytes, adipoenctin induces glucose transporter 4 (GLUT4) gene expression and improve insulin sensitivity [15]. Consistently, HMW adiponectin has been reported to enhance insulin action by regulation of GLUT4 in 3T3-L1 adipocytes [113]. Overexpression of AdipoRs in adipocytes suppresses the levels of ceramide in both fat and liver and improves whole-body insulin sensitivity [54]. To date, multiple mechanisms have been suggested to contribute to the insulin sensitizing effects of adiponectin (Figure 1), which are critical for the development of adiponectin-based therapeutic strategies.

Adiponectin serves as a starvation mediator

Adiponectin is induced by fasting [114] and calorie restriction [83, 115, 116], and elevated adiponectin by intermittent fasting (IF) [117] may mediate the beneficial effects of IF on cardioprotection and metabolic stress [118–120]. In agreement with this, circulating levels of adiponectin were markedly increased in patients with anorexia nervosa [121]. Nutritional stress also explains the increased adiponectin levels in the circulation of heart failure patients [122]. Consistent with this, the inducing effects on adiponectin/adiponectin signaling components in muscle, adipose and brain are also applied under nutritional stress conditions [123–125], suggesting the involvement of adiponectin/adiponectin signaling in fasting adaptation.

Furthermore, adiponectin contributes to fasting adaptation through its central and peripheral action. Infusion of

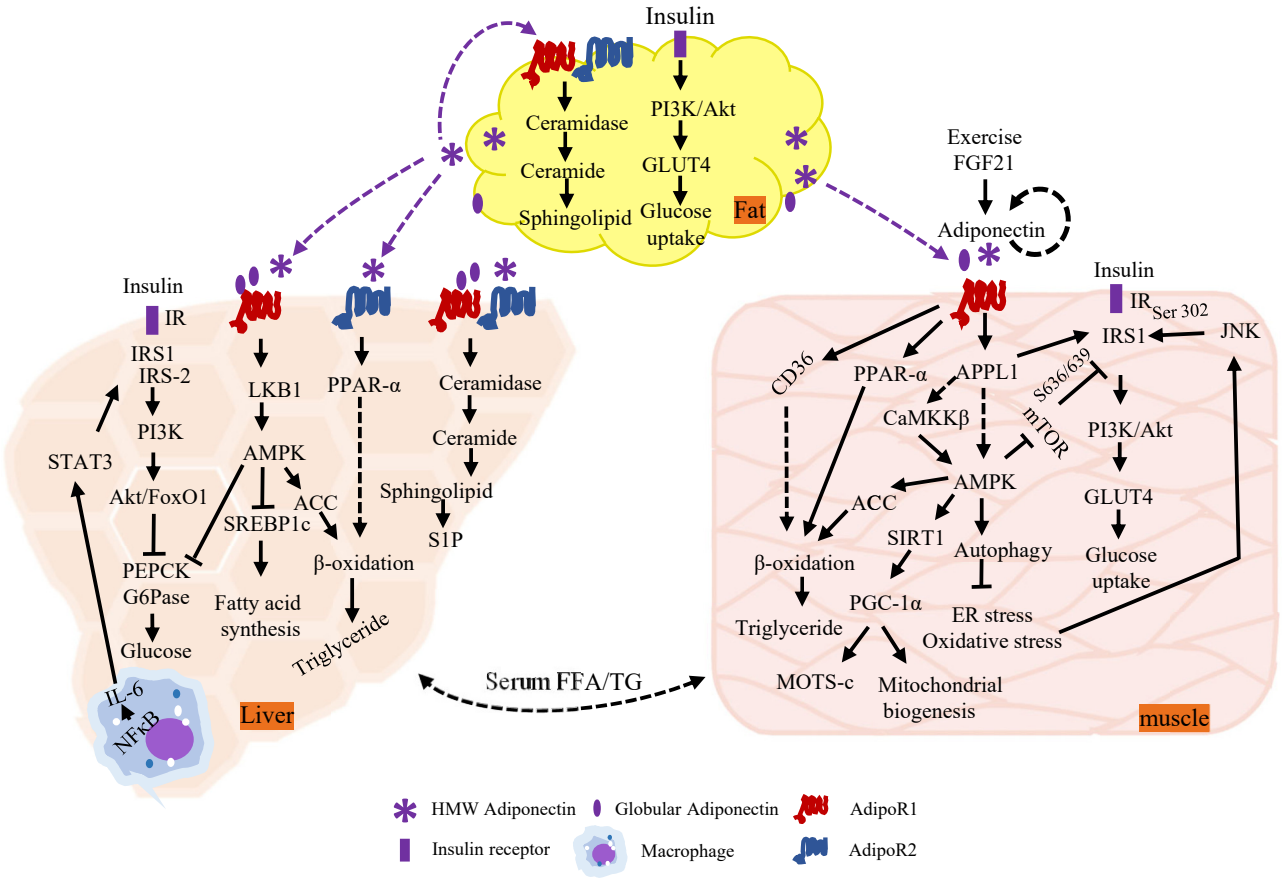

Figure 1: Insulin-sensitizing effects of adiponectin. Upon release from adipocytes, adiponectin circulates and targets three metabolic tissue/organs liver, muscle and adipose tissue, by binding to its own receptors AdipoR1 and AdipoR2, adiponectin activates AMPK and PPARα and subsequently sensitizes insulin signaling, promoting glucose update and inhibiting glucose production in liver and muscle respectively, in addition to enhanced fatty acid oxidation in both tissues. Adiponectin via APPL1 facilitates the binding of IRS1/2 to insulin receptor through which enhances insulin receptor downstream signaling. In addition, adiponectin stimulates the activation of ceramidase and reduces intracellular and circulating levels of ceramide, improving insulin resistance. IR, insulin receptor; IRS, insulin receptor substrate; PI3K, phosphoinositide 3-kinase; FoxO1, Forkhead Box O1; PEPCK, phosphoenolpyruvate carboxykinase; G6Pase, glucose-6-phosphatase; IL-6, interleukin-6; NF-κB, nuclear factor-κB; STAT3, signal transducer and activator of transcription 3; LKB1, liver kinase B1; AMPK, AMP-activated protein kinase; PPAR-α, peroxisome proliferator-activated receptor-α; SREBP1c, sterol regulatory element-binding protein 1c; ACC, acetyl coenzyme A carboxylase; S1P, sphingosine-1-phosphate; FFA/TG, free fatty acid/triglycerides; APPL1, adaptor protein, phosphotyrosine interacting with PH domain and leucine zipper 1; CaMBBβ, Calcium/calmodulin-dependent protein kinase kinase β; SIRT1, sirtuin 1; PGC-1α, Peroxisome proliferator-activated receptor-gamma coactivator-1α; ER, endoplasmic reticulum; JNK, c-Jun N-terminal kinase.

adiponectin increased food intake of mice on the high fat diet [84]. Adiponectin targets hypothalamus and stimulates food intake but reduces energy expenditure via AMPK-dependent mechanism [17]. In line with this, activating adiponectin-AMPK signaling in the hypothalamus has been shown to enhance food intake, a mechanism that thiazolidinediones (TZDs) increase body mass [126]. As a peripheral "starvation" signal, overexpressing adiponectin promotes the storage of triglycerides in adipose tissue with an improved metabolic profile [16]. Thus, the character of adiponectin as a starvation hormone and its related positive energy balance has became a concern for adiponectin-based therapeutics. However, the role of adiponectin in regulating food intake is of much debate [124]. Some studies showed that adiponectin deficiency had little effect on food intake in response to fasting or caloric restriction [116, 127, 128]. Adiponectin was also shown to decrease food intake and increase energy expenditure by directly regulating the cellular activity of arcuate Pomc and NPY/AgRP neurons [129]. In support of this, adiponectin enhances energy expenditure and suppresses ceramide by which it mediates the beneficial effects of FGF21, another well-known fasting hormone [89]. Although adiponectin regulation of appetite mainly depends on its central action [130], whether adiponectin moderates energy-expenditure through central nervous system remains incompletely understood. Only LMW form of adiponectin

was shown to be able to cross through the brain blood barrier [131]. Little is known whether LMW multimer directly binds to adiponectin receptor in specific neuron or needs to be assembled to MMW and HMW before its action.

Obesogenic effects of adiponectin

It has been debated for many years on the bona fide role of adiponectin in the regulation of energy homeostasis and thermogenesis [18]. Several studies show that adiponectin promotes energy expenditure and the cold-induced browning effect through its central and peripheral actions [76, 85, 89, 128, 132–134]. However, other studies have suggested that adiponectin may be a negative regulator of energy expenditure and thermogenesis [16–18, 126, 135–138]. These controversies may be partly due to the difference in the adiponectin isoform, dose, genetic background, administration approach or animal tools. It is worth noticing that although adiponectin deficiency does not appear to overtly alter insulin sensitivity under normal chow diet conditions [85, 139], adiponectin has been established to boost appetite, slow energy metabolism, and promote adipogenesis; all well-defined factors promoting obesity development [17, 135, 137]. This effect of adiponectin is similar to that of PPARγ agonists thiazolidinediones (TZDs) that improve insulin sensitivity but cause severe obesity [16, 140, 141]. The recent study using two adiponectin-deficient mouse models suggests that adiponectin inhibits energy expenditure and exerts pro-obesogenic effect by regulating cold-induced type 2 immunity in adipose tissue [18]. In support of this, adiponectin inhibits thermogenesis gene expression under cold stress by suppressing β3-adrenergic receptor expression in brown adipocytes independent of AdipoRs [137]. Kajimura et al. also reported that adiponectin suppresses energy expenditure, but their data suggest that the suppressing effect of adiponectin is mediated by the central nervous system [135]. Collectively, alteration of sympathetic tone, type 2 immunity, and β3-adrenergic signaling in adipose tissue may be responsible for adiponectin suppression of thermogenesis and energy expenditure. Adiponectin-based therapeutics may bring potential side effects such as anti-thermogenic and pro-obesity effects.

On the other hand, adiponectin is a well-accepted biomarker of adipogenesis and adipocyte differentiation in human mesenchymal stromal cells [142, 143]. It is induced during adipogenesis and has been suggested to facilitate adipogenesis [15, 144]. Consistently, adiponectin exhibits an ability to promote the adipogenesis of marrow osteoblasts [145] and hepatic stellate cells [146]. The inducing effect of adiponectin on adipogenesis is likely mediated by its feedforward activation of PPARγ, a master regulator of adipogenesis [144, 147–149]. The supporting evidence also include adiponectin-mediated induction of preadipocyte factor Pref-1 as well assuppression of C/EBPα, leading to the proliferation of pre-adipocytes rather than to promote adipocyte differentiation [132]. Given the adverse effect of PPARγ agonists TZDs as potent anti-diabetic drugs [84, 150], whether adiponectin-based therapeutics causes the similar side effects as TZD remains to be determined.

Dual role of adiponectin in inflammation

Besides the insulin sensitizing effect, the anti-inflammatory effect of adiponectin has gained lot of attention [28, 151–154]. Adiponectin modulates inflammatory response, mainly by targeting various types of immune cell [155–160], involving macrophage [161, 162], eosinophil [159], and mast cell [38]. A recent study reported a novel mechanism for the anti-inflammatory effect of adiponectin by promoting IL-10 release in human Tregs via adiponectin/AdipoR1 axis [163]. Besides, adiponectin in myotubes suppresses Toll-Like Receptor 4 (TLR4) signaling, leading to alleviated skeletal muscle inflammation [164]. Adiponectin inhibits diet-induced liver inflammation by suppressing MCP-1 expression and macrophage infiltration [165]. These findings suggest adiponectin signaling as a suitable therapeutic option for the treatment of inflammatory conditions.

However, there is a controversy as to whether adiponectin acts as a pro-inflammatory mediator [29, 59, 85, 97, 166–171]. Several studies showed the pro-inflammatory properties of adiponectin in cells such as macrophages [29, 97, 172, 173], monocytes [174, 175], synovial fibroblasts [169, 176], endothelial cells [115, 177] and osteoblasts [115]. Cot/tpl2 was reported to participate in the production of inflammatory mediators upon stimulation of macrophages with adiponectin [178]. Besides, adiponectin-induced pro-inflammatory response was also found in human astrocytes [179], human microglia [175] and isolated human macrophages and T cells [166]. However, Surendar et al. reported that adiponectin reduces pro-inflammatory CD4+ T cells from HFD mouse via restraining cell intrinsic glycolysis during obesity [180], suggesting the context-specific and cell-dependent manner of adiponectin pro-inflammatory properties [60]. In support of this, elevated adiponectin levels in children with multiple sclerosis enhances pro-inflammatory activation of innate and adaptive peripheral immune cells [175]. Consistently, increased levels of adiponectin in

muscle occurs 2 h post exercise and is required for the acute exercise-induced inflammatory response in muscle [181]. More importantly, it remains largely unknown whether adiponectin regulates thermogenesis and energy expenditure via inflammatory response, a key factor of WAT browning [182–185]. By using adiponectin knockout (KO) mice, Hui et al. found that adiponectin promotes WAT browning by direct stimulation of anti-inflammatory M2 macrophage proliferation with little effect on group 2 innate lymphoid cells (ILC2s) mediated pro-inflammatory effects [76]. This mouse model was shown to display a rather moderate phenotype in insulin sensitivity [139]. By employing the adiponectin KO mice which displayed magnified insulin resistance compared to the controls, when dietarily challenged [40], it was observed that adiponectin plays an inhibitory role in regulating adipose-resident ILC2s, type 2 immunity and energy expenditure [18], suggesting that the inhibitory effect of adiponectin on thermogenesis may be due to its pro-inflammatory property.

The dual role of adiponectin in the regulation of inflammation seems contrary but connected. Adiponectin isoforms may contribute to dual effects of adiponectin on inflammation as the full-length adiponectin was found to inhibit inflammation response in cells, while gAd promoted inflammation reaction in macrophage through activation of NF-κB signaling [179, 186, 187]. In support of this, gAd was found to activate NF-κB and promote pro-inflammatory cytokine production in macrophage, but full-length adiponectin exerts PI3K mediated anti-inflammatory effects to promote macrophage migration [188]. Kyoung-Hee et al. verified dual anti- and pro-inflammatory effects of adiponectin in macrophages, depending on divergent stimulation term [29, 58, 189]. It was suggested that the anti-inflammatory action of adiponectin in macrophage is mediated by its initial induction on inflammatory response and the subsequent tolerance to itself and to other pro-inflammatory signals [29, 172, 173]. In line with this, short-term treatment of macrophage with adiponectin initially increases TNF-alpha production, which in turn leads to increased expression of interleukin-10, autophagy induction, and an eventual decreasing of LPS-mediated production of inflammatory cytokine [29, 190–192]. Additional mechanism was proposed that adiponectin induced IRAK-M, an inactive isoform of the IRAK family of kinases, suppressing the production of proinflammatory mediators that are controlled by IRAK/TRAF6 signals [193]. A recent study showed that a lower concentration of adiponectin in women with the metabolic syndrome but not in men, suggesting that sex-specific regulation of adiponectin in systemic low-grade inflammation [194, 195].

Despite the downregulated adiponectin/adiponectin signaling in many metabolic diseases [196], higher adiponectin levels has been observed and could enhance inflammatory disorders such as preeclampsia [197], inflammatory bowel disease [198], rheumatoid arthritis [199, 200], multiple sclerosis [175], and chronic obstructive pulmonary disease [201–205] and heart failure with reduced ejection fraction (HFrEF) [206, 207]. Clinic studies revealed that increased serum adiponectin predicts the development of rheumatoid arthritis, especially in subjects with obesity [208–210]. In these inflammatory diseases, whether adiponectin persistently acts as a pro-inflammation factor or controls immune tolerance is still ambiguous [28, 211, 212]. The limitation of the studies on the pro-inflammatory action and immune tolerance of adiponectin is highly context-dependent and lack of establishment *in vivo* relevant *in vitro* systems. It is still not clear whether adiponectin exerts proinflammatory effects orchestrating the obesogenic function on the development of metabolic diseases. Thus, the detailed mechanisms underlying pro-inflammatory effects of adiponectin and its physiological significance under certain circumstances need to be further investigated (Figure 2).

Summary

Adiponectin is an adipose tissue-derived hormone that mediates inter-organ communication [213]. Dysregulation of adiponectin production has been implicated in the development and progression of metabolic diseases. As an insulin sensitizer, adiponectin has been proved to improve insulin resistance and protect against metabolic syndrome. The inverse correlation of adiponectin with metabolic diseases in humans emerges adiponectin as a noninvasive biomarker for disease state, indicative of that upregulating adiponectin could be an effective approach to prevent and treat hypoadiponectinemia-associated diseases such as obesity and diabetes [214]. However, the obesogenic effect of adiponectin, reflecting the induction of adipogenesis and food intake and the inhibition of thermogenesis, has gained increased attention (Figure 3). Similar to PPARγ agonists TZDs, adiponectin likely drives the development of healthy obesity with improved adipose tissue fibrosis and insulin sensitivity [16] through distinct mechanisms which necessitate to be further clarified. The accumulated evidence also raises a concern that adiponectin-based therapeutics may bring adverse effects such as obesity and inflammation. On the other hand, the positive correlation between adiponectin and inflammatory disorders suggests that adiponectin is a diversified player in immune system. Upon binding to its receptors AdipoR1, AdipoR2, and

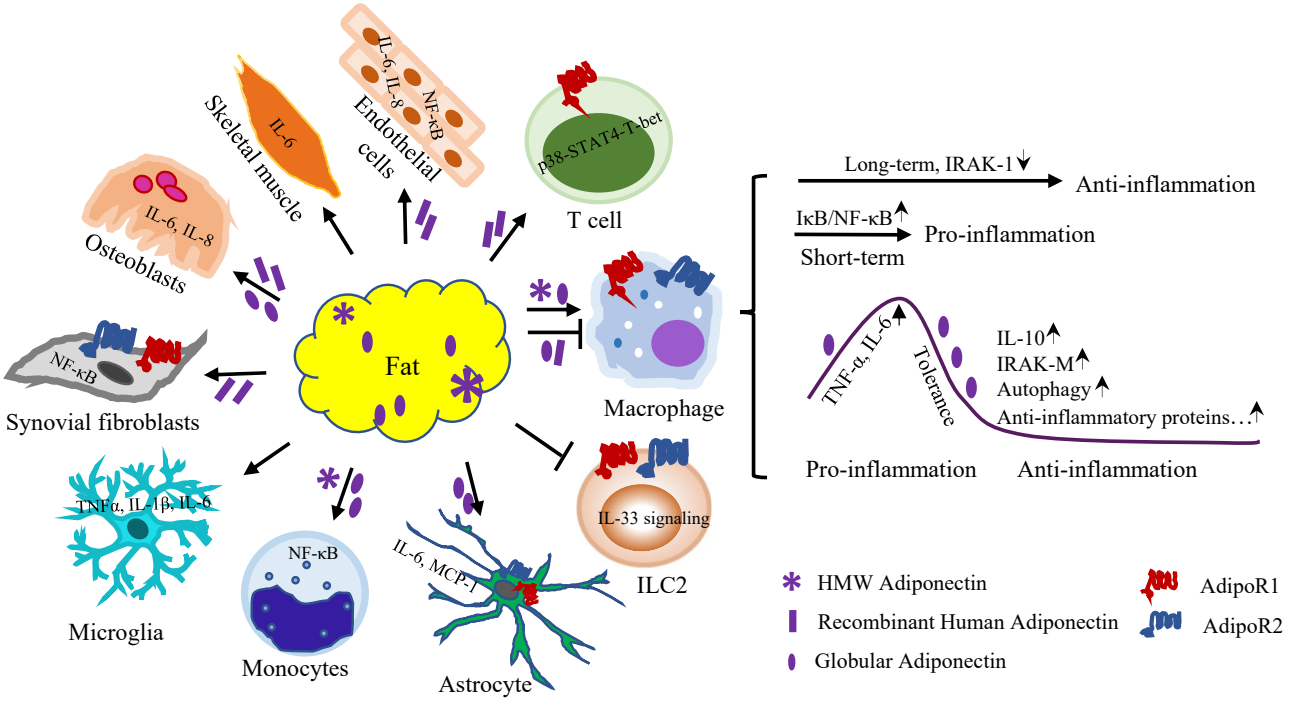

Figure 2: Pro-inflammatory properties of adiponectin under certain circumstances. Adiponectin level in circulation is positively correlated with a number of inflammatory disorders such as preeclampsia, rheumatoid arthritis and chronic obstructive pulmonary disease. αUnder certain circumstances, adiponectin induces the expression of inflammatory mediators in skeletal muscle, immune cells and non-immune cells, via various mechanisms. In macrophage, adiponectin acts as anti- and pro-inflammatory factor, which is mediated by its initial induction on inflammatory response and the subsequent tolerance to its own stimulation and/or to other pro-inflammatory signals. NF-κB, nuclear factor-κB; IL-6, interleukin-6; IL-8, interleukin-8; IL-10, interleukin-10; IL-33, interleukin-33; ILC2, group 2 innate lymphoid cells; MCP-1, monocyte chemoattractant protein-1; TNF-α, tumor necrosis factor-α; IRAK-1, interleukin-1 receptor-associated kinase-1. ↑ refers to increase, while ↓ means decrease.

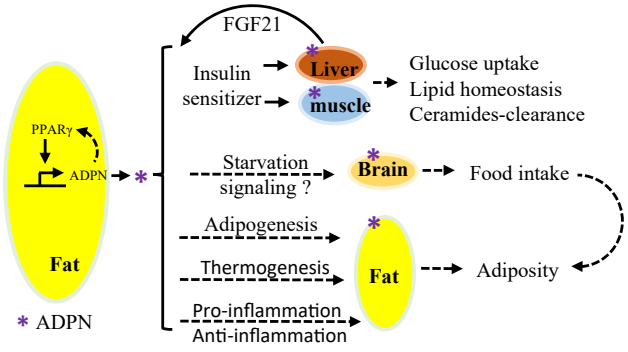

Figure 3: Adiponectin controls metabolic homeostasis via a variety of mechanisms. In addition to the insulin-sensitizing effect, adiponectin plays a critical role in regulating energy balance and inflammation. As a starvation signal, adiponectin promotes food intake and suppresses cold-induced thermogenesis, leading to positive energy balance and enhanced adipogenesis. This may interpret in part the obesogenic effect of adiponectin and potential side effects of adiponectin-based therapeutics. PPARγ, peroxisome proliferator-activated receptor-γ; ADPN, adiponectin; FGF21, fibroblast growth factor 21.

T-cadherin, adiponectin targets a variety of immune cells and acts on both innate and acquired immunity. However, while it is well documented that adiponectin talks to metabolically active tissue-resident immune cells, whether and how adiponectin controls the development and function of immune organ remain largely unknown. Therefore, the study on adiponectin regulation of inflammation and energy metabolism may be a key, given the emerging recognition of the interplay between immune system and metabolism in health and disease.

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