



# Adiponectin action: a combination of endocrine and autocrine/paracrine effects

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The widespread physiological actions of adiponectin have now been well characterized as clinical studies and works in animal models have established strong correlations between circulating adiponectin level and various disease-related outcomes. Thus, conventional thinking attributes many of adiponectin's beneficial effects to endocrine actions of adipose-derived adiponectin. However, it is now clear that several tissues can themselves produce adiponectin and there is growing evidence that locally produced adiponectin can mediate functionally important autocrine or paracrine effects. In this review article we discuss regulation of adiponectin production, its mechanism of action via receptor isoforms and signaling pathways, and its principal physiological effects (i.e., metabolic and cardiovascular). The role of endocrine actions of adiponectin and changes in local production of adiponectin or its receptors in whole body physiology is discussed.

**Keywords:** adiponectin, metabolic syndrome, cardiovascular disease

## INTRODUCTION

### ADIPONECTIN: REGULATION OF ITS EXPRESSION AND POST-TRANSLATIONAL MODIFICATION

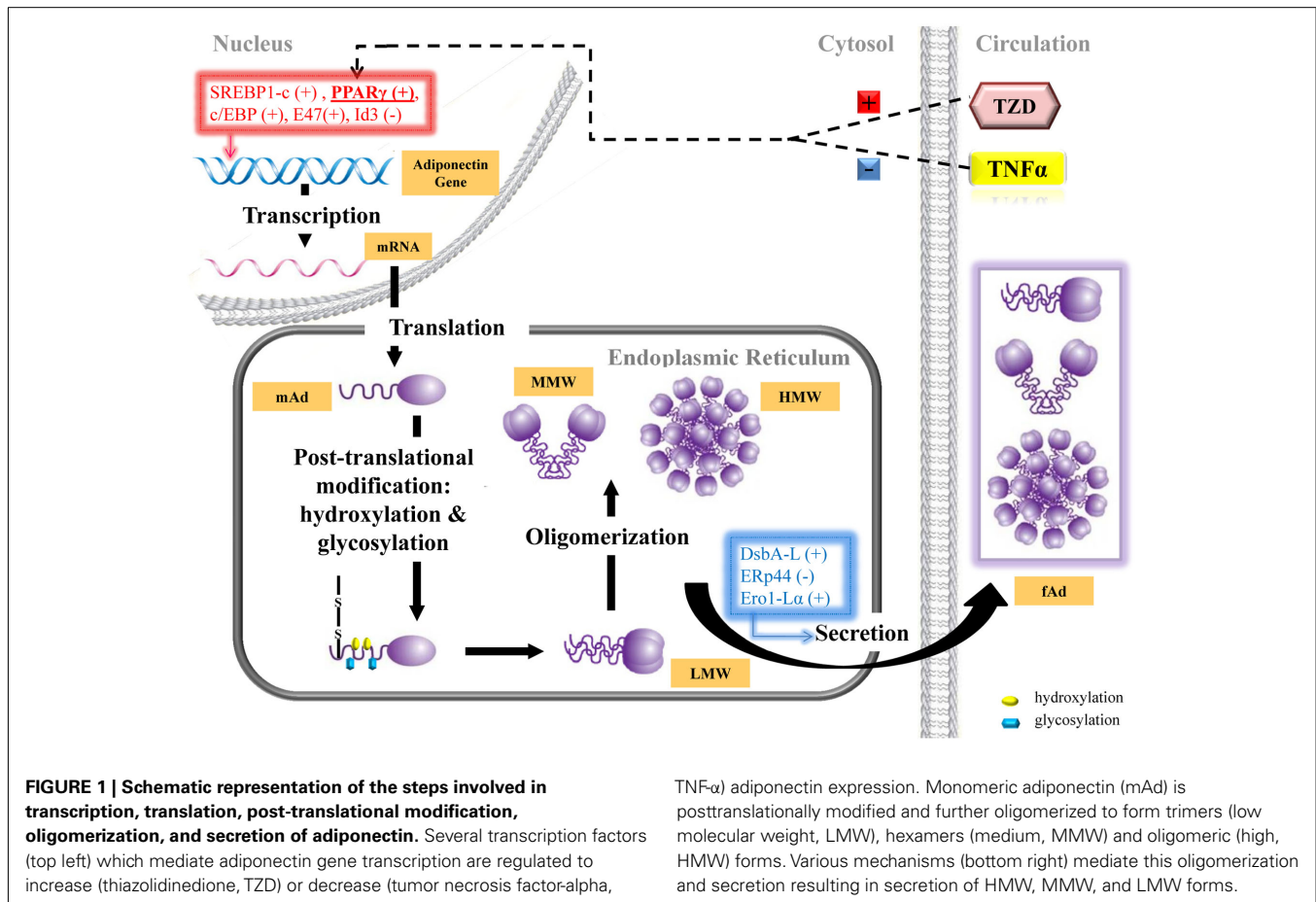
Adiponectin was discovered as an adipocyte-derived 30 kDa secretory protein, which consists of an amino-terminal signal sequence followed by a collagenous domain and a carboxyl-terminal globular domain (Scherer et al., 1995; Hu et al., 1996; Maeda et al., 1996; Nakano et al., 1996). Adiponectin is transcriptionally regulated by peroxisome proliferator-activated receptor  $\gamma$  (PPAR $\gamma$ ), C/EBP, SREBP, E47, and Id3 protein (Fajas et al., 1998; Osborne, 2000; Motoshima et al., 2002; Yilmaz et al., 2004; Doran et al., 2008; **Figure 1**). Drugs like rosiglitazone and pioglitazone, belonging to the thiazolidinedione (TZD) class of PPAR $\gamma$  agonists, have been clinically and experimentally proven to be potent inducers of adiponectin expression (Tsuchida et al., 2005; Phillips et al., 2008; Liu et al., 2009) and indeed many of the metabolic and cardioprotective effects of rosiglitazone or pioglitazone are absent/decreased in mice lacking adiponectin (Li et al., 2010; Tao et al., 2010; Zhou et al., 2010). Therefore, elevated adiponectin expression is a critical mechanism of action in mediating beneficial effects of this drug class. Regulation of SREBP-1c is another well known mechanism activating adiponectin transcription while more recently Id3 and E47 were demonstrated as novel regulators of this SREBP-1c-mediated adiponectin expression in adipocytes. E47 potentiates SREBP-1c-mediated adiponectin promoter activation and this is inhibited upon interaction with Id3. Decreased Id3 levels increased adiponectin expression and Id3-null mice had increased adiponectin expression in visceral fat tissue and serum (Doran et al., 2008).

Extensive post-translational modification plays a vital role for assembling adiponectin to form its functional oligomeric complexes (Wang et al., 2008; Simpson and Whitehead, 2010). The

initiation step of adiponectin multimerization involves the non-collagenous globular domain forming trimers (Waki et al., 2003). Subsequently, the disulfide bond formed via Cys39 (mouse) or Cys36 (human) is critical for adiponectin to form higher molecular weight multimers based on its trimeric form (Tsao et al., 2003). Post-translational modification including hydroxylation and glycosylation of the four conserved lysine residues (lys68, lys71, lys80, lys104) within the collagenous domain of adiponectin are required for the formation of HMW oligomeric complex (Wang et al., 2002, 2006). The disulfide bond A oxidoreductase-like protein (DsbA-L) was found to positively regulate the process of adiponectin multimerization. The secretion of adiponectin is specifically regulated by endoplasmic reticulum (ER) proteins ERp44 and Ero1- $\alpha$ . The covalent bond formed between ERp44 and the thiol group of Cys39 on adiponectin retains adiponectin in ER while the disulfide bond formed between ERp44 and Ero1- $\alpha$  releases adiponectin (Anelli et al., 2003; Wang et al., 2007; Schraw et al., 2008). Adiponectin exists abundantly in the plasma and circulates in its HMW (oligomer), MMW (hexamer), and LMW (trimer) oligomeric forms (Waki et al., 2003). The combination of these oligomeric forms is often referred to as full-length adiponectin (fAd). An additional circulating form of adiponectin, the albumin binding LMW, has been identified subsequently (Ebinuma et al., 2006). Moreover, upon protease cleavage the globular domain of fAd (referred to hereafter as gAd) can be liberated. Although significant circulating levels are not observed, gAd is proposed to be cleaved locally by specific tissues or at sites of inflammation (Fruebis et al., 2001; Waki et al., 2005).

### ADIPONECTIN RECEPTORS AND RECEPTOR ADAPTOR PROTEINS

Adiponectin exerts many of its cellular effects principally through binding to two receptor isoforms with seven



TNF- $\alpha$ ) adiponectin expression. Monomeric adiponectin (mAd) is posttranslationally modified and further oligomerized to form trimers (low molecular weight, LMW), hexamers (medium, MMW) and oligomeric (high, HMW) forms. Various mechanisms (bottom right) mediate this oligomerization and secretion resulting in secretion of HMW, MMW, and LMW forms.

putative transmembrane domains. These adiponectin receptor 1 (AdipoR1) and adiponectin receptor 2 (AdipoR2) isoforms have distinct distribution patterns in various tissues (Yamauchi et al., 2003a, 2007; Kadowaki et al., 2007, 2008). It was shown that skeletal muscle cells bound gAd more avidly than fAd and suppression of AdipoR1 expression with siRNA reduced high-affinity gAd binding (Yamauchi et al., 2003b). Conversely, suppression of AdipoR2 expression with siRNA largely reduced fAd binding, but only modestly reduced globular adiponectin binding. Collectively, available data indicates that AdipoR1 is a high-affinity receptor for gAd and a low-affinity receptor for fAd, whereas AdipoR2 is an intermediate-affinity receptor for fAd and gAd. Since AdipoR1 is the predominant form expressed in skeletal muscle, while AdipoR2 is predominantly expressed in liver, this correlated with the fact that gAd exerts its insulin mimetic and insulin-sensitizing effect more effectively compared to fAd in skeletal muscle and vice versa (Yamauchi et al., 2002). T-cadherin, was also found to competitively bind only the hexameric and HMW forms of adiponectin (Hug et al., 2004; Asada et al., 2007; Chan et al., 2008). Although T-cadherin lacks an intracellular domain (Hug et al., 2004), various studies have suggested the involvement of this protein in mediating functional effects of adiponectin. These include cardioprotective effects (Denzel et al., 2010), anti-atherosclerotic effects in vasculature (Takeuchi et al., 2007; Andreeva et al., 2010), anti-diabetic

effects in skeletal muscle (Hug et al., 2004) as well as anti-fibrotic effects in liver (Asada et al., 2007).

Several adiponectin receptor binding proteins have now been identified (Buechler et al., 2010; Heiker et al., 2010). The first and best characterized is adaptor protein containing pleckstrin homology domain, phosphotyrosine binding (PTB) domain, and leucine zipper motif (APPL1; Mao et al., 2006a). Other more recently identified adaptor proteins which have been suggested to be involved in adiponectin's intracellular signal transduction include activated protein kinase C1 (RACK1; Xu et al., 2009), ER protein 46 (ERp46; Charlton et al., 2010), and protein kinase CK2 $\beta$  (Heiker et al., 2009). Among the adaptor proteins, only APPL1 associates with both AdipoR1 and AdipoR2 while RACK1, ERp46, and CK2 $\beta$  bind to AdipoR1. APPL1 interacts with the intracellular region of adiponectin receptors through its PTB domain (Mao et al., 2006a) and sequentially activates downstream signaling. It has now been shown that APPL1 plays an important role in mediating many of adiponectin's effects, including metabolic effects in liver, muscle, and endothelial cells (Kobayashi et al., 2004; Mao et al., 2006a; Cheng et al., 2007, 2009; Chandrasekar et al., 2008; Wang et al., 2009a; Zhou et al., 2009; Cleasby et al., 2011; Xin et al., 2011) as well as cardioprotective effects (Fang et al., 2010; Park et al., 2011). The interaction between RACK1 or CK2 $\beta$  and AdipoR1 was indicated by yeast two-hybrid studies and confirmed

in cells by colocalization and coimmunoprecipitation (Heiker et al., 2009; Xu et al., 2009). RNAi-mediated RACK1 knockdown prevented adiponectin regulated glucose uptake in HepG2 cells (Xu et al., 2009). Pharmacological inhibition of CK2 $\beta$  attenuated adiponectin signaling in skeletal muscle cells (Heiker et al., 2009). Coimmunoprecipitation also confirmed the interaction between ERp46 and AdipoR1, but not AdipoR2, and interestingly the suppression of ERp46 expression resulted in increased cell surface AdipoR1 levels and enhanced adiponectin stimulated phosphorylation of AMP kinase (AMPK) but reduced phosphorylation of p38-mitogen-activated protein kinase (MAPK; Charlton et al., 2010).

## CIRCULATING ADIPONECTIN: REGULATION AND CHANGES IN NORMAL AND DISEASE STATES

### ADIPONECTIN ISOFORMS, THEIR CIRCADIAN RHYTHM AND CLEARANCE

Adiponectin circulates in the concentration range of  $\sim 3\text{--}30\ \mu\text{g/ml}$  in healthy individuals, with a lower level in male compare to female which is mainly attributed to lower amounts of hexameric HMW form (Xu et al., 2005; Wang et al., 2008). Studies on the metabolism and clearance of adiponectin have yielded variable results with a half-life of approximately 75 min reported recently based on tracking fluorescently labeled recombinant adiponectin in the circulation (Halberg et al., 2009) while a previous study (as the study performed in rabbit using recombinant human adiponectin) found HMW adiponectin had a half-life of 13 h and LMW a half-life of 17.5 h (Peake et al., 2005). A recent study indicated the important role of posttranslational modifications, including sialylation which modifies the O-linked glycans on Thr residues with sialic acid, in the regulation of adiponectin's half-life (Richards et al., 2010). Indeed, enzymatic removal of the sialic acid from adiponectin accelerates its clearance from circulation (Richards et al., 2010). Like many other metabolic hormones adiponectin, especially its HMW form, is regulated by the biological clock and shows circadian rhythms with a reduction occurring during the night (Froy, 2007; Cano et al., 2009; Gomez-Abellan et al., 2010; Scheer et al., 2010; Tan et al., 2011). The endocrine effects of adipose-derived adiponectin are conventionally believed to regulate many physiological processes, and many studies have established strong correlations between circulating adiponectin levels and various disease states.

### ADIPONECTIN IN OBESITY AND DIABETES

A decreased plasma adiponectin level has been found in patients with obesity and type 2 diabetes despite the increasing mass of adipose tissue (Arita et al., 1999; Ouchi et al., 2001; Weyer et al., 2001; Matsuda et al., 2002; Daimon et al., 2003; Spranger et al., 2003; Ryo et al., 2004; Liu et al., 2007). Moreover, many studies have shown that instead of the absolute total circulating level of adiponectin, the ratio between HMW and total adiponectin can more accurately predict insulin resistance and development of features of the metabolic syndrome (Araki et al., 2006; Hara et al., 2006; Katsuki et al., 2006; Liu et al., 2007; Hamilton et al., 2011). However, although HMW is often referred to as most biologically active for this reason, there remains a lack of direct metabolic studies have been conducted using only the HMW form of adiponectin.

Proinflammatory cytokines, in particular tumor necrosis factor  $\alpha$  (TNF $\alpha$ ), are considered to be a principal cause of the reduction in circulating adiponectin seen in obese/diabetic patients (Ouchi et al., 2003a,b; Takemura et al., 2007). Nevertheless, it is important to balance these strong clinical correlations with consideration of whether alterations in adiponectin are always a cause or, in some cases, a consequence of disease states and this will be highlighted below.

### ADIPONECTIN IN CARDIOVASCULAR DISEASE

A substantial amount of evidence indicates a potential pathophysiological contribution of adiponectin in cardiovascular disease (Shinmura, 2010; Xu et al., 2010; Hui et al., 2011; Okamoto, 2011). Clinical studies have generally identified negative correlations between plasma adiponectin levels and various aspects of cardiovascular disease such as atherosclerosis, myocardial infarction, heart failure, endothelial dysfunction and hypertension, and established as an independent risk factor for these. The HMW form of adiponectin has been generally regarded as the best predictor of cardiovascular outcome yet, interestingly, a recent study also identifies trimeric LMW adiponectin as a potentially useful biomarker in cardiovascular disease (Hamilton et al., 2011). Adiponectin knockout mice have been particularly informative in terms of elucidating the interaction between adiponectin and cardiovascular injury, with exaggerated degrees of induced cardiovascular defects typically observed in these mice which can be corrected by adiponectin replenishment. Additionally, several single nucleotide polymorphisms (SNPs) have been identified in the adiponectin gene that consequently cause a reduction of its serum concentration (Menzaghi et al., 2002, 2007; Tanko et al., 2005; Yang and Chuang, 2006). For example, clinical data has shown evidence of the correlation between adiponectin gene +45 and +276G SNPs with obesity, type 2 diabetes, insulin resistance, cardiovascular disease, and hypertension (Mousavinasab et al., 2006; Loos et al., 2007; Yang et al., 2007; Dolley et al., 2008). Adiponectin exerts its beneficial cardiovascular influence via targeting many cell types and inducing antioxidative, metabolic, anti-fibrotic, anti-apoptotic, anti-inflammatory, and vasodilator activities (Xu et al., 2010; Hui et al., 2011). The concept of adiponectin resistance, potentially due to changes in expression of AdipoRs and APPL1/2, may be an underestimated factor in the development of CVD (Lau et al., 2011).

### ADDITIONAL DISEASE PROCESSES RELATED TO CHANGES IN ADIPONECTIN LEVELS

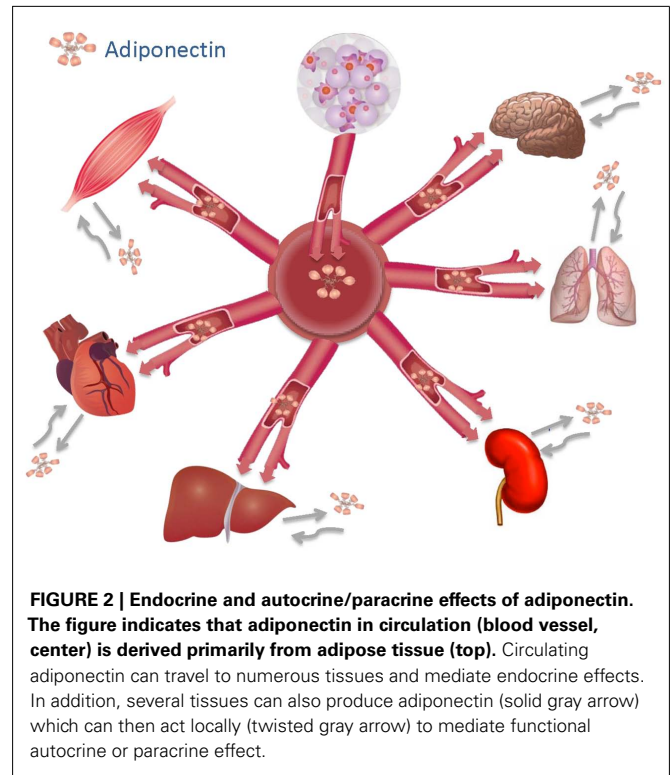
An extremely wide variety of physiological processes have been found to be regulated by adiponectin and, as a consequence, changes in circulating adiponectin have been implicated in various clinical settings (Kadowaki et al., 2008; Wang and Scherer, 2008; Yamauchi and Kadowaki, 2008; Shetty et al., 2009; Brochu-Gaudreau et al., 2010; Chiarugi and Fiaschi, 2010). Correlations have been established between changes in circulating adiponectin levels and cancer (Kelesidis et al., 2006; Jarde et al., 2011; Paz-Filho et al., 2011), hepatic fibrosis (Dogru et al., 2010), reproductive events (Michalakis and Segars, 2010), bone mass density (BMD; Napoli et al., 2010), and inflammation (Fantuzzi, 2008). Some of these are discussed in more detail below.

## ADIPONECTIN PHYSIOLOGY AND EVIDENCE FOR CONTRIBUTION OF ENDOCRINE AND LOCAL EFFECTS

### SKELETAL MUSCLE

Adiponectin has clearly been shown to regulate glucose and fatty acid metabolism in skeletal muscle, principally via studies which have used animal models with enhanced or suppressed circulating adiponectin or used recombinant forms of the protein to treat cells *in vitro* or skeletal muscle *ex vivo*. Cell based *in vitro* studies show adiponectin can increase both basal and insulin-stimulated glucose uptake by promoting GLUT4 translocation to the cell membrane (Ceddia et al., 2005; Fang et al., 2005, 2009; Mao et al., 2006a) and increase fatty acid uptake and oxidation (Tomas et al., 2002; Yoon et al., 2006) through the activation of AMPK, p38-MAPK, and PPAR $\alpha$  pathways (Yamauchi et al., 2002, 2003b; Yoon et al., 2006). Animal model studies *in vivo* correlate well with these observations as systemic infusion, adenoviral-based delivery or genetic overexpression of adiponectin can successfully correct high-fat diet-induced insulin resistance in skeletal muscle and decrease serum TG and FFA levels (Yamauchi et al., 2001, 2003c; Maeda et al., 2002; Combs et al., 2004). Although it is very well accepted that adiponectin mediates beneficial metabolic effects in skeletal muscle, the precise underlying molecular mechanisms were uncovered in more detail recently. Adiponectin can increase skeletal muscle mitochondrial mass and oxidative capacity, at least in part via inducing extracellular Ca<sup>2+</sup> influx and subsequently activating the Ca<sup>2+</sup>/calmodulin-dependent protein kinase kinase beta (CaMKK $\beta$ )–AMPK–Sirt1–peroxisome proliferator-activated receptor gamma coactivator-1alpha (PGC1 $\alpha$ ) pathway (Iwabu et al., 2010). Previous studies also showed transgenic mice overexpressing adiponectin had improved insulin sensitivity whereas adiponectin knockout mice exhibit some degree of insulin resistance and decreased expression of PGC1 $\alpha$  and PPAR $\gamma$  (Civitarese et al., 2006; Kadowaki et al., 2006). Most recently, Scherer's group identified another important mechanism underlying adiponectin's beneficial metabolic effects, namely enhanced ceramide catabolism in skeletal muscle (Holland et al., 2011).

The prevailing assumption was that the metabolic effects of adiponectin in skeletal muscle were due to endocrine effects of adipocyte-derived adiponectin (Figure 2). Importantly, emerging evidence (Delaigle et al., 2004, 2006; Krause et al., 2008; Liu et al., 2009; Amin et al., 2010; Jortay et al., 2010; Van Berendoncks et al., 2010) suggests that adiponectin can also be expressed and secreted by skeletal muscle and thus may also be classified as a myokine (Pedersen and Febbraio, 2008) which exerts its effect locally. We have shown an increased level of adiponectin mRNA, intracellular and secreted protein in response to rosiglitazone treatment *in vitro*; and subsequently verified that this skeletal muscle produced adiponectin exerted functional metabolic effects including enhanced insulin-stimulated Akt phosphorylation and glucose uptake (Liu et al., 2009). In agreement with this, Leff's group also demonstrated PPAR $\gamma$ -mediated skeletal muscle adiponectin production which mediated autocrine effects to improve insulin sensitivity and could protect against high-fat diet-induced insulin resistance *in vivo* (Amin et al., 2010). It has been suggested that skeletal muscle adiponectin content increases in response to certain inflammatory conditions and obesity in an attempt at providing local anti-inflammatory and antioxidative



protection (Delaigle et al., 2004, 2006; Jortay et al., 2010). Indeed, the globular form of adiponectin mediates potent metabolic effects in skeletal muscle (Fruebis et al., 2001; Tomas et al., 2002; Ceddia et al., 2005; Chen et al., 2005; Fang et al., 2005; Mao et al., 2006a) and it is conceivable that elevated local amounts of gAd are produced in inflamed tissue by elastase enzyme derived from infiltrating inflammatory cells (Waki et al., 2005). Finally, autocrine effects of gAd have recently been identified in the regulation of skeletal muscle cell differentiation (Fiaschi et al., 2009, 2010).

Local effects of adiponectin may also be determined by changes in expression of its receptor isoforms and signaling intermediates, although relatively little is known on this topic to date. Weight loss induced by either exercise or diet together with exercise enhance the expression of adiponectin receptor mRNA in skeletal muscle of humans and animal models (Vu et al., 2007; Christiansen et al., 2010). A study in non-diabetic Mexican Americans with or without a family history of Type 2 diabetes concluded that skeletal muscle expression levels of both AdipoR1 and AdipoR2 correlated positively with insulin sensitivity (Civitarese et al., 2004). Hyperglycemia and hyperinsulinemia can both alter AdipoR expression in muscle cells and consequently adiponectin sensitivity (Fang et al., 2005). Although it is generally believed that enhancing AdipoR–APPL1 signaling is beneficial (Mao et al., 2006a; Cheng et al., 2007, 2009; Saito et al., 2007; Zhou et al., 2009; Fang et al., 2010; Cleasby et al., 2011), recent studies have identified that the abundance of APPL1 mRNA is significantly higher in muscle of type 2 diabetic individuals (Holmes et al., 2011). Bariatric surgery corrected hyperglycemia and this was correlated with increased circulating adiponectin and skeletal muscle AdipoR1 expression with reduced APPL1 content (Holmes et al., 2011).



## CARDIOVASCULAR

As described above, many studies have established correlations between circulating adiponectin levels and various cardiovascular outcomes and the underlying mechanisms are now well understood. For example, adiponectin is now established as a cardio-protective adipokine as it mediates beneficial effects on cardiac remodeling events such as energy metabolism, hypertrophy, fibrosis, and apoptosis (Shibata et al., 2004, 2005, 2007; Liao et al., 2005; Palanivel et al., 2007; Fang et al., 2010; Li et al., 2010; Tao et al., 2010; Shimano et al., 2011). Anti-inflammatory, vasodilator, and anti-atherosclerotic effects confer further beneficial influences of adiponectin on the cardiovascular system (Fantuzzi, 2008; Brochu-Gaudreau et al., 2010; Xu et al., 2010; Hui et al., 2011).

Mice lacking adiponectin have been particularly informative in establishing the cardioprotective role of adiponectin, with numerous studies in these mice demonstrating an exaggerated response of the heart to cardiac stress (Shibata et al., 2004, 2005, 2007; Liao et al., 2005; Li et al., 2010; Tao et al., 2010; Shimano et al., 2011), which was attenuated upon restoration of circulating adiponectin. The ability of adiponectin to counteract deterioration in cardiac function was mediated by metabolic, anti-apoptotic, anti-fibrotic, and anti-hypertrophic effects (Shibata et al., 2004, 2005, 2007; Tao et al., 2007; Wang et al., 2009b; Fang et al., 2011; Park et al., 2011). Adiponectin has been shown to regulate fatty acid  $\beta$ -oxidation in the heart. In cell based *in vitro* studies of isolated cardiomyocytes, adiponectin was shown to stimulate the phosphorylation of AMPK, IRS1, and Akt (T308 and S473) correlating with the regulation of glucose and fatty acid uptake and metabolism (Palanivel et al., 2007), and to target cofilin to mediate remodeling of the actin cytoskeleton leading to the translocation of lipoprotein lipase (LPL) to the cell surface (Ganguly et al., 2011). Adiponectin was also shown to stimulate the phosphorylation of acetyl coenzyme A carboxylase (ACC), as well as to induce CPT-1 expression and activation through AMPK (Li et al., 2007a). Recently (Fang et al., 2010), we demonstrated that adiponectin increases fatty acid uptake, CD36 translocation, and insulin-stimulated glucose transport as well as Akt phosphorylation in isolated adult cardiomyocytes, and enhances fatty acid oxidation in conjunction with AMPK and ACC phosphorylation in the isolated working heart. However, despite an increase in fatty acid oxidation and myocardial oxygen consumption, adiponectin increased hydraulic work, and maintained cardiac efficiency (Fang et al., 2010).

The phosphorylation of AMPK was shown to attenuate norepinephrine induced cardiomyocyte hypertrophy and ERK phosphorylation (Shibata et al., 2004), angiotensin II induced NF- $\kappa$ B activation and hypertrophy (Wang et al., 2011), and also shown to fully (Shibata et al., 2005), or minimally (Wang et al., 2009a) attenuate hypoxia-reoxygenation induced apoptosis. Adiponectin was shown to attenuate hypoxia-reoxygenation induced apoptosis in H9C2 cells through the AdipoR1/APPL1 signaling pathway (Park et al., 2011). Cardiac fibrosis is associated with impaired cardiac function, and there are numerous studies demonstrating the exaggerated fibrotic response of the heart to cardiac stress in the absence of adiponectin (Shibata et al., 2004, 2005, 2007; Liao et al., 2005; Li et al., 2010; Tao et al., 2010; Shimano et al., 2011). Very

few studies have directly investigated regulation of extracellular matrix components by adiponectin *in vitro*. Cardiac fibroblasts express AdipoR1 (Huang et al., 2009) and treatment of adult rat fibroblasts with gAd was shown to increase IL-6 expression and secretion via the activation of AMPK, p38-MAPK, and ERK1/2 (Fan et al., 2011).

Although an overwhelming amount of data indicates numerous beneficial effects of adiponectin, there is also some contradictory evidence from clinical and experimental studies on the cardioprotective role of adiponectin. For example, recent clinical data have positively correlated high levels of adiponectin with mortality and severity in patients with congestive heart failure (Shinmura, 2010). Adiponectin knockout mice subjected to long-term pressure overload suggested that under chronic stress, adiponectin deficiency preserves oxidative capacity and cardiac function despite an increase in cardiac hypertrophy compared to wild-type mice, suggesting that adiponectin may in fact be playing a permissive role in long-term cardiac dysfunction (O'Shea et al., 2010).

Both cardiomyocytes (Pineiro et al., 2005; Ding et al., 2007) and epicardial adipose tissue (Gomez et al., 2011; Hirata et al., 2011) can produce adiponectin and thus increase autocrine/paracrine bioavailability. Indeed, epicardial adipose-derived adiponectin was recently identified as a predictor of positive outcome following cardiac surgery (Kourliouros et al., 2011), although it should be noted that expression of adiponectin from epicardial adipose tissue has been shown to be lower than that from subcutaneous adipose tissue (Bambace et al., 2011). Similarly, cardiomyocytes produce relatively small amounts of adiponectin (Pineiro et al., 2005; Ding et al., 2007), yet these are likely to be sufficient for locally mediated effects. A number of studies have found that cardiac adiponectin levels are altered in various cardiomyopathies. For example, a recent study has shown in patients with dilated cardiomyopathy that adiponectin expression was decreased sixfold and this was mirrored in immunohistochemical analysis of endomyocardial biopsies (Skurk et al., 2008). Additionally, the accumulation of adiponectin within the myocardial tissue following stress through leakage from the vascular compartment could also serve to increase the local supply of bioavailable adiponectin and serve to compensate for the inflammatory induced downregulation of both local and systemic adiponectin expression (Ouchi et al., 2000; Shibata et al., 2007; Fujita et al., 2008). Interestingly, adiponectin has also been shown to accumulate in atherosclerotic plaques and whether this is causative or protective against progression of atherosclerosis is still incompletely resolved, although the latter seems most likely (Li et al., 2007b; Cai et al., 2010; Reynolds et al., 2010).

Myocardial adiponectin resistance (Saito et al., 2007; Kollias et al., 2011; Ma et al., 2011) may necessarily be the first target in developing adiponectin-based therapeutics in the treatment of cardiovascular disease. Overall, circulating or local adiponectin levels tend to correlate negatively with cardiovascular disease incidence and prognosis, however since many cardiovascular events are progressive in nature there may in some cases be a temporal compensatory increase in adiponectin expression, particularly within the affected tissue. Thus, several paradoxical observations

have been reported in the literature and it is likely that the timing of targeting adiponectin therapeutically will be vital to its success in the cardiovascular arena (Dembinski, 2010).

## LIVER

Regulation of hepatic glucose and fatty acid metabolism plays an important role in the ability of adiponectin to improve whole body energy homeostasis (Kadowaki and Yamauchi, 2005; Fang and Sweeney, 2006; Kadowaki et al., 2007). For example, low levels or defects in adiponectin action correlate with steatosis, hepatomegaly, and local inflammation associated with various liver diseases. The intracellular signaling mechanisms via which adiponectin mediates effects in hepatocytes are similar to those in muscle (Wang et al., 2009c), with one apparent exception being a more important role of the AdipoR2 isoform in mediating the effects of adiponectin in liver (Yamauchi et al., 2003b, 2007; Yamauchi and Kadowaki, 2008). Adiponectin is known to exert its effects in the liver primarily through the activation of the AMPK and PPAR $\alpha$  pathways. In addition to the well characterized insulin-sensitizing and insulin-like effects of adiponectin in the liver, low serum adiponectin levels have been associated with high TNF $\alpha$  levels and the presence of non-alcoholic fatty liver disease (NAFLD) independent of insulin resistance (Hui et al., 2004; Aygun et al., 2006; Polyzos et al., 2011). In particular, adiponectin has been shown to mediate anti-fibrotic effects through the activation of AMPK in hepatic stellate cells (Adachi and Brenner, 2008), anti-apoptotic effects via PI3K and AMPK activation in hepatocytes (Jung et al., 2009), and to be anti-inflammatory through the inhibition of TNF $\alpha$  induced hepatotoxicity (Sennello et al., 2005). A role for T-cadherin has also been proposed in mediating the effects of adiponectin on liver fibrosis (Asada et al., 2007). Furthermore, circulating adiponectin levels have been found to be downregulated in morbidly obese patients with non-alcoholic steatohepatitis (NASH) compared to individuals with simple steatosis (Uribe et al., 2008; Ma et al., 2009), while a paradoxical increase in serum adiponectin levels were detected in patients with cirrhosis, independent of insulin resistance (Tietge et al., 2004; Kaser et al., 2005). It is worth bearing in mind that increased adiponectin levels in liver cirrhosis may reflect reduced hepatic clearance of adiponectin and/or a compensatory increase toward the overwhelming production of proinflammatory cytokines in cirrhosis. Thus, a potentially detrimental contribution of adiponectin as NAFLD progresses to cirrhosis must be considered (Polyzos et al., 2010).

Hepatic AdipoR1 and AdipoR2 mRNA expression levels were higher in insulin-resistant subjects, perhaps reflecting a compensatory mechanism for reduced plasma adiponectin (Felder et al., 2010). Liver fibrosis in individuals infected with hepatitis C virus was associated with hyperadiponectinemia and, interestingly, reduced AdipoR1 expression (Corbetta et al., 2011). A study in humans showed no change in AdipoR expression in patients with NASH (Uribe et al., 2008), but an important role for changes in AdipoR expression was also shown in a study using a high-fat and high-cholesterol diet in obese fa/fa Zucker rats to induce NASH was associated with decreased AdipoR1 and AdipoR2 expression (Matsunami et al., 2011). In addition, liver expression and localization of adiponectin were increased in wild-type mice in response

to carbon tetrachloride induced hepatofibrosis (Yoda-Murakami et al., 2001).

## LUNG

Respiratory complications are often observed in obese individuals (Ford, 2005; Shore, 2010). Importantly, decreased serum adiponectin levels correlate with poor lung function in asthma and chronic obstructive pulmonary disease (COPD, independent of adiposity (Sood et al., 2008; Stanciu et al., 2009; Sutherland et al., 2009; Chan et al., 2010; Thyagarajan et al., 2010). Indeed, clinical treatment of COPD with corticosteroids and antibiotics improved lung function concomitant with elevated circulating adiponectin levels and a decrease in systemic inflammatory markers such as IL-6 and TNF $\alpha$  (Krommidas et al., 2010). Note, it is possible that the increased adiponectin levels may result from diminished IL-6 and TNF $\alpha$  after treatment. Adiponectin knockout mice exhibited progressive alveolar enlargement and endothelial cell apoptosis, which was attenuated by adenoviral administration of adiponectin (Nakanishi et al., 2011). Continuous infusion of adiponectin via subcutaneously implanted osmotic pumps to replenish decreased levels was found to attenuate ovalbumin-induced airway inflammation in mice through the attenuation of inflammatory cell influx, corresponding with a reduction in IL-13 and IL-5 (Shore et al., 2006). Furthermore, chronic allergic airway inflammation and pulmonary vascular remodeling are also exacerbated in adiponectin deficient mice (Medoff et al., 2009; Nakagawa et al., 2009; Summer et al., 2009). Nevertheless, a double-blind randomized clinical trial found that asthmatic patients exhibited only a modestly beneficial effect in the late asthmatic response to inhaled allergen challenge after 28 days of rosiglitazone treatment to increase serum adiponectin levels (Richards et al., 2010).

Although the studies described above focused on endocrine effects of adiponectin, it is again important to consider the potential effects of locally produced adiponectin in the lung. Adiponectin was found to be localized to the murine pulmonary vascular endothelium under normal (Summer et al., 2009) or hypoxic (Nakagawa et al., 2009) conditions and bronchoalveolar fluid contained low levels of adiponectin (Summer et al., 2008). Adiponectin was overexpressed in the bronchoalveolar lavage (BAL) fluid of COPD patients and in a multimeric distribution profile differing from that found in serum (Zhu et al., 2010). Interestingly, these findings correlated with the increased localization of AdipoR1 to the airway epithelial cells of COPD patients (Miller et al., 2009).

## OTHERS

Numerous effects of adiponectin have been established in other peripheral tissues (Kadowaki et al., 2008), besides the obvious autocrine effects on adipocytes themselves (Wu et al., 2003). For example, the longstanding complication of nephropathy in obesity and diabetes has naturally led to studies on the pathophysiological role of adiponectin in this process (Chen et al., 2004; Srivastava, 2006; Stenvinkel, 2011). Increased circulating adiponectin levels are found in predialysis patients with end stage renal disease (ESRD; Shen et al., 2007; Stenvinkel, 2011) and adiponectin suggested to be a predictive factor for the progression of chronic kidney disease in men (Kollerits et al., 2007). General consensus

based on available literature indicates that adiponectin is renoprotective (Abe et al., 2010), for example via attenuating pathological progression toward renal fibrosis and glomerular hypertrophy (Ohashi et al., 2007). Even in the absence of a stressor, adiponectin deficient mice exhibited segmentally fused podocyte processes, increased albumin leakage into the urine (albuminuria), and kidney oxidant stress when compared to wild-type controls, while treatment with adiponectin reduced the degree of albumin permeability of a podocyte monolayer *in vitro* (Sharma et al., 2008).

Obesity is strongly associated with increased BMD due not only to the increased mechanical load, but also to adipocyte-derived hormonal factors mediating the cross-talk between adipocytes and bone (Confavreux et al., 2009). As such, there is accumulating and contradictory evidence indicating that adiponectin plays a role in bone maintenance and metabolism (Lenchik et al., 2003; Bozic et al., 2010; Barbour et al., 2011). Specifically, *in vitro*, adiponectin has been found to decrease osteoclast differentiation and bone-resorption activity (Oshima et al., 2005) via APPL1-mediated Akt1 suppression (Tu et al., 2011), while increasing osteoblast proliferation and differentiation via an AdipoR1 dependent p38-MAPK/JNK signaling pathway (Luo et al., 2005), suggesting that adiponectin positively influences bone growth. However, additional studies in adiponectin deficient or hyperadiponectinemic examining bone mass and fragility yielded some paradoxical observations (Oshima et al., 2005; Williams et al., 2009; Mitsui et al., 2011). Indeed, another study reported no abnormality in bone mass or turnover in adiponectin knockout mice or adiponectin transgenic mice overexpressing globular adiponectin (Shinoda et al., 2006). Interestingly, adiponectin has been found to be expressed by bone forming osteoblasts (Bernier et al., 2004; Shinoda et al., 2006) indicating a potential complex autocrine, paracrine, and endocrine role of adiponectin in mediating bone density.

Adiponectin also has centrally mediated effects, such as regulation of food intake and energy expenditure (Qi et al., 2004; Kadowaki et al., 2008). Although adiponectin was reportedly unable to cross the blood brain barrier (Spranger et al., 2006), it was found in the cerebrospinal fluid of rats (Qi et al., 2004) and humans (Neumeier et al., 2007) although at significantly lower levels and with different oligomeric profile than that in peripheral circulation (Ebinuma et al., 2007). Adiponectin mRNA expression and localization within the CNS has now been shown (Rodriguez-Pacheco et al., 2007; Psilopanagiotti et al., 2009). Several studies have documented the functionality of adiponectin (Rodriguez-Pacheco et al., 2007) *in vitro*, and through

intracerebral injection (Hoyda et al., 2009a; Iwama et al., 2009; Park et al., 2011), and also central expression of adiponectin receptors (Hoyda et al., 2009b).

## ADIPONECTIN ACTION AS A THERAPEUTIC TARGET

The rationale for targeting adiponectin is based on the well documented beneficial physiological actions of adiponectin spanning diabetes, inflammation, cardiovascular diseases, and cancer and it is expected that studies in animal models will translate well to human physiology in the case of adiponectin (Mao et al., 2006b; Zhu et al., 2008; Shetty et al., 2009; Wang et al., 2009c; Marette and Sweeney, 2011). Adiponectin-based therapeutics would have potentially wide-ranging applications in markets with widespread demographics. In diabetes alone there are still significant unmet therapeutic needs despite an annual global market value of around \$30 billion. Synthesis and administration of recombinant forms of adiponectin is generally not a viable therapeutic approach due to the cost of synthesizing correctly posttranslationally modified bioactive forms and the disadvantage of the route of administration, although the recombinant globular domain of adiponectin is in pre-clinical trials for Merck and Protomix have a highly glycosylated form of adiponectin in pre-clinical trials. There are several reports of compounds which increase adiponectin expression and secretion, although these increases tend to be very modest at non-supra-physiological doses (Zhu et al., 2008). The commonly prescribed TZD class of anti-diabetic agents act at least in part via elevating adiponectin (Pajvani et al., 2004; Kubota et al., 2006; Li et al., 2010). A more attractive therapeutic option would be the discovery of small molecule compounds which mimic or enhance adiponectin action. Presently, a small molecule adiponectin-mimetic developed by Rigel Pharmaceuticals that improves insulin sensitivity in a diabetic mouse model is in pre-clinical development and Kadowaki's group have also identified such a compound. However there are no potent and specific adiponectin-based therapeutics which are clinically available yet. Based on the information in this review article it is interesting to consider the future possibility of combining adiponectin-based therapeutics with tissue- or cell-specific delivery approaches.

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