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Metabolic Messengers: Adiponectin

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Abstract

Adiponectin is one of the most widely studied adipokines to date. First described in the mid-1990's, studying its regulation, biogenesis and physiological effects has proven to be extremely insightful and improved our understanding of the mechanisms that ensure systemic metabolic homeostasis. Here, we provide a brief overview of the current state of the field with respect to adiponectin, its history, sites and mechanisms of action, and the critical questions that will need to be addressed in the future.

Introduction

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], prior to its clearance in hepatocytes [9]. The gene encoding adiponectin and its protein product has 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 for cDNAs present in 3T3-L1 adipocytes (compared to 3T3-L1 fibroblasts), led to the identification of *A*dipose *C*omplement *R*elated *P*rotein of *30* kDa (*Acrp30*) (Fig. 1)[13]. Shortly thereafter, other groups independently cloned the same gene using other approaches, referring to it as AdipoQ [14], apM1 [15] or GBP28 [16]. A consensus name subsequently emerged, adiponectin, a name proposed by Matsuzawa and colleagues [17].

Adiponectin contains four major domains, including an N-terminal signal peptide domain, a hypervariable domain, a collagenous domain, and a carboxy-terminal globular domain [18]. Upon solving the structure of adiponectin's globular domain, an unexpected structural

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Competing Interests

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homology with protein members of the tumor necrosis factor family became apparent [19], which could not have been predicted based on the primary amino acid sequence.

Several congenital genetic deletions of the adiponectin gene were reported in rodents. Adiponectin knockout (KO) mice displayed a deterioration of insulin sensitivity upon feeding of chow or high-fat diets [20,21]. Conversely, one group reported only a rather moderate phenotype, which in some aspects contradicted the previous findings [22]. The phenotype of an inducible adipose tissue-specific KO allele was recently documented, which was very much consistent with the original diabetic phenotypes apparent in the congenital systemic KO mice, albeit even more pronounced [23]. Collectively, this suggests that some of the compensatory mechanisms may mask the phenotype when mice are missing adiponectin developmentally. 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 between 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 of the adiponectin receptors 1 and 2 (*Adipor1* and *Adipor2*) [26]. Between rodents and humans, the receptors are strongly conserved. Congenital deletions of *Adipor1* and *Adipor2* resulted in a disruption of the main adiponectin signaling events in target cells [27], thereby leading to insulin resistance and glucose intolerance. On the other side the ADIPOR agonist- called AdipoRon- improves diabetic symptoms [28]. The crystal structure of human ADIPORs revealed that the seven transmembrane spanning domains of ADIPOR1 and 2 form a cavity that directs three histidine residues to coordinate a zinc ion. The structure of these adiponectin receptors is however distinct from G-protein coupled receptors (GPCRs), as the N-terminus is cytoplasmic and the C-terminus is extracellular [29]. A more refined structural analysis revealed a ceramidase domain present within the receptors [30], 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 on hepatocytes, relate 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 etiology of multiple diseases. In 1999, adiponectin drew much attention as the first (and so far only) adipocyte-derived marker in plasma that shows an inverse correlation with fat mass (Fig. 1) [17]; thus distinguishing it from all other adipokines (including leptin) which display a positive correlation with fat mass [33]. Numerous additional studies further established inverse correlations of plasma adiponectin with several clinical pathophysiological disease states, such as type 2 diabetes (T2D), both prospectively and cross-sectionally [34,35], as well as coronary artery disease [36] and myocardial infarction [37].

Beneficial actions of adiponectin were also directly shown in rodent models. It became apparent that an increase in adiponectin levels could be therapeutically useful [38]. One highly effective approach to increase the circulating levels of adiponectin is through the exposure to

the anti-diabetic class of agents referred to as thiazolidinediones (TZDs), which serve as agonists of the transcription factor peroxisome proliferator activated receptor γ (PPARγ). In fact, the anti-diabetic actions of these TZDs are critically dependent on their ability to induce adiponectin [1]. Similar effects of TZDs have also been observed in clinical studies [39].

A high degree of local fibrosis and inflammation are at the root of metabolic disorders of insulin resistance. These detrimental effects go hand-in-hand with a significant reduction in adiponectin production and secretion. As such, the circulating levels of adiponectin can serve as a critical marker of adipose tissue health and reflect the tissue's overall metabolic flexibility during metabolic pertubations. While 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 a genetically-driven upregulation of circulating adiponectin levels can effectively offset any negative consequences of obesity [41].

Adiponectin as marker gene for mature adipocytes

Adiponectin can also serve as an excellent marker gene to distinguish mature adipocytes from other cell-types. While the gene regulatory elements of *Fabp4* (also termed *aP2*) mediate the gene expression pattern in macrophages [42], endothelial cells [43] and adipocyte precursors [44], adiponectin regulatory regions on the other hand, display a greater selectivity for mature adipocytes. However, despite its high degree of 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], as well as specific subsets of kidney cells [48]. Developmentally, the mRNA 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 taken advantage of to generate mouse models that eliminate gene products exclusively in the inguinal fat pad, through transient activation of adipocyte-specific inducible Cre models *in utero* that maintain their knock out phenotype for the rest of the rodent's life due to low turn-over 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 kb transgenic cassette used to drive expression of various constructs in a mature adipocyte-specific fashion [52]. To date, there is an ample amount of *in vitro* evidence identifying 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 shown 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 upon post-translational modifications [60,61]. The smallest form of secreted adiponectin is a trimer, the intermediate form is a hexamer (LMW), as well as a high molecular weight (HMW) form with 12-18 subunits. The different multimers show varying binding affinities for the AdipoRs and their effects on a particular

target tissue depends on the receptor and specific multimer bound to the receptor [62]. Specifically, the HMW form has been shown to be a better correlate to insulin sensitivity, 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 signaling through its receptors (Fig. 2). The over-expression of either adiponectin receptor (ADIPOR1 or 2) in hepatocytes or adipocytes, results in a potent insulin sensitizing and anti-lipotoxic phenotype [65]. Importantly, such effects were not observed upon overexpression of the receptors in an adiponectin null background; further substantiating a ligand / receptor interaction between adiponectin and its receptors [65]. In terms of endogenous regulation, under fasted conditions, transcription of both *Adipor* genes is up-regulated ubiquitously, whereas refeeding has the opposite effect [66]. With respect to additional potential receptors, T-cadherin is another molecule with affinity for adiponectin [67], and thus may serve as a co-receptor. T-cadherin itself is a cell surface glycoprotein with a glycosylphosphatidylinositol anchor that lacks signaling capacity, because it neither contains a transmembrane nor a cytoplasmic signaling domain [68]. The tissue distribution of T-cadherin- also called CDH13 in humans- overlaps widely with that of the Adiponectin receptors [69]. Interestingly, a genetic deletion of T-cadherin leads to an accumulation of adiponectin in circulation [70], a phenomenon not observed for the individual adiponectin receptor 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 adipose tissue, heart, kidney, liver and pancreas, the ubiquitous expression of the adiponectin receptors suggests that the beneficial effects that adiponectin exerts 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 cells, such as in cardiomyocytes and in pancreatic β cells [31]. An important question is whether adiponectin could possibly trigger the formation of cancer lesions. This is unlikely, since adiponectin is the only factor secreted by the adipose tissue that shows an inverse correlation with obesity, while obesity significantly elevates cancer risk [71,72]. For breast cancer, the anti-metastatic effects of adiponectin have been attributed to the inhibition of adhesion, invasion and migration of cancer cells, which is regulated through the AMPK-S6K cell signaling axis [73]. Adiponectin's pro-angiogenic effects can however lead to enhanced tumor growth, but this effect is limited to already established tumors [74,75]. As a member of the C1q/TNF superfamily, adiponectin shows not only structural homology to tumor necrosis factor alpha (TNFα), but also acts upon the immune system and the bone marrow [76]. 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 [77,78].

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 from hepatic and kidney fibrosis [80]. Furthermore, skin fibrosis is reduced as a consequence of increased

adiponectin levels, while the absence of adiponectin exaggerates dermal fibrosis [81]. Another key role adiponectin exerts systemically is tissue regeneration [3]. Podocytes are key functional constituents in the kidney. While 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 where adiponectin supports β cell reconstitution after an apoptotic insult [4].

Insights into ADIPOR signaling explains how adiponectin can maintain this broad range of effects (Fig. 3). Effects on ceramide turnover constitutes the most receptor-proximal signaling events of the adiponectin receptors [30,31,82]. ADIPORs were co-crystalized with a ceramide moiety. The structure of ADIPOR reveals a strong similarity to the 7 transmembrane alkaline ceramidases (ACERs) [83]. In ceramidase-deficient yeast, the human ADIPOR can promote ceramidase activity [84]. Ceramidases deacetylate ceramide to sphingosine, which in turn can be phosphorylated by sphingosine kinase (SphK) to S1P [85]. An increased S1P:Ceramide ratio suffices to potently inhibit apoptosis and even induces proliferation. Treatment with S1P or its pharmacological mimetic FTY720 can rescue apoptosis-prone cells [31]. The actions of the adiponectin receptors lead to an increase in S1P, thereby activating the S1P receptors (S1PRs). Downstream of S1PRs, the heterotrimeric G-protein $G_{\alpha q}$ mediates the ADIPOR-triggered calcium signaling by inducing phospholipase C (PLC) function. One of the products of PLC is inositol (1,4,5) triphosphate (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 impacted by the hepatic ADIPOR signaling [1]. Since high ceramide concentrations can inhibit insulin signaling [86], the reduction of hepatic ceramide concentrations reverts insulin resistance [87]. Ceramides act on the insulin signal transduction cascade at several distinct levels, inhibiting protein kinase B (PKB) by activating protein kinase C ζ (PKCζ) and protein phosphatase 2A (PP2A) [87]. Consistent with this model, adiponectin receptor signaling mediates translocation of GLUT4 to the plasma membrane [88], 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 (FoxO's), which positively regulate gene expression of gluconeogenic enzymes such as G6Pase and PEPCK. In addition, APPL1 (adaptor protein phosphotyrosine interacting with PH domain and leucine zipper 1) is a scaffold protein that interacts with important signaling proteins and thereby potentially links ADIPOR with insulin receptor (INSR) signaling [89,90].

More downstream signaling events of the ADIPOR include the Ca^{2+}/calmodulin-dependent protein kinase (CAMKK) and AMP-activated protein kinase (AMPK) cascades [91]. 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 [92,93]. Adiponectin's main suppressive effects on lipogenesis in the liver are mediated by AMPK through inhibition of sterol regulatory element binding transcription factor 1 (SREBF1) and acetyl-CoA carboxylase (ACC) [26,94]. Beyond AMPK signaling, prostaglandin-endoperoxide synthase 2 (Ptgs2 or Cox2) can be regulated by ADIPORs and are involved in protecting the heart from ischemia-reperfusion injury [95].

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 mechanism 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 signaling, its hydrolase activity might also affect other lipid substrates beyond the established action on ceramides. More generally, does the ADIPOR hydrolase also act upon other lipid species and potentially generate activating ligands for PPARs? What is the impact of adiponectin production and its degradation on the overall protein homeostasis? How does adiponectin expressed in kidney, heart and hepatic stellate cells contribute to the physiological responses within these tissues? Finally, how is the secretion of adiponectin orchestrated with that of other adipokines? Particularly with respect to leptin, would the assessment of 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 us with new insights, not only into adipose tissue physiology as a whole, but also into the critical whole-body signaling axis that maintains systemic metabolic homeostasis during obesity and insulin resistance. The quest for adiponectin receptor agonists has begun and promises to yield new pharmacological tools for anti-lipotoxic and anti-diabetic treatment regimens.

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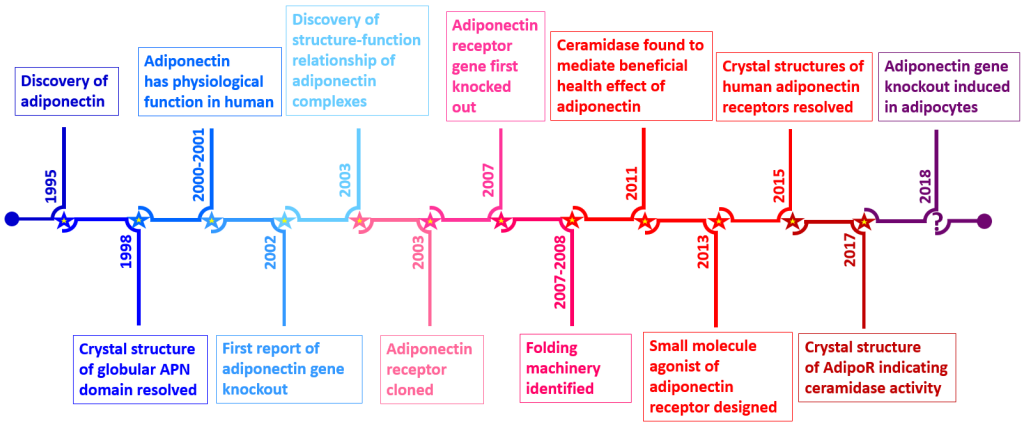

Figure 1: Timeline of the discovery of adiponectin

First discovered in 1995, adiponectin's physiological function in humans became soon apparent (2000-2001). Its receptor was discovered in 2003 and important signaling pathways were established. Not only were the genetic deletions of both adiponectin (2002 and 2018) and its receptors AdipoR1/2 (2007) published, but the pleiotropic effects of adiponectin was shown to be mediated by ceramidase function. The small molecule AdipoRon was the first AdipoR agonist (2013). The initial crystal structure of the AdipoR published in 2015 was further refined in 2017, which revealed that it contains an active site reminiscent of an enzymatic function consistent with a ceramidase activity within the receptor itself.

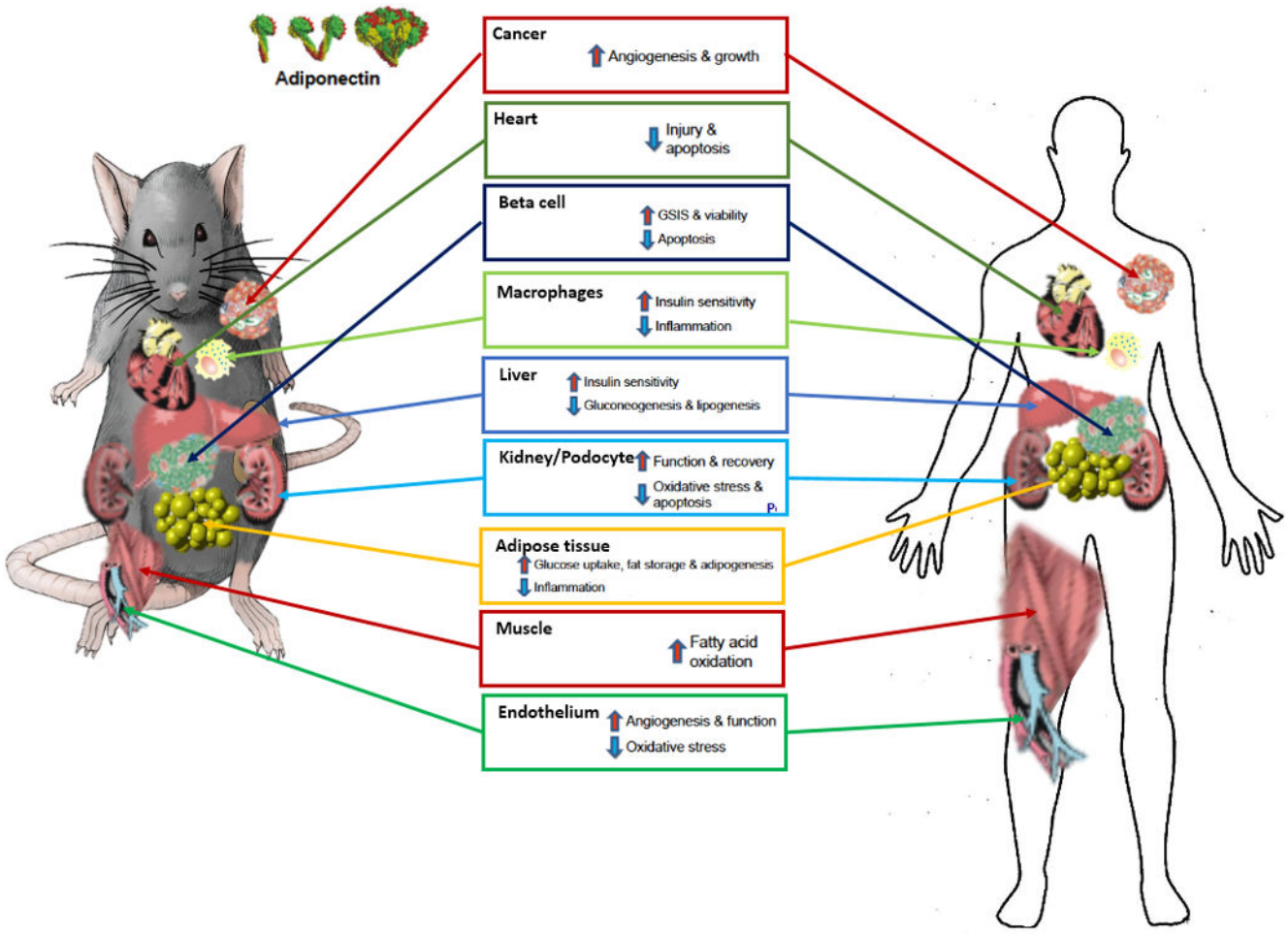

Figure 2: Target tissues and biological activity of adiponectin:

Both adiponectin as well as its receptors are highly conserved between mouse and human. Most observations were made in rodents, but are supported by strong correlational data in the clinic. 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 (HMW) 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.

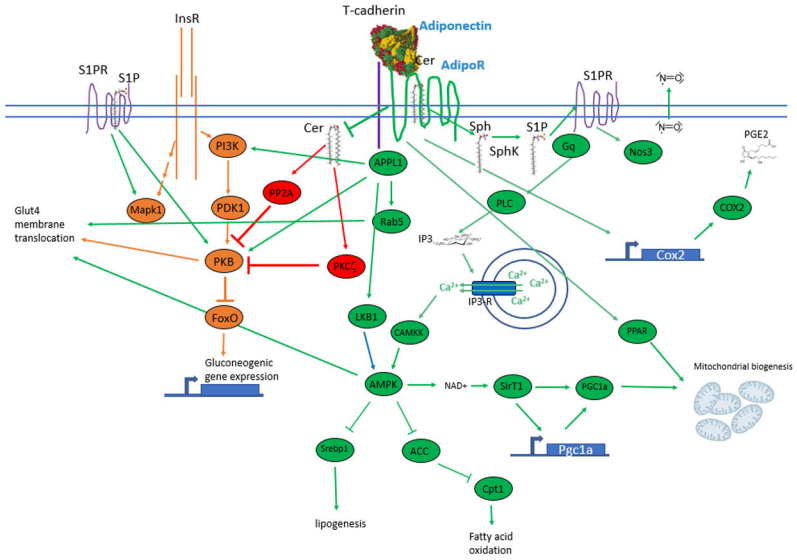

Figure 3: Downstream signaling cascade of AdipoRs:

Adiponectin binds to the AdipoR, and its binding may be enhanced by T-cadherin. AdipoR signaling targets the cellular metabolic pathways through regulation of mitochondrial biogenesis, lipogenesis and fatty acid oxidation. AdipoR signaling (green) interfaces with insulin receptor signaling (InsR) (orange), which is mediated by sphingosine-1-phosphate receptor (S1PR) and ceramide. High ceramide levels suppress insulin signaling mainly through the inactivation of serine/threonine protein phosphatase 2A (PP2A). By hydrolyzing Ceramide (Cer) to Sphingosine (Sph), AdipoR reduces Cer levels that de-repress PKB via PKCζ. De-repressed PKB inhibits FOXO and thereby downregulates gluconeogenic gene expression. Sph can be phosphorylated to sphingosine-1-phosphate (S1P) that activates S1PR which can induce the downstream mediators of InsR signaling Mapk1 and PKB. S1PR also initiates a PLC mediated IP3 downstream signal that triggers Calcium (Ca^{2+}) resulting in activation of AMPK by CAMKK. AMPK spreads the signal across many downstream factors e.g. SirT1, Srebp1 and ACC. AdipoR induces PPARs through a yet to be elucidated pathway. The localization of glucose transporter to the plasma membrane can be impacted by Rab5, AMPK and PKB. The scaffold protein APPL1 binds important signaling mediators and thereby contributes to the crosstalk of AdipoR and InsR as well. ADIPOR also regulates the expression of Cox2 that produces prostaglandin E2 (PGE2).