METABOLIC MESSENGERS
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Metabolic Messengers: adiponectin

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Adiponectin, first described in the mid-1990s, is one of the most widely studied adipokines to date. Studies of its regulation, biogenesis and physiological effects have yielded great insight and improved understanding of the mechanisms that ensure systemic metabolic homeostasis. Here, we provide a brief overview of the current state of the adiponectin field, describing adiponectin's history, sites and mechanisms of action, and the critical questions that must be addressed in the future.

Produced and secreted predominantly by fat cells in adipose tissue, adiponectin exerts pleiotropic effects on numerous tissues, including the liver[1,2], kidney[3], pancreatic β-cells[4], blood vessels[5], brain[6], bone[7] and immune cells[8], before its clearance in hepatocytes[9]. The adiponectin gene and protein have been extensively studied over decades in almost 20,000 publications. It would be an overwhelming task to summarize all the published data regarding adiponectin in a short overview. We will therefore limit ourselves to a brief synopsis of the history of the discovery of adiponectin, the regulation of its production and the critical effects on its target cells and tissues[10–12].

The discovery of adiponectin's function

In 1995, a subtractive cloning approach targeted at enriching cDNAs present in 3T3-L1 adipocytes (compared with 3T3-L1 fibroblasts) led to the identification of the gene encoding adipose complement-related protein of 30 kDa (Acrp30)[13] (Fig. 1). Shortly thereafter, other groups independently cloned the same gene through other approaches and referred to its product as AdipoQ[14], apM1 (ref. [15]) or GBP28 (ref. [16]). A consensus name, adiponectin, subsequently emerged, as proposed by Matsuzawa and colleagues[17].

Adiponectin contains four major domains, including an amino-terminal signal-peptide domain, a hypervariable domain, a collagenous domain and a carboxy-terminal globular domain[18]. After the structure of adiponectin's globular domain was solved, an unexpected structural homology with protein members of the tumour necrosis factor (TNF) family became apparent[19], which could not have been predicted on the basis of the primary amino acid sequence.

Several congenital genetic deletions of the adiponectin gene have been reported in rodents. Adiponectin-knockout mice display a deterioration of insulin sensitivity after feeding of chow or high-fat diets[20,21]. In contrast, one group has reported only a rather moderate phenotype, which in some aspects contradicts the previous findings[22]. The phenotype of an inducible adipose-tissue-specific knockout allele has recently been documented; this phenotype is largely consistent with the original diabetic phenotypes apparent in the congenital systemic knockout mice, albeit even more pronounced[23]. Collectively, these findings suggest that compensatory mechanisms may mask the phenotype when mice lack adiponectin during development. In several different genetically obese and diabetic mouse models, injecting adiponectin can improve diabetic symptoms, primarily by improving lipid homeostasis[1,2]. Importantly, these potent gluco- and lipo-regulatory effects of adiponectin are conserved among mice, non-human primates and humans[24,25].

A major breakthrough in the study of the molecular mechanism of adiponectin action was accomplished when Yamauchi and colleagues discovered the genes *Adipor1* and *Adipor2*, encoding adiponectin receptors 1 and 2 (ref. [26]), which are strongly conserved between rodents and humans. Congenital deletions of *Adipor1* and *Adipor2* disrupt the main adiponectin signalling events in target cells[27], thereby leading to insulin resistance and glucose intolerance. In contrast, the adiponectin receptor (AdipoR) agonist AdipoRon improves diabetes symptoms[28]. The crystal structure of the human AdipoR reveals that the seven transmembrane-spanning domains of ADIPOR1 and ADIPOR2 form a cavity that directs three histidine residues to coordinate a zinc ion. However, the structure of these AdipoRs is distinct from that of G-protein-coupled receptors, because the N terminus is cytoplasmic, and the C terminus is extracellular[29]. A more refined structural analysis has revealed a ceramidase domain present within the receptors[30], thus confirming previous reports demonstrating potent ceramide-lowering effects associated with adiponectin action[31,32]. In fact, the anti-apoptotic and anti-lipotoxic effects of adiponectin on cardiac myocytes and pancreatic β-cells, in addition to its insulin-sensitizing properties in hepatocytes, are related to the ceramidase activity that adiponectin triggers within target cells[31].

Adiponectin in disease

Clinical studies have implicated adiponectin as a possible causative factor in the aetiology of multiple diseases. In 1999, adiponectin drew much attention as the first (and, to date, only) adipocyte-derived marker in plasma that shows an inverse correlation with fat mass[17] (Fig. 1), thus distinguishing it from all other adipose-secreted cytokines (adipokines, including leptin), which display a positive correlation with fat mass[33]. Numerous studies have further established inverse correlations between plasma adiponectin and several clinical pathophysiological disease states, such as type 2 diabetes, both prospectively and cross-sectionally[34,35], as well as coronary artery disease[36] and myocardial infarction[37].

Beneficial actions of adiponectin have also been directly shown in rodent models, and it has become apparent that an increase in adiponectin levels may be therapeutically useful[38]. One highly effective approach to increasing the circulating levels of adiponectin is through exposure to the anti-diabetic class of agents referred to as thiazolidinediones (TZDs), agonists of the transcription factor peroxisome proliferator activated receptor γ (PPARγ). In fact, the anti-diabetic actions of TZDs critically depend on their ability to induce adiponectin[1]. Similar effects of TZDs have also been observed in clinical studies[39].

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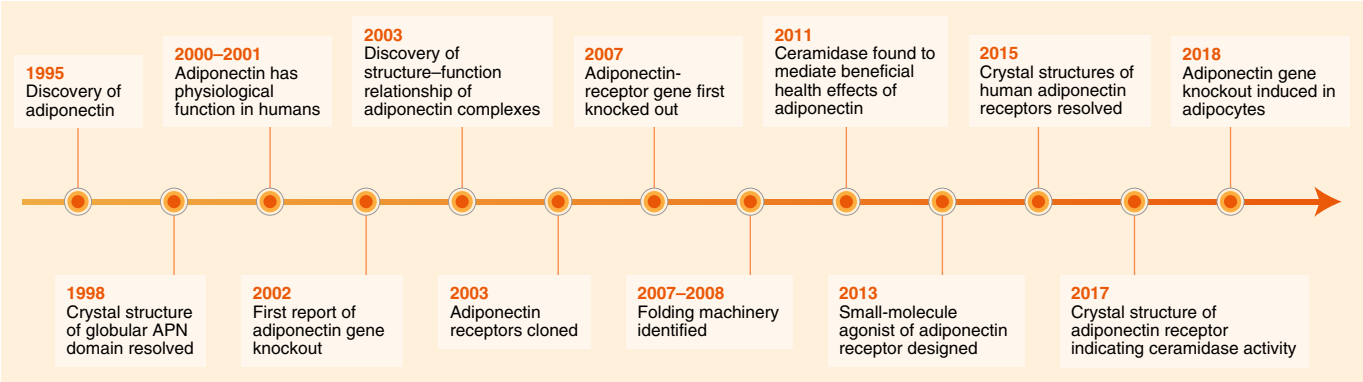

Fig. 1 | Timeline of the discovery of adiponectin. After the discovery of adiponectin in 1995, adiponectin's physiological function in humans soon became apparent (2000–2001). Its receptor was discovered in 2003, and important signalling pathways were established. Not only were the genetic deletions of both adiponectin (2002 and 2018) and its receptors ADIPOR1 and ADIPOR2 (2007) described, but the pleiotropic effects of adiponectin were shown to be mediated by ceramidase function. The small molecule AdipoRon was the first reported AdipoR agonist (2013). The initial crystal structure of the AdipoR published in 2015 was further refined in 2017, thus revealing an active site suggesting an enzymatic function consistent with a ceramidase activity within the receptor itself.

A high degree of local fibrosis and inflammation is at the root of metabolic disorders of insulin resistance. These detrimental effects go hand in hand with a substantial decrease in adiponectin production and secretion. As such, circulating levels of adiponectin can serve as a critical marker of adipose tissue health and reflect the tissue's overall metabolic flexibility during metabolic perturbations. Whereas healthy adipose tissue secretes more adiponectin[40], unhealthy adipose tissue, as in the case of fibrotic or inflamed adipose tissue, secretes less adiponectin. Adiponectin is widely thought to be the major hormonal factor mediating the beneficial health effects of adipose tissue, because genetically driven upregulation of circulating adiponectin levels can effectively offset any negative consequences of obesity[41].

Adiponectin as a marker gene for mature adipocytes

Adiponectin is also an excellent marker gene distinguishing mature adipocytes from other cell types. Whereas the gene regulatory elements of *Fabp4* (also known as *aP2*) mediate the gene expression pattern in macrophages[42], endothelial cells[43] and adipocyte precursors[44], adiponectin-regulatory regions, in contrast, display greater selectivity for mature adipocytes. However, despite its high selectivity for mature adipocytes, adiponectin has also been identified in cell types other than adipocytes, albeit at much lower levels and only under specific conditions. These additional cell types include cardiomyocytes[45], quiescent hepatic stellate cells[46,47] and specific subsets of kidney cells[48]. Developmentally, the messenger RNA for adiponectin can be detected as early as 15–17 days of gestation[49], primarily during the development of the inguinal fat pad. This key finding can be exploited to generate mouse models with gene products eliminated exclusively in the inguinal fat pad, through transient activation of adipocyte-specific inducible Cre models in utero that maintain their knockout phenotype for the rest of the rodent's life, owing to low turnover of inguinal adipocytes[50].

Human adiponectin gene regulatory elements have been systematically studied and shown to be conserved between humans and mice[51]. The most important regulatory sequences within the adiponectin gene[49] can be combined within a 5.4-kilobase transgenic cassette used to drive expression of various constructs in a mature-adipocyte-specific fashion[52]. To date, ample in vitro evidence has indicated the key transcription factors that regulate adiponectin gene expression[53–56]. In fact, PPARγ-agonist treatment has been shown to increase adiponectin transcription both in vitro and in vivo[57]. Insulin has also been demonstrated to regulate adiponectin levels[58,59]. At the protein level, adiponectin is multimerized within the secretory pathway of the adipocyte. As such, the protein is secreted in multimeric forms, and multimerization is heavily dependent on post-translational modifications[60,61]. The smallest form of secreted adiponectin is a trimer, the intermediate form is a hexamer, and a high-molecular-weight form with 12–18 subunits also exists. The different multimers have varying binding affinities for the AdipoRs, and their effects on a particular target tissue depend on the receptor and specific multimer bound to the receptor[62]. Specifically, the high-molecular-weight form has been shown to be a better correlate to insulin sensitivity than any of the other lower-molecular-weight forms, at least under some circumstances[63].

The key sites of adiponectin action

Circulating adiponectin has a plethora of effects on many different target tissues by signalling through its receptors (Fig. 2). The overexpression of either AdipoR (ADIPOR1 or ADIPOR2) in hepatocytes or adipocytes results in a potent insulin-sensitizing and anti-lipotoxic phenotype[64]. Importantly, such effects have not been observed after overexpression of the receptors in an adiponectin-null background, thus further substantiating a ligand–receptor interaction between adiponectin and its receptors[64]. In terms of endogenous regulation, under fasted conditions, transcription of both *Adipor1* and *Adipor2* is upregulated ubiquitously, whereas refeeding has the opposite effect[65]. With respect to additional potential receptors, T-cadherin is another molecule with affinity for adiponectin[66], and it may serve as a co-receptor. T-cadherin itself is a cell-surface glycoprotein with a glycosylphosphatidylinositol anchor that lacks signalling capacity, because it contains neither a transmembrane nor a cytoplasmic signalling domain[67]. The tissue distribution of T-cadherin—also called CDH13 in humans—overlaps widely with that of the AdipoRs[68]. Interestingly, a genetic deletion of T-cadherin leads to an accumulation of adiponectin in circulation[69], a phenomenon not observed for the individual AdipoR deletions.

Adiponectin's main functions can be categorized as anti-apoptotic, anti-inflammatory/anti-fibrotic and insulin sensitizing. Although the key sites of adiponectin's action are the adipose tissue, heart, kidney, liver and pancreas, the ubiquitous expression of the AdipoRs suggests that the beneficial effects exerted by adiponectin are not restricted to a limited number of tissues (Fig. 2).

The anti-apoptotic effects of adiponectin are considerable. When cells are genetically programmed to die by activation of caspase 8, adiponectin powerfully exerts anti-apoptotic activity in diverse

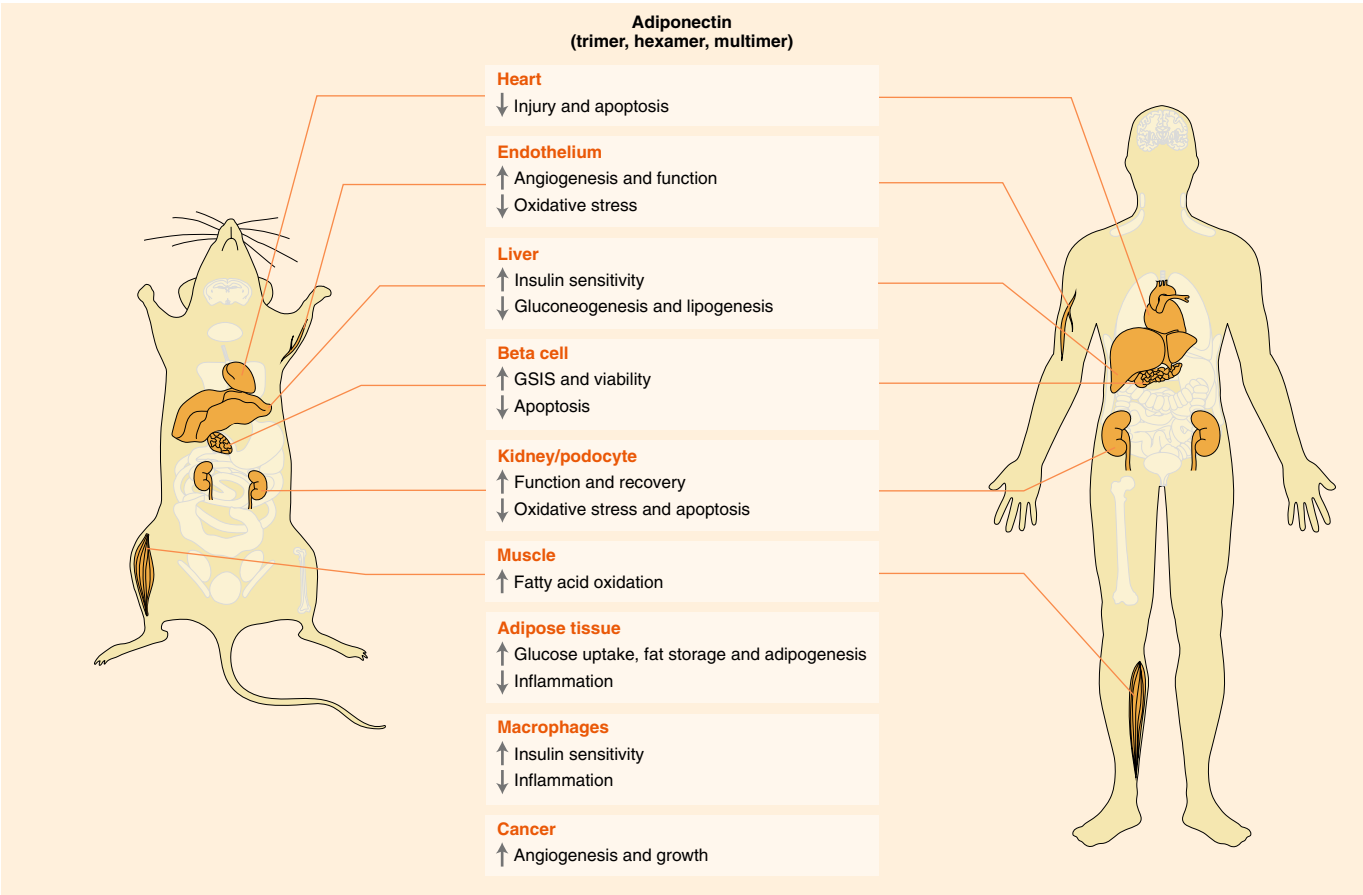

Fig. 2 | Target tissues and biological activity of adiponectin. Both adiponectin and its receptors are highly conserved between mice and humans. Most observations have been made in rodents but are supported by strong clinical correlational data. The physiological effects of adiponectin are therefore strongly preserved between rodents and humans. Adiponectin forms higher-order structures through multimerization. The high-molecular-weight multimer of adiponectin is the most biologically active form, targeting a diverse set of tissues and cell types and regulating important metabolic processes. Adiponectin's effects range from anti-inflammatory and anti-apoptotic to insulin sensitizing. GSIS, glucose-stimulated insulin secretion.

cells, such as in cardiomyocytes and pancreatic β-cells[31]. An important question is whether adiponectin could possibly trigger the formation of cancer lesions. This possibility is unlikely, because adiponectin is the only adipose-tissue-secreted factor with an inverse correlation with obesity, whereas obesity significantly elevates cancer risk[70,71]. In breast cancer, the anti-metastatic effects of adiponectin have been attributed to the inhibition of adhesion, invasion and migration of cancer cells, processes regulated through the AMPK–S6K cell signalling axis[72]. Adiponectin's pro-angiogenic effects can, however, lead to enhanced tumour growth, but this effect is limited to already established tumors[73,74]. As a member of the C1q/TNF superfamily, adiponectin not only shows structural homology to the cytokine TNFα but also acts on the immune system and the bone marrow[75]. Unlike TNFα, adiponectin antagonizes inflammation by reprogramming immune cells[8]. For example, adiponectin can shift Kupffer cells and other macrophages towards an anti-inflammatory phenotype[76,77].

The actions of adiponectin as an anti-fibrotic factor are seen in many tissues, particularly in the liver, kidney and adipose tissue itself. Elevated adiponectin levels protect against hepatic and kidney fibrosis[78]. Furthermore, skin fibrosis decreases as a consequence of increased adiponectin levels, whereas the absence of adiponectin exaggerates dermal fibrosis[79]. Tissue regeneration is another key role that adiponectin exerts systemically[3]. Podocytes are key functional constituents in the kidney. Whereas podocyte ablation in adiponectin-deficient mice causes irreversible renal failure, the overexpression of adiponectin leads to a rapid recovery of kidney function. These regenerative effects extend to several other tissues, including pancreatic β-cells, in which adiponectin supports β-cell reconstitution after apoptotic insult[4].

Insights into AdipoR signalling explain how adiponectin can maintain this broad range of effects (Fig. 3). Effects on ceramide turnover constitute the most receptor-proximal signalling events of the AdipoRs[30,31,80]. AdipoRs have been co-crystalized with a ceramide moiety. The receptor's structure has a strong similarity to the seven-transmembrane alkaline ceramidases[81]. In ceramidase-deficient yeast, the human AdipoR promotes ceramidase activity[82]. Ceramidases deacetylate ceramide to sphingosine, which in turn can be phosphorylated by sphingosine kinase to sphingosine-1-phosphate (S1P)[83]. An increased S1P/ceramide ratio potently inhibits apoptosis and even induces proliferation. Treatment with S1P or its pharmacological mimetic FTY720 rescues apoptosis-prone cells[31]. The actions of the AdipoRs lead to an increase in S1P, thereby activating the S1P receptors (S1PRs). Downstream of S1PRs, the heterotrimeric G protein $G_{\alpha q}$ mediates AdipoR-triggered calcium signalling by inducing phospholipase C (PLC) function. One of the products of PLC is inositol (1,4,5)-trisphosphate (IP_3), the ligand of the IP_3 receptor. This signal elicits Ca^{2+} release from the endoplasmic reticulum. Insulin-resistant livers display a dysregulated lipogenesis that eventually leads to lipotoxicity. Insulin sensitivity is affected by hepatic AdipoR signaling[1]. Because high ceramide concentrations can inhibit insulin signaling[84], the decreased hepatic

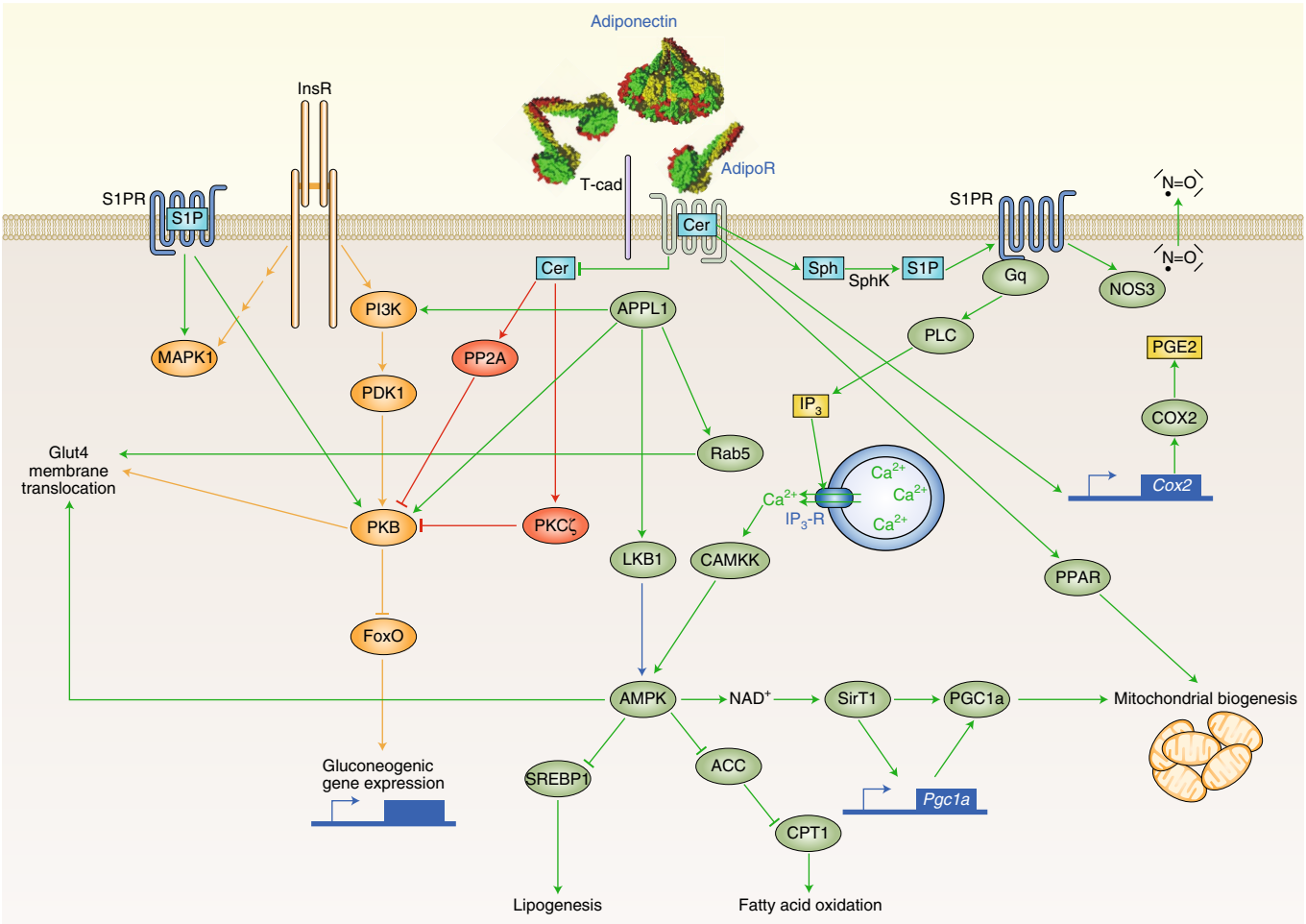

Fig. 3 | Downstream signalling cascade of AdipoRs. Adiponectin binds the AdipoR, and its binding may be enhanced by T-cadherin. AdipoR signalling targets the cellular metabolic pathways through regulation of mitochondrial biogenesis, lipogenesis and fatty acid oxidation. AdipoR signalling (green) interfaces with insulin-receptor (InsR) signalling (orange), which is mediated by sphingosine-1-phosphate receptor (S1PR) and ceramide (Cer). High ceramide levels suppress insulin signalling mainly through the inactivation of serine/threonine protein phosphatase 2A (PP2A). By hydrolysing ceramide to sphingosine (Sph), AdipoR decreases ceramide levels that de-repress PKB via protein kinase C ζ (PKCζ). De-repressed PKB inhibits forkhead box O (FoxO) and thereby downregulates gluconeogenic gene expression. Sphingosine can be phosphorylated to sphingosine-1-phosphate (S1P), which activates S1PR, which in turn induces the downstream mediators of InsR signalling MAPK1 and PKB. S1PR also initiates a PLC-mediated IP_3-downstream signal that triggers Ca^{2+}, thereby resulting in activation of AMPK by Ca^{2+}/calmodulin-dependent protein kinase (CAMKK). AMPK spreads the signal across many downstream factors, for example, SirT1, SREBP1 and acetyl-CoA carboxylase (ACC). AdipoR also induces PPARs through a yet-to-be-elucidated pathway. The localization of glucose transporter to the plasma membrane is affected by Rab5, AMPK and PKB. The scaffold protein APPL1 binds important signalling mediators and thereby contributes to the cross-talk of AdipoR and InsR as well. The AdipoR also regulates the expression of COX2, which produces prostaglandin E2 (PGE2). Activation of nitric oxide synthase 3 (NOS3) by S1PR induces nitric oxide production downstream of the AdipoR.

ceramide concentrations revert insulin resistance[85]. Ceramides act on the insulin signal-transduction cascade at several distinct levels, inhibiting protein kinase B (PKB) by activating protein kinase C ζ and protein phosphatase 2 A[85]. In agreement with this model, AdipoR signalling mediates translocation of the glucose transporter Glut4 to the plasma membrane[86], thereby leading to an increase in glucose uptake in muscle and adipose tissue. The de-repression of PKB can lead to inhibition of forkhead box O family members, which positively regulate the gene expression of gluconeogenic enzymes such as glucose 6-phosphatase and phosphoenolpyruvate carboxykinase. In addition, the scaffold protein adaptor protein phosphotyrosine interacting with PH domain and leucine zipper 1 (APPL1) interacts with important signalling proteins and thereby potentially links AdipoRs with insulin-receptor signaling[87,88].

More downstream signalling events of the AdipoR include the Ca^{2+}/calmodulin-dependent protein kinase and AMP-activated protein kinase (AMPK) cascades[89]. Other aspects of adiponectin's anti-lipotoxic effects may be explained by enhanced fatty acid oxidation, which the receptors induce through enhanced activity of PPARα and PGC1α[90,91]. Adiponectin's main suppressive effects on lipogenesis in the liver are mediated by AMPK through inhibition of sterol regulatory element binding transcription factor 1 and acetyl-CoA carboxylase[26,92]. Beyond AMPK signalling, prostaglandin-endoperoxide synthase 2 (PTGS2 or COX2) can be regulated by AdipoRs and are involved in protecting the heart from ischemia–reperfusion injury[93].

Critical questions for future research

Several questions regarding adiponectin remain to be answered. The sheer abundance of adiponectin mRNA at any given time puts the spotlight on the study of how post-transcriptional mechanisms may regulate adiponectin secretion. How does the metabolic state

of the adipocyte, particularly with respect to the functional integrity of its mitochondria, affect adiponectin production? With respect to AdipoR signalling, the receptor's hydrolase activity might also affect other lipid substrates beyond the established action on ceramides. More generally, does the AdipoR hydrolase also act on other lipid species and potentially generate activating ligands for PPARs? What are the effects of adiponectin production and degradation on overall protein homeostasis? How does adiponectin expressed in the kidney, heart and hepatic stellate cells contribute to the physiological responses within these tissues? Finally, how is the secretion of adiponectin orchestrated with respect to that of other adipokines? Particularly with respect to leptin, would assessing the combined actions of adiponectin and leptin, rather than examining these factors individually, provide better insights into how these adipokines work? Finding answers to these critical questions will certainly provide new insights not only into adipose tissue physiology as a whole but also into the critical whole-body signalling axis that maintains systemic metabolic homeostasis during obesity and insulin resistance. The quest for AdipoR agonists has begun and promises to yield new pharmacological tools for anti-lipotoxic and anti-diabetic treatment regimens.

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Competing interests

The authors declare no competing interests.

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