Adiponectin Increases Fatty Acid Oxidation in Skeletal Muscle Cells by Sequential Activation of AMP-Activated Protein Kinase, p38 Mitogen-Activated Protein Kinase, and Peroxisome Proliferator–Activated Receptor α

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Adiponectin has recently received a great deal of attention due to its beneficial effects on insulin resistance and metabolic disorders. One of the mechanisms through which adiponectin exerts such effects involves an increase in fatty acid oxidation in muscle and liver. In the present study, we demonstrate that 5′-AMP-activated protein kinase (AMPK) and p38 mitogen-activated protein kinase (MAPK) are involved in the activation of peroxisome proliferator–activated receptor (PPAR)α by adiponectin in muscle cells. Adiponectin increases the transcriptional activity of PPARα and the expression of its target genes, including ACO, CPT1, and FABP3 in C2C12 myotubes. These effects were suppressed by the overexpression of a dominant-negative form of AMPK. Moreover, chemical inhibitors of AMPK and p38 MAPK potently repressed fatty acid oxidation and the induction of PPARα target gene expression by adiponectin. Interestingly, araA, an AMPK inhibitor, prevented the activation of p38 MAPK, whereas SB203580, a p38 MAPK inhibitor, did not affect AMPK activation, suggesting that p38 MAPK is a downstream signaling factor of AMPK. Taken together, these results suggest that adiponectin stimulates fatty acid oxidation in muscle cells by the sequential activation of AMPK, p38 MAPK, and PPARα. Diabetes 55:2562–2570, 2006

A diponectin (also known as Acrp30, AdipoQ, and GBP28), an adipocytokine secreted by adipocytes, has been receiving a great deal of attention due to its insulin-sensitizing effects and possible therapeutic use for metabolic disorders (1–6). Accumulating evidence has suggested that a certain level of serum adiponectin is required to maintain energy homeostasis and prevent metabolic diseases. For example, serum levels of adiponectin are lowered in subjects with obesity and type 2 diabetes (7,8), and administration of adiponectin enhances insulin sensitivity by decreasing the levels of plasma free fatty acid and triglyceride (9,10). In addition, adiponectin was shown to inhibit atherosclerotic lesion formation in apoE–deficient mice (11,12). These beneficial effects of adiponectin have been attributed to, among other things, its ability to increase fatty acid oxidation in peripheral tissues (10).

Stimulation of fatty acid oxidation by adiponectin appears to be primarily mediated by the activation of 5′-AMP-activated protein kinase (AMPK). Treatment with adiponectin or ectopic expression of its receptors has been shown to increase AMPK phosphorylation and fatty acid oxidation in muscles, and this effect was abolished by the use of dominant-negative AMPK (13,14). AMPK is a multi-subunit protein kinase that functions as a sensor of intracellular energy state (15). It is activated by high AMP-to-ATP ratio, which occurs under stress conditions such as heat shock, hypoxia, starvation, and exercise. In addition, AMPK is also directly activated by one or more of the upstream kinases via phosphorylation of a threonine residue within the activation loop of the α-subunit kinase domain (15). In skeletal muscle cells, it is well established that AMPK increases fatty acid oxidation by inhibiting acetyl-CoA carboxylase (ACC) through phosphorylation. A decrease in ACC activity reduces intracellular malonyl-CoA levels and stimulates carnitine palmitoyl transferase 1 (CPT1). This ultimately increases the influx of long-chain fatty acids into the mitochondria, where they are oxidized (16,17).

Another key regulator of fatty acid metabolism is peroxisome proliferator–activated receptor (PPAR)α. PPARα is a ligand-activated nuclear hormone receptor that is highly expressed in tissues that derive most of their energy from fatty acid oxidation, including liver, heart, kidney, and skeletal muscle (18). PPARα controls the expression...
of a number of genes involved in peroxisomal (19, 20) and mitochondrial β-oxidation (21, 22), such as ACO, CPTI, and FABP3. Several studies using PPARα-null mice have demonstrated the critical role of PPARα in the fasting response. When fasted, these mice suffer from defects in fatty acid oxidation and ketogenesis, resulting in elevated plasma free fatty acid levels, hypoketogenesis, and hypothermia (23–25). Furthermore, recent reports have demonstrated that PPARα ligands improve insulin sensitivity and lower lipid levels in insulin-resistant rodent models such as obese Zucker rats and high-fat–fed mice (26–28).

p38 mitogen-activated protein kinase (MAPK) is activated by inflammatory cytokines and plays an important role in activating immune responses. A number of conditions that evoke metabolic stress, such as muscle contraction, hypoxia, ischemia, and hyperosmolality, are also known to stimulate mammalian p38 MAPK activity (29). Most of these physiological conditions are similar to those associated with AMPK activation (30), suggesting a possible crosstalk between the AMPK and p38 MAPK signaling pathways.

It has recently been reported that adiponectin stimulates AMPK, p38 MAPK, and PPARα activity in target tissues (14). However, the detailed downstream pathway of adiponectin, which comprises these three components, has not been thoroughly investigated. Here, we provide evidence that adiponectin enhances fatty acid oxidation in muscle cells by stimulating PPARα transcriptional activity via the sequential activation of AMPK and p38 MAPK.

**RESEARCH DESIGN AND METHODS**

**Cell culture and viral infection.** Induction of myogenic differentiation was carried out as previously described (31). In brief, mouse C2C12 myoblasts were maintained in Dulbecco’s modified Eagle’s medium (DMEM) containing 10% fetal bovine serum. To induce differentiation, confluent cells were serum-starved for 18 h and incubated with 10% fetal bovine serum. To induce differentiation, confluent cells were

**Purification of adiponectin from HEK293 cell cultures.** Recombinant adiponectin protein was purified using a modified version of a previously described protocol (32). In brief, HEK293 cells were transfected with plasmid vectors expressing myc-His-tagged adiponectin (pcDNA3.1-adiponectin-myc-His). After 48 h, the cells were incubated in non-serum-free DMEM with 0.1 g/l l-aspartic acid for 48 h. The medium was then collected and centrifuged at 3,000 rpm for 10 min to remove cellular debris. After adding saturated ammonium sulfate at 80% (wt/vol) and incubating at 4°C for 4 h with shaking, the protein fraction was precipitated by centrifugation at 3,000 rpm for 3 h at 4°C. The precipitate was resuspended in 10 mM HEPES (pH 8.0) buffer containing 50 mM sodium phosphate, 300 mM NaCl, and 20 mM imidazole, and adiponectin was collected with elution buffer (50 mM sodium phosphate, 300 mM NaCl, and 250 mM imidazole). The pH of the washing and elution buffers was adjusted to 8.0 with NaOH before use. Only batches containing adiponectin >90% purity, which was determined by Coomassie staining, were used for subsequent experiments.

**Transient transfection and luciferase assay.** HEK293 cells were grown in DMEM containing 10% bovine calf serum. Luciferase reporter constructs were cotransfected with PPARα, retinoid X receptor α, and/or adiponectin expression vectors by using the calcium phosphate method. After transfection, the cells were serum-starved for 18 h and incubated with 10 μM 1,25(OH)2D3 (BioSmol), 1 μM dexamethasone (Sigma), 5 μM SB203580 (A.G. Scientific), or vehicle (DMSO) for an additional 24 h before lysis. The luciferase activity was normalized to β-gal activity.

**Fatty acid oxidation assay.** Cytoplasmic lysates were used for subsequent experiments. For immunoprecipitated kinase assays, cell extracts were precipitated with anti-p38 MAPK antibodies and washed with 20 mM imidazole (pH 7.0), 80 mM NaCl, 5 mM magnesium acetate, 1 mM dithiothreitol, 200 μM each of AMP and ATP, and 2 μCi [γ-32P] ATP with or without 200 μM SAMS peptide (Upstate). For immunoprecipitated kinase assays, cell lysates were immunoprecipitated with anti-PPARα or α2 antibodies (Upstate), washed with 40 mM HEPES (pH 7.0), and suspended in 20 μl reaction buffer. The reaction mixtures were spotted onto PS1 cation exchange papers, washed three times with 1% phosphoric acid, and measured using a scintillation counter. AMPK activity was expressed as [32P] incorporated per micromgram of protein.

**Quantitative RT-PCR analysis.** Total RNA was isolated with Trizol (Invitrogen) according to the manufacturer’s protocol. Total RNA, 5 μg, was reverse transcribed with oligo dT using ReverTaid M-MuLV Reverse Transcriptase (MBI Fermentas, ON, Canada). cDNA levels were quantified by real-time PCR with SYBR Green using the MyIQ single-color real-time PCR detection system (Bio-Rad). The primer sequences used were as follows: acyl-CoA oxidase forward

**RESULTS**

**Adiponectin stimulates PPARα transcriptional activity and target gene expression.** One of the most profound characteristics of adiponectin is its ability to stimulate fatty acid oxidation in peripheral tissues (6). To understand how adiponectin achieves this, we examined the changes in the expression level of genes involved in fatty acid oxidation. When differentiated C2C12 cells were treated with purified adiponectin, the mRNA levels of ACO and CPT1 were increased in a dose-dependent manner (Fig. 1A). Because these genes are known to be transcriptionally regulated by PPARα, we then performed reporter assays to determine whether PPARα transcription activity can be regulated by adiponectin. As shown in Fig. 1B, cotransfection with adiponectin increased the transcriptional activity of PPARα on a reporter construct driven by multiple PPAR response elements (DR-1). This stimulatory
effect was observed both in the presence and absence of Wy14643, a synthetic ligand of PPARα, indicating that regulation of PPARα by adiponectin appeared to be ligand independent. This result is consistent with a previous report in which adiponectin was shown to enhance the activation of UAS-luciferase reporter by GAL4-PPARα fusion protein (13,14). These results imply that the stimulation of fatty acid oxidation by adiponectin in muscle cells could occur through the activation of PPARα.

AMPK and p38 MAPK are involved in the activation of PPARα by adiponectin. Since AMPK is a well-established mediator of adiponectin action, we tested whether direct activation of AMPK could similarly stimulate PPARα transcription activity. 5-Aminoimidazole-4-carboxamide-1-D-ribofuranoside (AICAR), which activates AMPK after being metabolized to 5-aminoimidazole-4-carboxamide-1-D-ribofuranoside-5-monophosphate in the cells, also increased the transcriptional activity of PPARα at the promoter of muscle-type carnitine palmitoyl transferase (Fig. 2A). Cotreatment with araA, an inhibitor of AMPK, potently inhibited this effect, confirming that the stimulation of PPARα activity by AICAR was the result of AMPK activation (Fig. 2A). Furthermore, araA also reduced the stimulation of PPARα activity by adiponectin, demonstrating that AMPK is indeed involved in the activation of PPARα by adiponectin (Fig. 2B). Since it was recently reported that adiponectin activates p38 MAPK in addition to AMPK in C2C12 cells (14), we tested whether p38 MAPK might also be involved in this pathway. As shown in Fig. 2B, inhibition of p38 MAPK using SB203580 also significantly inhibited the effect of adiponectin on PPARα activity.

To confirm the roles of AMPK and p38 MAPK in the activation of PPARα, we examined the effects of araA and SB203580 on the mRNA levels of PPARα target genes in C2C12 myotubes. Consistent with the results shown in Fig. 1A, adiponectin increased the expression levels of ACO, CPT1, and FABP3 (Fig. 3A). However, pretreatment of cells with araA or SB203580 abolished the adiponectin-dependent increase in PPARα target gene expression. Furthermore, dominant-negative AMPK similarly repressed the stimulation of PPARα target gene expression by adiponectin (Fig. 3B). Together, these data indicate that the activation of PPARα by adiponectin occurs through a pathway that requires activation of both AMPK and p38 MAPK.

AMPK stimulates PPARα-dependent fatty acid oxidation. The results from the reporter assays and gene expression analyses suggested that AMPK might be able to stimulate fatty acid oxidation by activating PPARα in muscle cells. To test this possibility, we performed in vitro fatty acid oxidation assays in C2C12 cells using radioisotope-labeled palmitate. As expected, fatty acid oxidation was enhanced by the activation of PPARα or AMPK using Wy14643 or AICAR, respectively (Fig. 4A, lanes 2 and 3).
Notably, we observed that cotreatment of Wy14643 and AICAR further elevated fatty acid oxidation (Fig. 4A, lane 4).

Thus far, stimulation of fatty acid oxidation by AMPK was believed to be primarily mediated by phosphorylation of ACC (35). The ACC-dependent regulation of fatty acid oxidation does not require synthesis of new proteins, while PPARγ exerts its effect by increasing the expression of its target genes. We took advantage of this difference to determine whether AMPK can indeed stimulate fatty acid oxidation by activating PPARγ. When cells were treated with cycloheximide to block protein synthesis, AICAR-induced fatty acid oxidation was reduced by ~30% (Fig. 4B). This reduction can probably be attributed to the inhibition of effect of PPARγ activity, which would act downstream of AMPK to induce the expression of genes involved in fatty acid oxidation.

The roles of AMPK and p38 MAPK in the stimulation of fatty acid oxidation by adiponectin were also examined using fatty acid oxidation assays. As previously reported (10), adiponectin increased fatty acid oxidation by ~40% (Fig. 4C). This stimulation was suppressed by araA or SB203580 (Fig. 4C, lanes 3 and 4), and cotreatment with

FIG. 3. Stimulation of PPARγ target gene expression by adiponectin is repressed by inhibition of AMPK and p38 MAPK. The relative mRNA levels of PPARγ target genes in differentiated C2C12 myotubes were measured 3 h after treatment with adiponectin (2 μg/ml). Before adiponectin treatment, the cells were either preincubated with araA (1 mmol/l) for 1 h or SB203580 (10 μmol/l) for 20 min (A) or infected with dominant-negative (D/N) AMPK–expressing adenovirus (B). The amount of mRNA was normalized to GAPDH.

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FIG. 4. Adiponectin increases fatty acid oxidation via AMPK and p38 MAPK. Fatty acid oxidation was measured using 1H-labeled palmitate in differentiated C2C12 myotubes as described in RESEARCH DESIGN AND METHODS. A: Cells were incubated in oxidation media containing 1H-labeled palmitate with 1 mmol/l AICAR, 10 μmol/l Wy14643, or vehicle (DMSO) for 24 h. Wy, Wy14643. B: Cells were preincubated in the presence or absence of cycloheximide (CHX; 20 μmol/l) for 1 h before adding AICAR (1 mmol/l), Wy14643 (10 μmol/l), or DMSO. C: Fatty acid oxidation was measured after stimulating with 2 μg/ml adiponectin for 24 h. AraA and/or SB203580 was pretreated 1 h before adiponectin. •P < 0.01, †P < 0.05. Ad, adiponectin; SB, SB203580.
both araA and SB203580 did not result in additive or synergistic effects (Fig. 4C, lane 5). Taken together, these data reveal the presence of a pathway through which adiponectin stimulates fatty acid oxidation by activating PPARα. p38 MAPK is phosphorylated and activated by AMPK in adiponectin signaling. To get a clearer picture of the adiponectin signaling pathway, we examined the changes in the level of AMPK and p38 MAPK phosphorylation induced by adiponectin. Consistent with previous reports (14,34), adiponectin enhanced the phosphorylation of AMPK, p38 MAPK, and ACC in C2C12 myotubes (Fig. 5A). However, when AMPK was chemically inhibited with araA, the stimulation of AMPK, p38 MAPK, and ACC phosphorylation was attenuated. On the other hand, inhibition of p38 MAPK with SB203580 did not affect adiponectin-induced phosphorylation of AMPK and ACC. Similar results were obtained when AMPK was directly activated.

FIG. 5. Adiponectin signaling via AMPK and p38 MAPK. A–C: The levels of AMPK, p38 MAPK, and/or ACC phosphorylation in C2C12 myotubes were measured after 30 min incubation with adiponectin (5 μg/ml) or AICAR (2 mmol/l). Cells were pretreated with 2 mmol/l araA (1 h), 10 μmol/l SB203580 (20 min), or adeno-D/N AMPK before the addition of adiponectin or AICAR. D: In vitro AMPK and p38 MAPK kinase assays were performed using differentiated C2C12 myotubes under conditions identical with Fig. 5B. The level of p38 MAPK was determined as loading control. E: The kinase activity of the α1 and α2 subunits of AMPK from C2C12 cells were measured by IP-kinase assays with or without adiponectin or AICAR. Ad, adiponectin; SB, SB203580.
using AICAR (Fig. 5B and D). AICAR increased the phosphorylation and kinase activities of AMPK and p38 MAPK, and these effects were inhibited by araA. Likewise, when AMPK was blocked using dominant-negative AMPK, both adiponectin and AICAR did not induce p38 MAPK phosphorylation (Fig. 5C). Conversely, insulin, which activates p38 MAPK in muscle cells, did not affect AMPK phosphorylation or kinase activity (online appendix Fig. 1A and C [available at http://diabetes.diabetesjournals.org]). Therefore, these results indicate that p38 MAPK might function as a downstream signaling molecule of AMPK in the adiponectin signaling pathway.

In an attempt to determine which catalytic subunit of AMPK, α1 or α2, mediates adiponectin signaling in muscle cells, we performed in vitro kinase assays using antibodies specific for each isoform. The kinase activity of both α1 and α2 isoforms was increased by adiponectin treatment, the α1 isoform by ~50% and the α2 isoform by over twofold (Fig. 5D). Thus, it is possible to speculate that AMPKα2 might be the major mediator of adiponectin function in muscle cells, although the role of α1 cannot be ruled out.

**p38 MAPK directly stimulates PPARα transcription activity.** Previously, it has been demonstrated that the transcriptional activity of PPARα can be stimulated by p38 MAPK through the phosphorylation of three serine residues in the AF-1 domain (serines 6, 12, and 21) (36). In addition, we found three putative AMPK phosphorylation sites (serines 167, 373, and 453) in PPARα through sequence analysis. To test whether AMPK might directly modulate PPARα activity, we performed reporter assays using PPARα mutants in which these serine residues were substituted with alanine. Mutation at the p38 MAPK phosphorylation sites (S6/12/21A) resulted in the loss of stimulation of transcriptional activity by AICAR that is observed in wild-type PPARα (Fig. 6, lanes 3 and 11). In contrast, the S167/373/453A mutant retained its sensitivity to AICAR (Fig. 6, lanes 3 and 7). These results indicate that p38 MAPK, but not AMPK, is directly involved in regulating the transcriptional activity of PPARα.

**Adiponectin stimulates long-term fatty acid oxidation.** The regulation of fatty acid oxidation by adiponectin through PPARα would be expected to have a longer-lasting effect compared with the pathway involving ACC phosphorylation. To analyze the short- and long-term effects of adiponectin on fatty acid utilization, we compared the time-dependent changes in the phosphorylation of signaling molecules, expression of PPARα target genes, and fatty acid oxidation. As shown in Fig. 7A, phosphorylation of AMPK was transient, lasting for only 30 min after induction by adiponectin. Phosphorylation of p38 MAPK and ACC lasted longer and was detected at 60 min. During this short period, adiponectin would transiently induce fatty acid oxidation by phosphorylating and inhibiting ACC, which is confirmed by the fatty acid oxidation assay results (Fig. 7D). Meanwhile, the expression of PPARα target genes, specifically ACO and CPT1, peaked at 3 h after adiponectin treatment and slowly receded to basal levels after 24 h (Fig. 7B). Interestingly, the rate of fatty acid oxidation constantly remained higher in adiponectin-treated cells throughout the entire duration (Fig. 7C and D). Therefore, adiponectin seems to be able to increase fatty acid oxidation for a prolonged period by inducing the synthesis of proteins involved in fatty acid oxidation, in addition to the transient stimulation via ACC phosphorylation.

**DISCUSSION**

In this study, we have discovered a new mechanism by which adiponectin can stimulate fatty acid oxidation in muscle cells via sequential activation of AMPK, p38 MAPK, and PPARα. These results represent the first detailed characterization of the adiponectin signaling pathway that stimulates fatty acid oxidation via the activation of PPARα.

Accumulating results have unveiled adiponectin as a promising candidate for the treatment of obesity-associated metabolic syndromes. In animal models and human subjects with obesity and type 2 diabetes, adiponectin stimulates fatty acid oxidation, decreases lipid accumulation in muscles, lowers plasma free fatty acid levels, and enhances insulin sensitivity (10,37). Adiponectin has been shown to increase fatty acid oxidation via activation of AMPK and phosphorylation of ACC (35). However, the phosphorylation of ACC induced by adiponectin is short lived (35) (Fig. 7A). Therefore, this pathway cannot fully explain the long-term effects of adiponectin on weight loss and fatty acid oxidation. On the other hand, activation of PPARα would be a promising pathway by which adiponectin can trigger long-term stimulation of fatty acid oxida-
tion, even after the initial signaling is gone, because this would promote the amounts of relatively long-lived enzymes involved in fatty acid metabolism. Indeed, we found that adiponectin, via AMPK, enhanced the transcriptional activity of PPARα and the expression of its target genes (Figs. 1 and 2). This result is supported by the fact that activation of AMPK has a potent lipid-lowering effect that is equivalent to the effect of PPARα agonists in obese animal models. In vivo infusion of AICAR significantly decreases plasma free fatty acid levels and the triglyceride concentration in both lean and obese Zucker rats (38,39).

Using dominant-negative AMPK and chemical inhibitors of AMPK and p38 MAPK, we revealed that AMPK and p38 MAPK are sequentially activated (Fig. 5 and online appendix Fig. 1). Previous studies have also suggested that the activation of p38 MAPK is associated with the stimulation of AMPK in glucose metabolism. For example, in skeletal muscle, AICAR increases glucose uptake by activating p38 MAPK, which is involved in the activation of GLUT4 translocation to the plasma membrane (40). In the same manner, p38 MAPK acts downstream of AMPK in cardiomyocytes, and the inhibition of the AMPK/p38 MAPK signaling pathway partially abolishes the stimulation of glucose uptake in response to hypoxia (41). Therefore, p38 MAPK and AMPK appear to be components in the adiponectin signaling pathway in muscle cells that work to increase insulin sensitivity by activating both glucose uptake and fatty acid utilization. However, treatment with adiponectin did not elevate fatty acid oxidation in primary hepatocytes (11,42) (unpublished data), suggesting that muscle and liver tissues may respond differently to adiponectin in terms of fatty acid oxidation.

Adiponectin circulates in serum as trimers and hexamers of relatively low molecular weight (LMW) and middle molecular weight and larger multimeric forms of high molecular weight (HMW) (32,42,43). Several studies have pointed to a greater role of HMW adiponectin in improving insulin sensitivity (31,43). Moreover, thiazolidinediones increased the level of circulating HMW adiponectin (44,45). When we compared different fractions of adiponectin containing either the HMW or LMW forms, the HMW adiponectin containing fractions exhibited pronounced effect on both PPARα target gene expression and AMPK and p38 MAPK phosphorylation, while LMW adiponectin exerted only marginal effects (online appendix Fig. 2). This is in concert with a previous study demonstrating a higher correlation between HMW adiponectin and whole-body fat oxidation than LMW adiponectin in human and rodents (46).

The mutation of putative AMPK phosphorylation sites on PPARα did not affect its responsiveness to AICAR. In contrast, mutant PPARα in which the potential p38 MAPK phosphorylation sites at serine residues were substituted to alanine (S6/12/21A) was unresponsive to AMPK activation (Fig. 6). This implies that AMPK controls the transcriptional activity of PPARα through p38 MAPK and not by direct modification. Of note, p38 MAPK is known to phosphorylate PPARα and increase its association with a coactivator PPARγ coactivator-1α (36). However, the possibility of the presence of other AMPK phosphorylation sites in addition to the serine residues examined in our experiments cannot be ruled out. In addition, it has been proposed that adiponectin can enhance PPARα activity through the production of its ligands (47). These results suggest the presence of multiple pathways that could mediate the effect of adiponectin on fatty acid metabolism.
Adiponectin

AdipoR

AICAR

AMPK

ACC

p38 MAPK

active

p38 MAPK

SB203580

increased fatty acid oxidation

PPARα

RXRα

ACO, CPT, FABP3

FIG. 8. Schematic model of adiponectin signaling on fatty acid oxidation in muscle cells. Sequential activation of AMPK, p38 MAPK, and PPARα leads to the induction of PPARα target genes involved in fatty acid utilization. This allows sustained stimulation of fatty acid oxidation via PPARα activation in addition to the transient induction triggered by ACC phosphorylation. RXRα, retinoid X receptor α.

in muscles. Further research is required to validate these ideas.

Collectively, we have provided evidence that adiponectin, through the sequential activation of AMPK and p38 MAPK, stimulates PPARα activity in muscle cells (Fig. 8). There still remains missing links to be connected in this pathway, such as how adiponectin activates AMPK or what factors mediate the signaling pathways between AMPK and p38 MAPK. Nonetheless, our results have provided a possible explanation as to how adiponectin triggers sustained increases in fatty acid oxidation in muscle cells. Intervention of this pathway may provide a means by which obesity-related metabolic disorders may be treated.

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