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The multifaceted and controversial immunometabolic actions of adiponectin

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Adiponectin, one of the most abundant adipose-derived hormones, has variable actions in many tissues and organs. Although principally known for its insulin-sensitizing activity, recent data also highlight its homeostatic function, which is mediated both by direct actions on metabolic cells and indirectly through immunomodulatory effects on immune cells. Here we review the multifaceted immunometabolic actions of adiponectin and attempt to unify some of the contradictory reports on adiponectin function in inflammatory processes. We propose that a holistic understanding of adiponectin function can be garnered only from understanding its actions both on the immune system and on metabolism.

Introduction

Adiponectin is well recognized for the important role it plays in metabolic diseases. Most of the beneficial properties of this protein are attributed to its insulin-sensitizing and anti-inflammatory effects, despite evidence that it might increase inflammation in some contexts [1–3]. Here we discuss how the homeostatic functions of adiponectin are mediated by its direct actions on metabolic cells and also indirectly through immunomodulatory effects on immune cells. We attempt to unify contradicting reports in the literature on the biological function of adiponectin by integrating a breadth of current knowledge that encompasses immunology and metabolism.

Fundamentals of adiponectin and its receptors

Adiponectin

Adiponectin, also known as 30-kDa adipocyte complement-related protein (ACRP30), is an adipokine produced by adipocytes that plays important roles in glucose and lipid homeostasis and in insulin sensitivity [4]. Its genomic locus maps to chromosome 3q27, which is also a susceptibility site for early-onset diabetes and the metabolic syndrome [5]. Adiponectin exists as the full-length protein (fAd) or a proteolytic cleavage fragment known as globular adiponectin (gAd). Once synthesized, adiponectin forms trimers [low molecular weight (LMW)] that oligomerize to form hexameric middle molecular weight (MMW) and high molecular weight (HMW) forms. The HMW form appears to have the strongest insulin-sensitizing activity in hepatocytes [6].

The mRNA expression of adiponectin is reduced in obese and diabetic mice [7] and plasma protein levels are lower in obese compared with lean humans [8]. Adiponectin levels also inversely correlate with insulin resistance in mouse models of altered insulin sensitivity [9]. For example, in lipodystrophic mice, insulin resistance can be completely reversed by a combination of physiological doses of recombinant adiponectin and leptin but only partially by either adiponectin or leptin alone, attesting to the complex multifaceted regulation of insulin sensitivity [9]. Adiponectin is also effective in ameliorating hepatomegaly, steatosis, and alanine aminotransferase abnormalities in obese *ob/ob* mice. These therapeutic effects are partly related to the ability of adiponectin to enhance liver fatty acid (FA) oxidation and to suppress hepatic tumor necrosis factor alpha (TNFα) production [10].

Adiponectin receptors

Adiponectin acts via three receptors: AdipoR1, AdipoR2, and T-cadherin, the latter of which is to date known to have ligand-binding properties only. Mouse AdipoR1 encodes a protein of 375 amino acids with a predicted molecular mass of 42.4 kDa, whereas mouse AdipoR2 encodes a protein of 311 amino acids with a predicted molecular mass of 35.4 kDa. AdipoR2 shares 67% amino acid homology with AdipoR1 [11]. AdipoR1 and AdipoR2 are integral signaling membrane proteins with seven transmembrane domains that lack significant homology with other mammalian proteins, but are distantly related to other G protein-coupled receptors [12]. AdipoR1 is ubiquitously expressed, with the most abundant expression in skeletal muscle, whereas AdipoR2 is prominently expressed in the liver [12]. AdipoR1 has a high affinity for gAd and a low affinity for fAd, whereas AdipoR2 has intermediate affinity for both forms of adiponectin [12]. In mouse liver, AdipoR1 promotes AMP-activated protein kinase (AMPK) activation, whereas AdipoR2 mediates activation of peroxisome

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proliferator-activated receptor alpha (PPARα), both of which are involved in FA oxidation [13]. The HMW and hexameric forms of adiponectin, but not the trimer or globular forms, bind to T-cadherin expressed on endothelial and smooth muscle cells. The functional significance of this interaction is not completely defined [14].

In the normal liver, T-cadherin is present on the endothelial cells of large blood vessels and on myofibroblasts. It is also weakly expressed in the sinusoidal endothelial cells of the liver, but is not expressed by hepatocytes or Kupffer cells [15,16]. It has been reported that intraperitoneal injection of recombinant adiponectin in AdipoR1 and AdipoR2 double-knockout (KO) mice can induce inhibitor of nuclear factor kappa B (IκBα) degradation and interleukin-6 (IL-6) production in perigonadal white adipose tissues. Further investigations revealed that the IL-6 was produced in the stromal vascular fraction (SVF) of adipose tissue and IL-6 immunostaining demonstrated macrophages as the source of the IL-6. Because macrophages do not express T-cadherin, the existence of other adiponectin receptors has been suggested (Figure 1), but this remains to be proven [16].

Adiponectin, adiponectin receptors, and insulin sensitivity

The principal role of adiponectin in the liver is to promote insulin sensitivity, which may be mediated through multiple pathways (Figure 1). Berg *et al.* [17] demonstrated that, in wild type (WT) C57BL6J, *ob/ob*, nonobese diabetic, and streptozotocin-treated mice, in the basal state with low insulin concentrations, intraperitoneal injection of recombinant fAd but not globular adiponectin decreases blood glucose levels. This reduction of blood glucose in the postabsorptive state (low insulin levels) was related to the suppression of hepatic glucose production (HGP) and not mediated by muscle or adipose tissue glucose disposal. The latter effect appears to require higher insulin concentrations. Likewise, in isolated primary rat hepatocytes, 1–5 μg/ml of recombinant adiponectin, which is close to the normal range in serum (5–15 μg/ml), suppressed HGP in the presence of low concentrations of insulin (35 pM). Neither insulin nor adiponectin alone at these concentrations demonstrated any significant effect on HGP. On the basis of these physiological effects, the authors suggested that slight increases in adiponectin might have a strong insulin-sensitizing effect [17]. Other studies also support the notion that adiponectin reduces blood glucose by suppressing HGP without effects on hepatic glucose uptake or disposal [18]. It is noteworthy that the effect on liver is isoform specific, because only fAd reduces the activity of enzymes involved in hepatic gluconeogenesis.

Kadowaki *et al.* have demonstrated that adenovirus-mediated overexpression of AdipoR1 in the liver of leptin

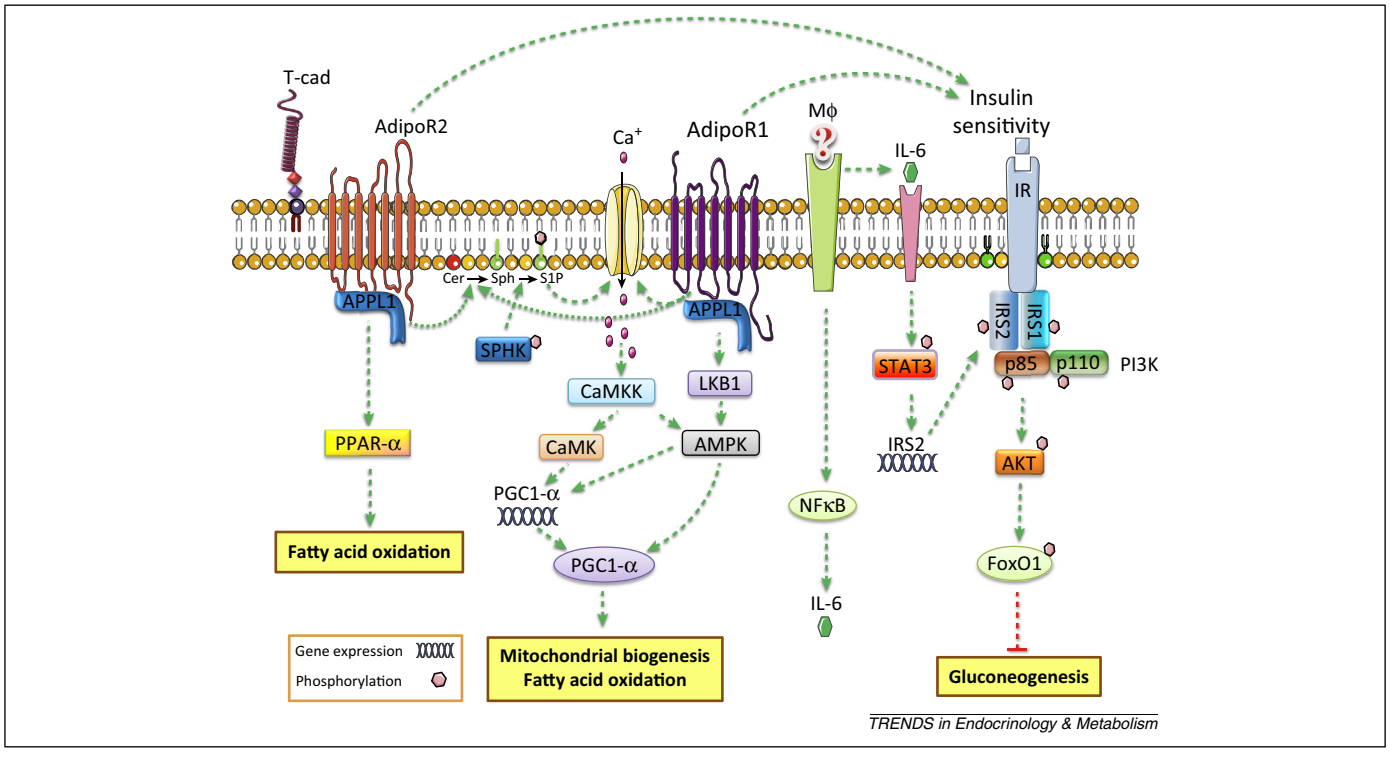

Figure 1. Adiponectin signaling. Adiponectin has three known receptors: AdipoR1, AdipoR2, and T-cadherin (T-cad). AdipoR1 and AdipoR2 are seven-transmembrane receptors, whereas T-cad does not have an intracellular domain. AdipoR1/2 can interact with adaptor protein containing pleckstrin homology domain, phosphotyrosine-binding domain, and leucine zipper motif (APPL1), which together with AKT and phosphoinositide 3-kinase (PI3K) increases insulin sensitivity [19]. AdipoR1 increases calcium influx to activate Ca^{2+}/calmodulin-dependent protein kinase kinase (CaMKK) and subsequent downstream kinases. Ca^{2+}/calmodulin-dependent protein kinase (CaMK) and AMP-activated protein kinase (AMPK) can increase peroxisome proliferator-activated receptor (PPAR) gamma coactivator 1 alpha (PGC-1α) mRNA expression. PGC-1α increases mitochondrial biogenesis and fatty acid (FA) oxidation. AdipoR1 activates liver kinase B1 (LKB1) and AMPK. AdipoR2 is predominantly expressed in the liver and can activate PPARα to increase FA oxidation and insulin sensitivity. AdipopR1/2 also has ceramidase activity and can catalyze the conversion of ceramide (Cer) to sphingosine, which can be phosphorylated by sphingosine kinase 1 (SPHK1) to produce sphingosine-1-phosphate (S1P). S1P has insulin-sensitizing and antiapoptotic properties and is involved in increasing calcium flux to cells. At least in macrophages, an unknown adiponectin receptor has been suggested that through fAd stimulation can activate nuclear factor kappa B (NFκB) to increase interleukin-6 (IL-6) and subsequently insulin receptor substrate 2 (IRS2) mRNA expression in hepatocytes through signal transducer and activator of transcription 3 (STAT3) activation [16]. Insulin-stimulated FoxO1 phosphorylation through PI3K and AKT can reduce hepatic gluconeogenesis. Figure prepared using templates on the Servier medical art website (http://www.servier.fr/servier-medical-art).