AMPK and SIRT1: a long-standing partnership?

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Ruderman NB, Xu XJ, Nelson L, Cacicedo JM, Saha AK, Lan F, Ido Y. AMPK and SIRT1: a long-standing partnership. Am J Physiol Endocrinol Metab 298: E751–E760, 2010. First published January 26, 2010; doi:10.1152/ajpendo.00745.2009—AMP-activated protein kinase (AMPK) and the histone/protein deacetylase SIRT1 are fuel-sensing molecules that have coexisted in cells throughout evolution. When a cell’s energy state is diminished, AMPK activation restores energy balance by stimulating catabolic processes that generate ATP and downregulating anabolic processes that consume ATP but are not acutely needed for survival. SIRT1 in turn is best known historically for producing genetic changes that mediate the increase in longevity caused by calorie restriction. Although the two molecules have been studied intensively for many years, only recently has it become apparent that they have similar effects on diverse processes such as cellular fuel metabolism, inflammation, and mitochondrial function. In this review we will examine the evidence that these similarities occur because AMPK and SIRT1 both regulate each other and share many common target molecules. In addition, we will discuss the clinical relevance of these interactions and in particular the possibility that their dysregulation predisposes to disorders such as type 2 diabetes and atherosclerotic cardiovascular disease and is a target for their therapy.

AMPK and SIRT1: a long-standing partnership? in the absence of LKB1 (32). It is a major regulator of AMPK in brain and also appears to function in vascular endothelium.

AMPK is a fuel-sensing enzyme that is activated by decreases in a cell’s energy state as reflected by an increased AMP/ATP ratio. When activated, it initiates metabolic and genetic events that restore ATP levels by stimulating processes that generate ATP (e.g., fatty acid oxidation) and inhibiting others that consume ATP but are not acutely required for survival (e.g., triglyceride and protein synthesis, cell proliferation) (40). In addition, AMPK sets in motion changes in mitochondrial biogenesis and function (37) that could more chronically increase the ability of a cell to generate ATP and diminish oxidative stress and other potentially adverse cellular events (78). The sirtuins are a family of evolutionarily conserved NAD+-dependent histone/protein deacetylases that are also widely regarded as fuel-sensing molecules. They have many actions (see below) but are perhaps best known for their role in mediating the increase in longevity caused by caloric restriction in various species, including yeast, worms, and possibly mammals (21, 85). Seven sirtuins have been identified in mammalian cells. Of these the most studied and the focus of this review is silent information regulator T1 (SIRT1).

AMPK and the sirtuins are present in all eukaryotic cells and probably have coexisted throughout evolution (7, 29). Although both molecules have been studied intensively, the similarities in their regulation and in their actions on such diverse processes as cellular metabolism, inflammation, and mitochondrial function have only recently become apparent. In this review we will examine the evidence that these similarities occur, at least in part, because AMPK and SIRT1 both regulate each other and share many common target molecules. In addition, we will discuss the clinical ramifications of the interaction of these molecules and in particular the possibility that their dysregulation predisposes humans and experimental animals to the metabolic syndrome and associated disorders and is a target for their therapy.

REGULATION OF AMPK AND SIRT1

AMPK

The currently accepted mechanisms of AMPK activation are depicted in Fig. 1 (29, 88, 99). Two upstream kinases, serine/threonine liver kinase B1 (LKB1; the primary AMPK kinase) and calcium/calcmodulin kinase kinase-β (CaMKKβ; an AMPK kinase), activate AMPK by phosphorylating a threonine residue (Thr172) on its catalytic α-subunit (9). LKB1 is the principal AMPK kinase that catalyzes this phosphorylation when it occurs in response to a decrease in energy state, such as that produced by nutrient deprivation or increased energy expenditure (e.g., exercise). CaMKKβ phosphorylates Thr172 and activates AMPK in response to increases in intracellular Ca2+ caused by various hormones and possibly shear stress, and it can do so in the absence of LKB1 (32). It is a major regulator of AMPK in brain and also appears to function in vascular endothelium.
AMPK, SIRT1, AND THE METABOLIC SYNDROME

Fig. 1. AMP-activated protein kinase (AMPK) activation and its regulation (29). AMPK is a heterotrimer consisting of a catalytic α-subunit (α1, α2) and regulatory β- and γ-subunits (β1, β2, α1, α2, and α3), all of which are required for its activity. Heterotrimers containing the α1 subunit are exclusively cytoplasmic; however, α2-containing AMPK is also found in the nucleus, where its presence may increase after exercise (56). The γ-subunit contains several cystathionine β-synthase domains that under baseline conditions predominantly bind ATP. When a cell is energy stressed and the AMP/ATP ratio increases, AMP replaces ATP on 2 of these domains (83). This results in a conformational change that J causes a modest increase in AMPK activity (2- to 10-fold) and 2 enhances the phosphorylation of Thr172 on the α-subunit, which results in a much greater activation of the enzyme. The active enzyme then phosphorylates multiple molecules (enzymes, transcriptional activators, and coactivators), with the end result a restoration of the cell’s energy state. Serine-threonine liver kinase B1 (LKB1) is required for this phosphorylation; however, it is less clear whether changes in LKB1 activity specifically regulate it. Thus studies, predominantly in skeletal muscle, have suggested that LKB1 is constitutively active and that the conformational change induced by an increase in the AMP/ATP ratio results from a change in its conformation that makes phosphorylated AMPK resistant to the action of protein phosphatases. As shown in Fig. 1, when activated in an energy-stressed cell, AMPK sets in motion a wide variety of events that both acutely and subacutely increase ATP. The latter is due to its effects on various transcriptional activators and coactivators, including peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α), as will be discussed in more detail later.

SIRT1

SIRT1 (21, 46, 85) is widely expressed in mammalian cells and has been studied in many tissues, including liver, skeletal muscle, adipose tissue, pancreas (β-cells), brain (101), and endothelium (69). Its regulation is somewhat less clear than that of AMPK; however, a substantial body of evidence suggests that, like AMPK, SIRT1 responds to increases and decreases in nutrient availability (caloric restriction or starvation) (10, 13, 60) and energy expenditure (8, 93). Regulation of SIRT1 has been attributed to changes in NAD+ abundance and the NAD+/NADH ratio, the concentration of nicotinamide (NAM), an end product of the deacetylase reaction and a SIRT1 inhibitor, and the activity of NAM phosphoribosyltransferase (Nampt; visfatin), which catalyzes the reconversion of NAM to NAD+ (see Fig. 2) (53, 57, 73). In contrast, there appears to be genetic regulation of SIRT1 by the action of forkhead box-containing protein and p53 (60) on the SIRT1 promoter as well as regulation by various other factors (see Fig. 2 and its legend).

AMPK Regulation by SIRT1

Downregulation of AMPK in response to high glucose exposure and in the apparent absence of a change in energy state was first shown to occur in an incubated rat extensor digitorum muscle preparation (36). Several years later, a similar change in response to high glucose, together with a decrease in SIRT1 activity, was observed in cultured HepG2 cells (90, 107). In both situations an increase in the release of lactate occurred, suggesting a decrease in the NAD+/NADH ratio, which could have contributed to the decrease in SIRT1 activity. These findings and the concurrent demonstration by many laboratories of common activators, actions, and target molecules of SIRT1 and AMPK (Fig. 3) led to an examination of a possible linkage between SIRT1 and the AMPK kinase LKB1. In one study, Lan et al. (48) demonstrated that overexpression of SIRT1 in human embryonic kidney-293T cells diminished lysine acetylation of LKB1 (K48) and caused its movement from the nucleus to the cytoplasm, where LKB1 can associate with the adaptor proteins STE20-related adaptor protein and mouse embryo scaffold protein, resulting in its own activation and subsequently that of AMPK. Consistent with these findings in cultured cells, the same group found decreased LKB1 and AMPK activity and increased lysine acetylation of LKB1, suggestive of SIRT1.
AMPK, SIRT1, and the Metabolic Syndrome

ACTIVATION

Caloric Restriction

Exercise

TARGETS

PGC1α
eNOS
FOXO
OTHER

Catabolic metabolism (+)
Mitochondrial function (+)
Angiogenesis (+)
Inflammation (+)
Insulin resistance (-)
Cell survival (+/-)

Fig. 2. Regulation of SIRT1 (21). SIRT1 is an NAD⁺-dependent histone/protein deacetylase whose activity is regulated by nutrient availability. It has been proposed that nutrient deprivation (shown in the figure) increases SIRT1 activity by increasing the abundance of NAD⁺ and decreasing the abundance of nicotinamide (NAM), a product of the reaction, and NADH, both of which inhibit SIRT1. NAM phosphoribosyltransferase (Nampt) catalyzes the conversion of NAM to NAD⁺; therefore, it activates SIRT1 both by increasing cellular NAD⁺ and diminishing NAM. Exercise has been shown to increase Nampt activity in human muscle (14). Nutrient excess appears to have opposite effects on SIRT1 activity and these regulatory factors. Nampt, sometimes referred to as visfatin, is also found in both the nucleus and the cytoplasm, depending on cell type and relevance of this with regard to SIRT1 regulation is unclear. Finally, SIRT1 can be downregulated by p53 and a H1C1:CtBP corepressor complex (not shown). Of the latter molecules, AMPK has been demonstrated to influence eNOS, p53, and biological actions (7, 22, 46). A case in point: the transcriptional coactivator peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α), which in muscle (26) and other tissues is a master regulator of mitochondrial biogenesis and function, is illustrated in Fig. 5. FOXO, forkhead box-containing protein.

Fig. 3. Commonalities between AMPK and SIRT1. Both AMPK and SIRT1 are activated in vivo in many tissues by caloric restriction and exercise as well as treatment with resveratrol and 5-aminoimidazole-4-carboxamide-1-β-D-ribofuranside (see below). In addition, they have many common target molecules and biological actions (7, 22, 46). A case in point: the transcriptional coactivator peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α), which in muscle (26) and other tissues is a master regulator of mitochondrial biogenesis and function, is illustrated in Fig. 5. FOXO, forkhead box-containing protein.

Fig. 4. Proposed mechanism for activation of LKB1 and LKB1 target molecules by SIRT1. Activation of SIRT1 by genetic or pharmacological means in human embryonic kidney-293T cells (and presumably others) leads to deacetylation of Lys⁴⁸ and possibly other key lysine residues on LKB1. This in turn enhances LKB1 binding to STE20-related adaptor protein (STRAD) and mouse embryo scaffold protein (MO25), which activates its kinase activity and leads to the phosphorylation of AMPK. The scheme assumes that SIRT1 is primarily nuclear and that LKB1 acetylation occurs in the nucleus and in some way enhances its movement to the cytoplasm (where it binds to STRAD). Since under some circumstances SIRT1 may be found in the cytoplasm, it is also possible that LKB1 acetylation could be an extranuclear event. In addition to AMPK, LKB1 phosphorylates and activates MARK1 and 12 other AMPK-related kinases (ARKs). CaMK kinase (CaMKK), which phosphorylates and activates AMPK even in the absence of LKB1, presumably would not activate the ARKs unless the increase in AMPK activity activated SIRT1 and, secondarily, LKB1 (adapted from Ref. 48).

Fig. 5. FOXO, forkhead box-containing protein.
much earlier decrease in cellular ATP and an increase in the activity of AMPK. They also found that incubation for 36 h with 5-aminoimidazole-4-carboxamide-1-β-D-ribofuranoside (AICAR), a more direct AMPK activator, produced a similar sequence of events. In both situations, the inhibition of myoblast differentiation was accompanied by an increased transcription of the NAD biosynthetic enzyme Nampt, which in turn increased the NAD+/NADH ratio and decreased the concentration of NAM. Conversely, both myoblasts derived from SIRT1−/− mice and cells transduced with shRNAi for SIRT1 were resistant to the effect of AMPK activation on muscle differentiation, strongly suggesting that it was SIRT1 mediated.

In a subsequent study, Canto and Auwerx (7) demonstrated that AMPK activation by AICAR increased PGC-1α-mediated gene expression in a SIRT1-dependent manner in C2C12 myocytes and mouse embryonic fibroblasts. They went on to show that various AMPK activators, including AICAR, metformin, and the mitochondrial uncoupler dinitrophenol, none of which can directly activate SIRT1, increased NAD+ levels and the NAD+/NADH ratio and that this resulted in SIRT1 activation, as evidenced by the deacetylation and activation of PGC-1α (Fig. 5). Importantly, an increased NAD+/NADH ratio was also observed in skeletal muscle after an exhaustive bout of exercise, suggesting that a similar sequence of events may also take place in vivo (7). Thus two independent groups have shown that SIRT1 activity increases following AMPK activation. They differ in that Fulco et al. (23) proposed that upregulation of Nampt was the key linkage between increased AMPK and SIRT1 activities, whereas Canto et al. (8) found that AMPK could alter the NAD+/NADH ratio and activate SIRT1 apparently independently of Nampt.

THE PUTATIVE SIRT1/AMPK CYCLE AND ITS REGULATION

The observation that AMPK and SIRT1 can activate each other raises the possibility that they are components of a cycle. Such a notion is attractive since one molecule responds to changes in energy state and the other to alterations in NAD+, and they both appear to regulate cellular biology and metabolism in a similar manner. On the other hand, the relevant data supporting the existence of such a cycle are preliminary, and many questions need to be addressed. For instance, it is known that the citric acid (Krebs) and urea cycles involve events that appear to be quite rapid (s/min). In contrast, in contracting muscle in vivo and cultured C2C12 cells incubated with AICAR and other AMPK activators, AMPK activation is an early event (s/min), but SIRT1 activation appears to take place much later (4–12 h) (8, 23), although an increase in SIRT1 protein expression has been observed in rat muscle 2 h after exercise (93). Presumably, if a cycle exists, the activation of SIRT1 in these circumstances, at least in muscle, is a later event and would presumably act to sustain the activation of AMPK. However, this remains to be proven.

Also requiring study is the relation between changes in SIRT1 and AMPK under different conditions and in tissues other than skeletal muscle. With respect to the latter, concurrent decreases in AMPK and apparently SIRT1 activity have been observed in the liver of 48-h-starved rats 24 h after refeeding (48), and both molecules appear to be activated by starvation in adipose tissue (65, 86). Likewise, in HepG2 cells (90), pyruvate activates and NAM inhibits both AMPK and SIRT1, and they do so within 1–2 h, suggesting that their interaction is much more rapid than in C2C12 cells. Finally, under some conditions, it is clear that the proposed cycle does not operate as described here. Thus, in mice carrying two null alleles, for SIRT1, decreased SIRT1 in liver was associated...
with increased rather than decreased AMPK phosphorylation (Thr$^{172}$), a finding attributed to a decrease in energy state as a result of impaired mitochondrial function (5).

THE AMPK AND SIRT1 PARTNERSHIP: CLINICAL IMPLICATIONS

The Metabolic Syndrome

Just as research in the SIRT1 field has focused substantially on the notion that in some fashion SIRT1 and other sirtuins provide the connection between what we eat and how long we live (21), research on the clinical relevance of AMPK has focused on its relation to the metabolic syndrome and associated diseases (29, 40, 78, 79). As shown in Fig. 6, the metabolic syndrome is a disorder in which genetic factors coupled with overnutrition and inactivity produce pathogenic changes that predispose individuals to a wide array of common diseases, including type 2 diabetes, atherosclerosis, hypertension, nonalcoholic fatty liver disease, certain cancers, and possibly Alzheimer’s disease. It is presently diagnosed clinically by the presence of at least three of the following: abdominal obesity, hyperglycemia (fasting glucose $>100$ mg/dl), hypertension, hypertriglyceridemia, and decreased HDL cholesterol (18). The putative pathogenetic changes, including hyperinsulinemia, insulin resistance, and abnormalities in lipid metabolism and mitochondrial gene expression, may antedate these diagnostic criteria and even more so the diseases that follow their appearance by many years (77). A fundamental question is whether abnormalities in AMPK and SIRT1 accompany or precede these pathogenic changes. Another is whether therapies that activate AMPK and/or SIRT1 are useful for their treatment and prevention.

AMPK and SIRT1 Activity in the Setting of the Metabolic Syndrome

Humans. Assays of AMPK and SIRT1 in humans with the metabolic syndrome have been limited. With respect to AMPK, studies in skeletal muscle of obese, insulin-resistant humans have yielded mixed results, with some showing decreased AMPK activity or impaired activation (2, 17, 87) and others no difference from control individuals (33). Recently, decreased AMPK activity has been found in adipose tissue of patients with high circulating glucocorticoids due to Cushing’s Syndrome (11) and of markedly obese insulin-resistant individuals undergoing bariatric surgery (25). SIRT1 was not assayed in either study; however, it is noteworthy that, in another study, SIRT1 mRNA and AMPK activity were significantly increased (as was insulin sensitivity) in muscle of obese, insulin-resistant patients by 6 mo of caloric restriction that resulted in a 10% loss of body weight (12). Likewise, increased SIRT1 mRNA expression has been observed in subcutaneous adipose tissue of human volunteers after 6 days of total starvation, and in the same study, significantly greater SIRT1 expression was observed in lean compared with obese women (65).

Experimental animals. In contrast to the findings in humans, clear-cut decreases in AMPK activity have been observed in multiple tissues of rodents with the metabolic syndrome, including ob/ob (105) and IL-6-knockout mice (41), fa/fa (80), Zucker diabetic fatty (105), and Otsuka Long-Evans Tokushima fatty (OLETF) rats (50), and rats and mice with various forms of diet-induced obesity (75). Decreased SIRT1 activity in turn has been observed in cardiac muscle of the OLETF rat (54) and adipocytes from ob/ob mice (72, 89); however, measurements of SIRT1 in other rodents with the metabolic syndrome and decreased AMPK activity appear to be lacking.

Effects of AMPK and SIRT1 Activation on the Metabolic Syndrome and Its Pathogenetic Factors

Humans. Studies in humans have demonstrated that regular exercise, calorie restriction, metformin, and thiazolidinediones, all of which have been shown to activate AMPK in humans as well as in rodents, diminish many of the pathogenetic factors for the metabolic syndrome (75, 78, 98), as well as endothelial cell dysfunction, which is generally regarded as an early manifestation of atherosclerotic vascular disease (69). In keeping with this presumption, these treatments also have been shown to diminish the prevalence of metabolic syndrome-associated diseases, including type 2 diabetes, atherosclerosis, certain cancers, and possibly even Alzheimer’s disease (see legend of Table 1) (75). Studies of the effects of drugs that activate SIRT1 in humans with the metabolic syndrome are currently in progress (49, 58). Interestingly, 3 wk of physical training has been shown to increase Nampt protein by 127% in muscle of previously sedentary individuals, and in the same study, twofold higher levels of Nampt protein were found in
that likely mediate their effects

AMPK (phosphorylation) was reported as a late-occurring diet-induced obesity. Where measured (20, 58), increased activity in adipose tissue, skeletal muscle, and liver of mice with proved insulin sensitivity, and increased mitochondrial capac-
ity was not assessed (67). In other studies (20, 58), potent small B. AMPK activity

activation, and downmodulation of NF-

that have been shown to improve insulin sensitivity, decrease ectopic lipid deposition, and prevent the development of dia-

betes and pancreatic β-cell damage (68, 105). Likewise, sim-
ilar results have been obtained in other rodents in which the metabolic syndrome was accompanied by decreased AMPK activity (75, 98).

Positive effects of SIRT1 activation have also been observed in rodents with the metabolic syndrome. Thus, moderate SIRT1 overexpression produced with a bacterial artificial chromo-

some overexpressor was demonstrated to increase insulin sensitivity and prevent the development of diabetes in both C57BL6 mice fed a high-fat diet and db/db mice (3). Likewise, moderate overexpression of SIRT1 under the control of its natural promoter had similar effects in mice fed a high-fat diet (67). Interestingly, in the first study, increased levels of adi-

ponecin (an AMPK activator) were observed in plasma and increased AMPK activity in liver, white adipose tissue, and muscle. In the second study (67), SIRT1 prevented glucose intolerance, hepatic steatosis, and various manifestations of inflammation, effects attributed to the induction of antioxidant proteins such as manganese superoxide dismutase, PGC-1α activation, and downmodulation of NF-κB. AMPK activity was not assessed (67). In other studies (20, 58), potent small molecule activators of SIRT1 lowered plasma glucose, improved insulin sensitivity, and increased mitochondrial capacity in adipose tissue, skeletal muscle, and liver of mice with diet-induced obesity. Where measured (20, 58), increased AMPK (phosphorylation) was reported as a late-occurring event.

Resveratrol. Similar effects have been described in rodents with diet-induced obesity and glucose intolerance when treated with resveratrol (4, 47, 106), another SIRT1 activator. In addition, treatment with resveratrol has been shown to dimin-

ish atherosclerosis in LDL receptor-deficient mice fed a high-

fat, high-sucrose diet (106). However, resveratrol has also been shown to activate AMPK independent of SIRT1 (16), possibly by binding to and inhibiting mitochondrial ATP synthase and causing a decrease in energy state (98). Thus, the precise mechanism responsible for its benefits is unclear.

A list of some of the pathogenetic factors and/or markers for the metabolic syndrome that are diminished by both AMPK and SIRT1 and the putative target molecules through which they act is presented in Table 1. The table is constructed on the basis of studies carried out in humans and experimental ani-
mals and to some extent the effects of AMPK and SIRT1 and the factors that activate them in cultured cells. As already noted, exercise and calorie restriction have been demonstrated to diminish many of these pathogenetic factors in humans, as shown to activate AMPK independent of SIRT1 (16), possibly by binding to and inhibiting mitochondrial ATP synthase and causing a decrease in energy state (98). Thus, the precise mechanism responsible for its benefits is unclear.

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Table 1. Pathogenetic factors for the metabolic syndrome that are improved by AMPK and SIRT1 and the target molecules that likely mediate their effects

<table>
<thead>
<tr>
<th>Pathogenetic Factors or Markers</th>
<th>AMPK</th>
<th>SIRT1</th>
<th>Likely Target Molecules</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin resistance</td>
<td>−78</td>
<td>(52, 91, 104)</td>
<td>PGC-1α, NF-κB, eNOS, p53</td>
</tr>
<tr>
<td>Oxidative stress</td>
<td>(24, 45)</td>
<td>(52, 89)</td>
<td>PGC-1α</td>
</tr>
<tr>
<td>Inflammation</td>
<td>(6, 31)</td>
<td>(52, 103, 104)</td>
<td>NF-κB</td>
</tr>
<tr>
<td>Lipid abnormalities</td>
<td>(29, 78)</td>
<td>(21, 51)</td>
<td>PGC-1α, SREBP-1c, LXR</td>
</tr>
<tr>
<td>Mitochondrial dysfunction</td>
<td>(8, 35, 62, 74)</td>
<td>(21, 55, 62, 64, 69)</td>
<td>PGC-1α, eNOS</td>
</tr>
<tr>
<td>Endothelial cell dysfunction</td>
<td>(35, 109)</td>
<td>(71, 72)</td>
<td>eNOS</td>
</tr>
<tr>
<td>Decreased plasma adiponectin</td>
<td>(30, 39, 59)</td>
<td>Unknown</td>
<td></td>
</tr>
</tbody>
</table>

Relevant references are in parentheses. AMPK, AMP-activated protein kinase; SIRT1, silent information regulator T1; PGC-1α, peroxisome proliferator-activated receptor-γ coactivator-1α; eNOS, endothelial nitric oxide synthase; SREBP-1c, sterol regulatory element-binding protein-1c; LXR, liver X receptor. Lipid abnormalities could include impaired fatty acid oxidation, increased diacylglycerol and ceramide synthesis, and ectopic lipid deposition, all of which are associated with the metabolic syndrome. Adiponectin is an AMPK activator, and decreases in its plasma concentration have been associated with a predisposition to both diabetes and coronary heart disease. SIRT1 has been shown to increase adiponectin synthesis by adipocytes. In keeping with the likely clinical relevance of these effects, multiple pharmacological and physiological AMPK and SIRT1 activators have been shown to diminish or prevent atherosclerosis (106, 108), type 2 diabetes (3, 67, 68, 105), hepatic steatosis (nonalcoholic fatty liver disease) (70, 78), and Alzheimer’s disease (75) in experimental animals. Likewise, calorie restriction and exercise, and for some diseases pharmacological AMPK activators such as metformin, have shown similar benefits in humans (44, 75, 97).
have, to some extent, pharmacological agents that activate AMPK, such as metformin and the thiazolidinediones (27, 63).

CONCLUDING REMARKS

A schematic depiction of the hypothetical SIRT1/AMPK cycle and its physiological significance are presented in Fig. 7. The partnership between AMPK and SIRT1 is long standing, and it has many potential implications for our understanding of the pathogenesis and therapy of disorders associated with the metabolic syndrome and aging. On the other hand, many aspects of this partnership require further study. For instance, SIRT1 is one of seven class III histone/protein deacetylases (7, 21), and the relation of the others to AMPK is not well known. Such knowledge may be relevant since some of these sirtuins, in contrast to SIRT1, are mainly mitochondrial (SIRT3, -4, and -5) and others shuttle between the nucleus and cytoplasm (SIRT2), and their overlap in function with SIRT1 and their effects on AMPK are incompletely understood (7, 21). Likewise, LKB1, the principal upstream kinase for AMPK, activates 13 other ARKs, and their overlap in function with AMPK is unresolved. In this context, recent studies suggest that mice deficient in one of the ARKs [sucrose nonfermenting protein kinase/AMPK-related protein kinase (SNARK)] develop a metabolic syndrome phenotype (96), although at a molecular level SNARK has not been shown to mimic many of the actions of AMPK (19). Finally, it is likely that SIRT1 and AMPK have actions independent of the other, and these also need to be sorted out.

These and other questions aside, the evidence that SIRT1 and AMPK can work in tandem raises some intriguing possibilities. For instance, SIRT1 abundance and activity (5, 13, 38) and AMPK activation (74) diminish in at least some mammalian tissues with aging. Thus, if treatment with an AMPK or a SIRT1 activator individually does not reverse aging-associated abnormalities, might dual therapy be more effective? If so, treatment with SIRT1 activators might diminish the impaired ability of exercise to activate AMPK that has been observed in skeletal muscle of aging rodents (74) and obese, insulin-resistant humans (17, 87).

It has also become increasingly apparent that both AMPK and SIRT1 mediate the biological response of cells to nutrient availability and that in doing so they regulate, often interdependently, metabolism, gene expression, and many aspects of cell biology. The resultant changes in enzymes, transcriptional activators and coactivators, and the genes they regulate are often quite complex. Hopefully, the relation of such changes to SIRT1 and AMPK, which appear to act predictably to maintain cellular function and integrity, will help to unravel this complexity. Finally, recent studies have revealed that various hormones (e.g., leptin, gherelin, adiponectin, and catecholamines) and paracrine factors (endocannabinoids) regulate AMPK and that AMPK in turn mediates their actions on individual tissues and/or whole body fuel homeostasis (40, 75). Whether SIRT1 is also regulated by these molecules and mediates their actions clearly warrants investigation.

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DISCLOSURES

No conflicts of interest are declared by the author(s).

REFERENCES

2. Bandyopadhyay GK, Yu JG, Ofrecio J, Olefsky JM. Increased malonyl-CoA levels in muscle from obese and type 2 diabetic subjects lead to decreased fatty acid oxidation and increased lipogenesis; thiazolidinedione treatment reverses these defects. Diabetes 55: 2277–2285, 2006.
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Review

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