International Journal of Obesity (2008) 32, S7–S12
 0307-0565/08 $30.00
www.nature.com/ijo

REVIEW

AMPK: a key regulator of energy balance in the single cell and the whole organism

DG Hardie

Division of Molecular Physiology, College of Life Sciences, University of Dundee, Dundee, UK

The AMP-activated protein kinase (AMPK) system is a key player in regulating energy balance at both the cellular and whole-body levels, placing it at centre stage in studies of obesity, diabetes and the metabolic syndrome. It is switched on in response to metabolic stresses such as muscle contraction or hypoxia, and modulated by hormones and cytokines affecting whole-body energy balance such as leptin, adiponectin, resistin, ghrelin and cannabinoids. Once activated, it switches on catabolic pathways that generate adenosine triphosphate (ATP), while switching off ATP-consuming anabolic processes. AMPK exists as heterotrimeric complexes comprising a catalytic α-subunit and regulatory β- and γ-subunits. Binding of AMP to the γ-subunit, which is antagonized by high ATP, causes activation of the kinase by promoting phosphorylation at threonine (Thr-172) on the α-subunit by the upstream kinase LKB1, allowing the system to act as a sensor of cellular energy status. In certain cells, AMPK is activated in response to elevation of cytosolic Ca^{2+} via phosphorylation of Thr-172 by calmodulin-dependent kinase kinase-β (CaMKKβ). Activation of AMPK, either in response to exercise or to pharmacological agents, has considerable potential to reverse the metabolic abnormalities associated with type 2 diabetes and the metabolic syndrome. Two existing classes of antidiabetic drugs, that is, biguanides (for example, metformin) and the thiazolidinediones (for example, rosiglitazone), both act (at least in part) by activation of AMPK. Novel drugs activating AMPK may also have potential for the treatment of obesity.
International Journal of Obesity (2008) **32,** S7–S12; doi:10.1038/ijo.2008.116

Keywords: diabetes; metabolic syndrome; LKB1; calmodulin-dependent kinase kinase

Introduction

The AMP-activated protein kinase (AMPK) system was discovered in mammalian cell extracts as activities that phosphorylated and inactivated key enzymes of lipid biosynthesis, that is, acetyl-CoA carboxylase and 3-hydroxy-3-methylglutaryl-CoA reductase, which regulate fatty acid and cholesterol synthesis, respectively.[1] In 1987 the author's laboratory showed that these activities, which had been presumed to be distinct, were in fact functions of the same protein kinase. This kinase was allosterically activated by 5′-AMP and was also activated by phosphorylation by upstream kinases, and was renamed AMPK in 1988.[1]

Structure and regulation of AMPK

AMP-activated protein kinase and its orthologues in lower eukaryotes, for example, budding yeast, are now known to exist as heterotrimeric complexes consisting of catalytic α-subunits and regulatory β- and γ-subunits. Humans and rodents express two isoforms of α and β (α1, α2; β1, β2), and three isoforms of γ (γ1, γ2 and γ3) encoded by distinct genes.[2] Some of these are also subject to alternative splicing, leading to a large and diverse array of heterotrimeric complexes. The α-subunits have conventional serine/threonine kinase domains at the N-terminus, containing a conserved threonine residue (Thr-172) whose phosphorylation by upstream kinases is absolutely required for their activity. The primary upstream kinase was recently identified to be a complex between the tumour suppressor, LKB1, and two accessory subunits, STRAD (STE-20 related adaptor protein) and MO25.[3,4] These findings were exciting, because *LKB1* was originally identified as the gene mutated in Peutz–Jeghers syndrome, an inherited predisposition to cancer in humans. LKB1 is a classical tumour suppressor: subjects with this syndrome have heterozygous loss-of-function mutations in the *LKB1* gene and develop numerous polyps (benign tumours) in the intestine, probably due to loss of expression of their functional gene copy. They also have a 15-fold increased risk of developing malignant tumors at other sites.[5] LKB1 is now known to act upstream of 12 other members of the AMPK-related kinase family, in addition to

Correspondence: Dr DG Hardie, Division of Molecular Physiology, College of Life Sciences, University of Dundee, Sir James Black Centre, Dow Street, Dundee DD1 5EH, UK.
E-mail: d.g.hardie@dundee.ac.uk

the two isoforms of the AMPK catalytic subunit (α1 and α2).[5] There is evidence (discussed further below) that activation of AMPK inhibits cell growth and proliferation. This makes it likely that the ability of LKB1 to activate AMPK explains much of its tumour suppressor effect, although a role for the alternate downstream kinases cannot be discounted at present.

The LKB1 complex appears to be constitutively active and is not regulated by AMP. Binding of AMP to AMPK promotes net phosphorylation of Thr-172 by inhibiting its dephosphorylation (by making the kinase a less efficient substrate for protein phosphatases), as well as allosterically activating the phosphorylated form of the kinase. These two effects of AMP effectively multiply together, so that a small increase in AMP can produce a much larger effect on the kinase activity.[6] Both effects are also antagonized by high concentrations of ATP, so that AMPK is activated in a sensitive manner by a small rise in the AMP/ATP ratio. If the adenylate kinase reaction is at equilibrium (as appears to be the case in most mammalian cells), the AMP/ATP ratio will vary as the square of the ADP/ATP ratio, making the former ratio a very sensitive indicator of cellular energy status.

Some cells express an alternate pathway for AMPK activation that is triggered by increases in cytoplasmic Ca^{2+}, leading to activation of calmodulin-dependent kinase kinase-β (CaMKKβ) which, like LKB1, can phosphorylate Thr-172 on the AMPK α-subunit.[7–9] However, unlike the effect of LKB1, phosphorylation by CaMKKβ appears to be AMP-independent. The tissue distribution of CaMKKβ is more restricted than that of LKB1, with the former being most abundant in neurones and cells of the endothelial/haemopoietic lineage.

The AMPK β-subunits have two conserved regions, a central glycogen-binding domain and a C-terminal domain required for forming a complex with the α- and γ-subunits.[10] The glycogen-binding domain causes the complex to partially associate with glycogen particles. The function of this interaction is not known, although glycogen synthase (another component of glycogen particles) is a downstream target that is known to be phosphorylated and inactivated by AMPK.[11] One interesting possibility is that the AMPK system can sense some aspect of glycogen structure and provide a feedback regulation on glycogen synthesis. The γ-subunits contain four tandem repeats of a structure known as a cystathionine-β-synthase motif: these are now known to act in pairs to form two modules (termed Bateman domains) each of which binds one molecule of AMP or ATP in a mutually exclusive manner.[12] Bateman domains also occur in a few other proteins, where they bind adenosine-containing ligands, such as AMP, ATP or *S*-adenosyl methionine.[12] Intriguingly, mutations in these domains lead to a variety of human hereditary diseases that are all caused by defective ligand binding. In the case of AMPK these mutations, which cause heart disease of varying severity associated with excessive glycogen storage, prevent both binding of AMP and allosteric activation, proving that the Bateman domains on the γ-subunit form the regulatory binding sites for AMP and ATP.[12,13]

Activation of AMPK by metabolic stress

As the LKB1→AMPK signalling pathway is activated by elevation of the AMP/ATP ratio, it is switched on by any metabolic stress that disturbs energy balance by interfering with ATP synthesis, such as glucose deprivation, hypoxia or ischaemia, or metabolic poisons that inhibit glycolysis (for example, 2-deoxyglucose), the tricarboxylic acid cycle (for example, arsenite) or oxidative phosphorylation (for example, oligomycin, antimycin A, rotenone).[2] With most mammalian cells, glucose deprivation is unlikely to be a major issue *in vivo*, because they express isoforms of glucose transporter and hexokinase that are saturated by low concentrations of glucose, such that inhibition of ATP synthesis and activation of AMPK would only occur when plasma glucose dropped to levels incompatible with life. However, specialized glucose-sensing cells such as the β-cells in the Islets of Langerhans in the pancreas, and glucose-regulated neurones in the hypothalamus, express isoforms of glucose transporter (GLUT2) and hexokinase (hexokinase IV, also known as glucokinase) with a much higher K_m for glucose, so that AMPK in these cells is activated by decreases in blood glucose within the more normal physiological range. Thus, in cell lines derived from rodent pancreatic β-cells, AMPK is activated by low glucose and inhibited by high glucose[14] whereas, in fasted mice, intracerebroventricular injection of glucose, or refeeding, inhibits the α2-isoform of AMPK in regions of the hypothalamus.[15] Moreover, the known downstream consequences of lowering external glucose in both cell types, that is, decreased insulin secretion (β-cells) or increased feeding behaviour (hypothalamus) can be mimicked by the activation of AMPK at these sites, either by pharmacological or molecular biological interventions.[14–16] Thus, the AMPK system is a key player in the regulation of energy balance at the whole-body level, not just at the cellular level.

Just as there are specialized glucose-sensing cells in the pancreas and hypothalamus, so there are specialized oxygen-sensing cells where AMPK is regulated by normal physiological variations in oxygen tension. These include the glomus cells in the carotid body, which sense hypoxia in blood supplied to the brain and regulate breathing, and pulmonary artery smooth muscle cells, which contract in response to hypoxia (unlike most arterial smooth muscle cells, which *relax*), thus diverting blood flow away from poorly oxygenated regions of the lung. In collaboration with the laboratories of Evans and Peers,[17] the author has recently shown that activation of AMPK mimics the effects of hypoxia in these cells: (i) in glomus cells, entry of extracellular Ca^{2+} via voltage-gated Ca^{2+} channels and firing of action potentials in afferent neurones leading to the brain; and (ii) in pulmonary artery smooth muscle, release of

Ca^{2+} from the endoplasmic reticulum and consequent contraction.

All of the metabolic stresses mentioned above increase cellular AMP/ATP by inhibiting ATP production. A stress that activates AMPK by increasing ATP consumption is contraction in skeletal muscle.[18] There is now good evidence that many of the acute metabolic responses to exercise, including increased glucose uptake and fatty acid oxidation,[19,20] as well as the long-term adaptations to regular endurance exercise, such as increased expression of the glucose transporter GLUT4[21] and increased mitochondrial biogenesis,[22] are at least partly mediated by AMPK activation.

Regulation of AMPK by hormones and cytokines

Although orthologues of AMPK are present in primitive single-celled eukaryotes, suggesting that the system existed prior to the evolution of hormones and cytokines, the latter nevertheless appear to have acquired the ability to regulate the AMPK system. In particular, AMPK is modulated by cytokines released by adipocytes (termed *adipokines*) that regulate whole-body energy balance, such as leptin, adiponectin and resistin (reviewed in Kahn *et al*.[2]). Leptin and adiponectin both activate AMPK and increase glucose uptake and fatty acid oxidation in skeletal muscle, thus stimulating whole-body energy expenditure. Adiponectin also activates AMPK in liver, stimulating fatty acid oxidation and inhibiting glucose production, whereas resistin appears to have the opposite effects. Remarkably, although leptin activates AMPK in skeletal muscle, it causes inhibition of the α2-isoform of the kinase in regions of the hypothalamus in fasted mice, concomitant with repression of food intake. Other anorexigenic agents, such as insulin, melanocortin receptor agonists and high glucose, also inhibit AMPK in the hypothalamus of fasted mice, whereas orexigenic agents such as agouti-related protein, the gut hormone ghrelin, and cannabinoids activate the kinase in the hypothalamus of fed mice.[2,23] In addition, artificially increasing AMPK activity in the hypothalamus by using drugs or by expressing activated mutants stimulates food intake even in the fed state.[2] Taken together, these findings suggest that AMPK, acting both in the hypothalamus and in the periphery, is a key player in the regulation of the balance between whole-body energy intake and energy expenditure, and hence in the development of obesity.

The mechanisms by which adipokines and other agents affecting food intake modulate AMPK activity remain unclear. However, in cells of the endothelial/haematopoietic lineage the $Ca^{2+} \rightarrow$CaMKK pathway (discussed above) switches on AMPK in response to activation of certain receptors. In human umbilical vein endothelial cells, thrombin increases cytoplasmic Ca^{2+} via receptor-mediated release of inositol-1,4,5-trisphosphate and consequent release of Ca^{2+} from the endoplasmic reticulum. This activates AMPK, an effect that is reduced by the inhibition of CaMKKβ by pharmacological means or by interfering RNA approaches.[24] AMPK is also activated by stimulation of the antigen receptor in T lymphocytes, an effect that can be mimicked by Ca^{2+} ionophores and is blocked by pharmacological inhibitors of CaMKK.[25] The function of AMPK activation under these circumstances is not clear, but one can speculate that the Ca^{2+} trigger represents a feed-forward signal that anticipates the large demand for ATP that often follows an increase in cytoplasmic Ca^{2+} (for example, the rapid growth and proliferation that follows activation of T lymphocytes).

Downstream targets of AMPK

A full discussion of this topic is beyond the scope of this brief review, and the reader is referred elsewhere for detailed discussion.[2] In general (as summarized in Figure 1), AMPK switches on catabolic processes that provide alternative routes to generate ATP (for example, glucose uptake, glycolysis, fatty acid oxidation and mitochondrial biogenesis), while switching off anabolic processes that consume ATP, such as the synthesis of fatty acids, triglyceride, cholesterol, glucose (via gluconeogenesis) and glycogen. These effects can occur through distinct mechanisms with different time courses: (i) acute effects on metabolism due to direct phosphorylation of metabolic enzymes (for example, inhibition of cholesterol synthesis due to phosphorylation of 3-hydroxy-3-methylglutaryl-CoA reductase); (ii) longer-term effects due to changes in gene expression (for example, upregulation of glucose and fat oxidation due to increased expression of mitochondrial genes, downregulation of gluconeogenic genes); and (iii) combined acute and longer-term effects (for example, inhibition of fatty acid synthesis via direct phosphorylation of the ACC1 isoform of acetyl-CoA carboxylase, combined with inhibition of expression of the ACC1 and fatty acid synthase genes). Although not shown in Figure 1, AMPK activation also inhibits protein synthesis, both via inhibition of the target-of-rapamycin pathway[26] (thus inhibiting initiation of translation), and via activation of elongation factor-2 kinase[27] (thus inhibiting elongation of translation). The ability of AMPK to inhibit protein synthesis and other biosynthetic pathways contributes to its effects to limit hypertrophy of non-dividing cells, whereas in proliferating cells, progress through the cell cycle is also blocked by AMPK activation.[28]

Role of AMPK in obesity, diabetes and the metabolic syndrome

The ability of AMPK to switch cells from an anabolic to a catabolic state suggests that activators of the kinase might be effective agents for treatment of obesity, type 2 diabetes and the metabolic syndrome. Type 2 diabetes is characterized by an elevated plasma glucose primarily caused by insulin

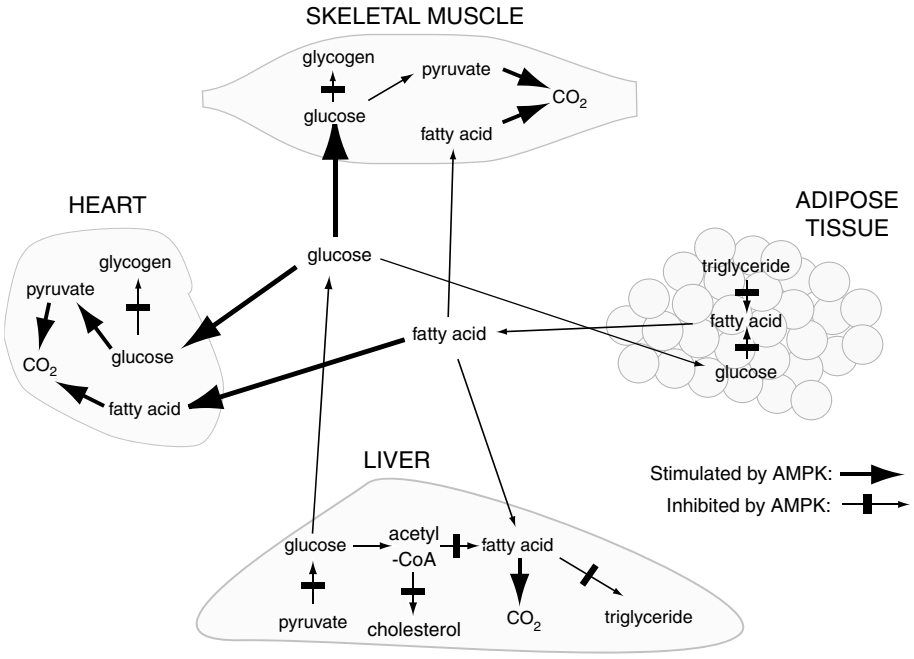

Figure 1 Summary of the acute and longer-term changes in carbohydrate and lipid metabolism induced by AMPK activation in the liver, heart, skeletal muscle and adipose tissue of mammals. Processes stimulated by AMPK activation are shown with thick arrows, those inhibited by AMPK activation are shown by thin arrows with bars across.

resistance, and risk of developing this condition is greatly increased by obesity. Activation of AMPK has the potential to lower plasma glucose both by repressing expression of enzymes of gluconeogenesis in the liver, and by increasing glucose uptake by muscle and other tissues (Figure 1). Insulin resistance is also often associated with elevated storage of triglycerides in tissues other than adipose tissue such as muscle and liver, together with a relative deficit in mitochondrial oxidative capacity in those organs.[29] By inhibiting fatty acid and triglyceride synthesis and stimulating fatty acid oxidation and mitochondrial biogenesis, AMPK activation has the potential to reduce hypertriglyceridemia, as well as elevated storage of triglycerides in muscle and liver. Finally, the metabolic syndrome involves a cluster of related metabolic abnormalities that are all potentially reversed by AMPK activation, including insulin resistance, abdominal obesity, hypertension, and altered plasma lipids, especially hypertriglyceridemia and low high-density lipoprotein cholesterol. These abnormalities are all risk factors for cardiovascular disease.

The developing epidemic of obesity and type 2 diabetes in developed and developing countries is generally thought to be due to increasing urbanization, with consequent decreased levels of exercise in the general population, coupled with all-day and all-year availability of high-energy foodstuffs. It is well established that regular exercise is an effective method of treating insulin resistance and type 2 diabetes, as well as preventing their onset in susceptible individuals, and it seems likely that the beneficial effects of exercise are at least partly mediated by AMPK activation. The ability to more directly test the efficacy of AMPK activation came with the development of 5-aminoimidazole-4-carboxamide ribonucleoside (which is taken up into cells and converted to the AMP mimetic ZMP) as a method to activate AMPK in intact cells. *In vivo* treatment with 5-aminoimidazole-4-carboxamide ribonucleoside of several animal models of insulin resistance and the metabolic syndrome, such as genetically obese (ob/ob or fa/fa) mice and rats, and fat-fed rats, showed that the drug was able to reverse glucose intolerance and insulin resistance, lower plasma triglycerides and free fatty acids, increase high-density lipoprotein cholesterol, and even reduce hypertension (see Hardie (2004)[30]). Further proof of the concept that AMPK activators had potential for treatment of insulin resistance and type 2 diabetes came with findings that two existing classes of drug used to treat these conditions, that is, the biguanides (for example, metformin) and the thiazolidinediones (for example, rosiglitazone) can both activate AMPK.[31,32] Both classes of drug may activate AMPK in part by inhibiting Complex I of the respiratory chain[33] and thus elevating cellular AMP/ATP ratios. The thiazolidinediones are also agonists for peroxisome proliferator-activated receptor-γ (PPAR-γ) in adipocytes,[34] through which they are known to increase the expression and release of adiponectin.[35] Release of adiponectin explains, at least in part, the therapeutic actions of thiazolidinediones,[36] although the downstream effects of adiponectin are, of course, also thought to be mediated by AMPK. In the case of metformin, there is now good evidence

that activation of liver AMPK mediates its antihyperglycemic effects, because they are completely ablated in a mouse with a liver-specific knockout of the upstream kinase, LKB1, in which AMPK can no longer be activated by the drug.[37]

It remains unclear at present whether activators of AMPK would be effective treatments for obesity *per se*. However, encouraging pointers in that direction are findings that three mouse strains that are resistant to diet-induced obesity, that is: (i) stearoyl-CoA desaturase-1 knockouts;[38] (ii) mice overexpressing uncoupling protein-1 in white adipocytes;[39] and (iii) mice overexpressing uncoupling protein-3 in skeletal muscle,[40] all exhibit increased basal activity of AMPK in the tissues affected.

Conclusions

The AMPK system is switched on either by LKB1, triggered by increases in cellular AMP/ATP ratio or (in specific cell types) by elevated Ca^{2+} and CaMKKβ. Whatever the upstream trigger(s), AMPK activation causes a switch from an anabolic state promoting increased synthesis and storage of glucose, glycogen, fatty acids, cholesterol and triglycerides, together with increased cell growth (that is, hypertrophy) and/or proliferation, to a catabolic state involving oxidation of glucose, fatty acids and triglycerides, and inhibition of cell growth and proliferation. Activation of AMPK, either by increased levels of exercise or by pharmacological means, has great potential to reverse the metabolic abnormalities of type 2 diabetes and the metabolic syndrome, and perhaps also obesity.

Acknowledgements

Recent studies in the author's laboratory have been funded by Programme Grants from the Wellcome Trust, and by the EXGENESIS Integrated project (LSHM-CT-2004-005272) funded by the European Commission.

Conflict of interest

The author states no conflict of interest.

References

1 Hardie DG, Carling D, Sim ATR. The AMP-activated protein kinase—a multisubstrate regulator of lipid metabolism. *Trends Biochem Sci* 1989; **14**: 20–23.
2 Kahn BB, Alquier T, Carling D, Hardie DG. AMP-activated protein kinase: ancient energy gauge provides clues to modern understanding of metabolism. *Cell Metab* 2005; **1**: 15–25.
3 Hawley SA, Boudeau J, Reid JL, Mustard KJ, Udd L, Mäkelä TP *et al*. Complexes between the LKB1 tumor suppressor, STRADa/b and MO25a/b are upstream kinases in the AMP-activated protein kinase cascade. *J Biol* 2003; **2**: 28.
4 Woods A, Johnstone SR, Dickerson K, Leiper FC, Fryer LG, Neumann D *et al*. LKB1 is the upstream kinase in the AMP-activated protein kinase cascade. *Curr Biol* 2003; **13**: 2004–2008.
5 Alessi DR, Sakamoto K, Bayascas JR. Lkb1-dependent signaling pathways. *Annu Rev Biochem* 2006; **75**: 137–163.
6 Hardie DG, Salt IP, Hawley SA, Davies SP. AMP-activated protein kinase: an ultrasensitive system for monitoring cellular energy charge. *Biochem J* 1999; **338**: 717–722.
7 Hawley SA, Pan DA, Mustard KJ, Ross L, Bain J, Edelman AM *et al*. Calmodulin-dependent protein kinase kinase-beta is an alternative upstream kinase for AMP-activated protein kinase. *Cell Metab* 2005; **2**: 9–19.
8 Woods A, Dickerson K, Heath R, Hong SP, Momcilovic M, Johnstone SR *et al*. Ca2+/calmodulin-dependent protein kinase kinase-beta acts upstream of AMP-activated protein kinase in mammalian cells. *Cell Metab* 2005; **2**: 21–33.
9 Hurley RL, Anderson KA, Franzone JM, Kemp BE, Means AR, Witters LA. The Ca^{2+}/calmoldulin-dependent protein kinase kinases are AMP-activated protein kinase kinases. *J Biol Chem* 2005; **280**: 29060–29066.
10 Hudson ER, Pan DA, James J, Lucocq JM, Hawley SA, Green KA *et al*. A novel domain in AMP-activated protein kinase causes glycogen storage bodies similar to those seen in hereditary cardiac arrhythmias. *Current Biol* 2003; **13**: 861–866.
11 Jørgensen SB, Nielsen JN, Birk JB, Olsen GS, Viollet B, Andreelli F *et al*. The alpha2-5′AMP-activated protein kinase is a site 2 glycogen synthase kinase in skeletal muscle and is responsive to glucose loading. *Diabetes* 2004; **53**: 3074–3081.
12 Scott JW, Hawley SA, Green KA, Anis M, Stewart G, Scullion GA *et al*. CBS domains form energy-sensing modules whose binding of adenosine ligands is disrupted by disease mutations. *J Clin Invest* 2004; **113**: 274–284.
13 Burwinkel B, Scott JW, Bührer C, van Landeghem FK, Cox GF, Wilson CJ *et al*. Fatal congenital heart glycogenosis caused by a recurrent activating R531Q mutation in the g2 subunit of AMP-activated protein kinase (PRKAG2), not by phosphorylase kinase deficiency. *Am J Hum Genet* 2005; **76**: 1034–1049.
14 da Silva Xavier G, Leclerc I, Varadi A, Tsuboi T, Moule SK, Rutter GA. Role for AMP-activated protein kinase in glucose-stimulated insulin secretion and preproinsulin gene expression. *Biochem J* 2003; **371**: 761–774.
15 Minokoshi Y, Alquier T, Furukawa N, Kim YB, Lee A, Xue B *et al*. AMP-kinase regulates food intake by responding to hormonal and nutrient signals in the hypothalamus. *Nature* 2004; **428**: 569–574.
16 Andersson U, Filipsson K, Abbott CR, Woods A, Smith K, Bloom SR *et al*. AMP-activated protein kinase plays a role in the control of food intake. *J Biol Chem* 2004; **279**: 12005–12008.
17 Evans AM, Mustard KJ, Wyatt CN, Peers C, Dipp M, Kumar P *et al*. Does AMP-activated protein kinase couple inhibition of mitochondrial oxidative phosphorylation by hypoxia to calcium signaling in O_2-sensing cells? *J Biol Chem* 2005; **280**: 41504–41511.
18 Winder WW, Hardie DG. Inactivation of acetyl-CoA carboxylase and activation of AMP-activated protein kinase in muscle during exercise. *Am J Physiol* 1996; **270**: E299–E304.
19 Mu J, Brozinick JT, Valladares O, Bucan M, Birnbaum MJ. A role for AMP-activated protein kinase in contraction- and hypoxia-regulated glucose transport in skeletal muscle. *Mol Cell* 2001; **7**: 1085–1094.
20 Sakamoto K, McCarthy A, Smith D, Green KA, Hardie GD, Ashworth A *et al*. Deficiency of LKB1 in skeletal muscle prevents AMPK activation and glucose uptake during contraction. *EMBO J* 2005; **24**: 1810–1820.
21 Zheng D, MacLean PS, Pohnert SC, Knight JB, Olson AL, Winder WW *et al*. Regulation of muscle GLUT-4 transcription by AMP-activated protein kinase. *J Appl Physiol* 2001; **91**: 1073–1083.

22 Zong H, Ren JM, Young LH, Pypaert M, Mu J, Birnbaum MJ *et al*. AMP kinase is required for mitochondrial biogenesis in skeletal muscle in response to chronic energy deprivation. *Proc Natl Acad Sci USA* 2002; **99**: 15983–15987.
23 Kola B, Hubina E, Tucci SA, Kirkham TC, Garcia EA, Mitchell SE *et al*. Cannabinoids and ghrelin have both central and peripheral metabolic and cardiac effects via AMP-activated Protein Kinase. *J Biol Chem* 2005; **280**: 25196–25201.
24 Stahmann N, Woods A, Carling D, Heller R. Thrombin activates AMP-activated protein kinase in endothelial cells via a pathway involving Ca2+/calmodulin-dependent protein kinase kinase beta. *Mol Cell Biol* 2006; **26**: 5933–5945.
25 Tamás P, Hawley SA, Clarke RG, Mustard KJ, Green K, Hardie DG *et al*. Regulation of the energy sensor AMP-activated protein kinase by antigen receptor and Ca2+ in T lymphocytes. *J Exp Med* 2006; **203**: 1665–1670.
26 Inoki K, Zhu T, Guan KL. TSC2 mediates cellular energy response to control cell growth and survival. *Cell* 2003; **115**: 577–590.
27 Horman S, Browne G, Krause U, Patel J, Vertommen D, Bertrand L *et al*. Activation of AMP-activated protein kinase leads to the phosphorylation of Elongation Factor 2 and an inhibition of protein synthesis. *Current Biol* 2002; **12**: 1419–1423.
28 Imamura K, Ogura T, Kishimoto A, Kaminishi M, Esumi H. Cell cycle regulation via p53 phosphorylation by a 5′-AMP activated protein kinase activator, 5-aminoimidazole-4-carboxamide-1-beta-d-ribofuranoside, in a human hepatocellular carcinoma cell line. *Biochem Biophys Res Commun* 2001; **287**: 562–567.
29 Lowell BB, Shulman GI. Mitochondrial dysfunction and type 2 diabetes. *Science* 2005; **307**: 384–387.
30 Hardie DG. AMP-activated protein kinase: a master switch in glucose and lipid metabolism. *Rev Endocr Metab Disord* 2004; **5**: 119–125.
31 Fryer LG, Parbu-Patel A, Carling D. The anti-diabetic drugs rosiglitazone and metformin stimulate AMP-activated protein kinase through distinct pathways. *J Biol Chem* 2002; **277**: 25226–25232.
32 Zhou G, Myers R, Li Y, Chen Y, Shen X, Fenyk-Melody J *et al*. Role of AMP-activated protein kinase in mechanism of metformin action. *J Clin Invest* 2001; **108**: 1167–1174.
33 Brunmair B, Staniek K, Gras F, Scharf N, Althaym A, Clara R *et al*. Thiazolidinediones, like metformin, inhibit respiratory complex I: a common mechanism contributing to their antidiabetic actions. *Diabetes* 2004; **53**: 1052–1059.
34 Lehmann JM, Moore LB, Smith-Oliver TA, Wilkison WO, Willson TM, Kliewer SA. An antidiabetic thiazolidinedione is a high affinity ligand for peroxisome proliferator-activated receptor gamma (PPAR gamma). *J Biol Chem* 1995; **270**: 12953–12956.
35 Maeda N, Takahashi M, Funahashi T, Kihara S, Nishizawa H, Kishida K *et al*. PPARγ ligands increase expression and plasma concentrations of adiponectin, an adipose-derived protein. *Diabetes* 2001; **50**: 2094–2099.
36 Kubota N, Terauchi Y, Kubota T, Kumagai H, Itoh S, Satoh H *et al*. Pioglitazone ameliorates insulin resistance and diabetes by both adiponectin-dependent and -independent pathways. *J Biol Chem* 2006; **281**: 8748–8755.
37 Shaw RJ, Lamia KA, Vasquez D, Koo SH, Bardeesy N, Depinho RA *et al*. The kinase LKB1 mediates glucose homeostasis in liver and therapeutic effects of metformin. *Science* 2005; **310**: 1642–1646.
38 Dobrzyn P, Dobrzyn A, Miyazaki M, Cohen P, Asilmaz E, Hardie DG *et al*. Stearoyl-CoA desaturase 1 deficiency increases fatty acid oxidation by activating AMP-activated protein kinase in liver. *Proc Natl Acad Sci USA* 2004; **101**: 6409–6414.
39 Matejkova O, Mustard KJ, Sponarova J, Flachs P, Rossmeisl M, Miksik I *et al*. Possible involvement of AMP-activated protein kinase in obesity resistance induced by respiratory uncoupling in white fat. *FEBS Lett* 2004; **569**: 245–248.
40 Schrauwen P, Hardie DG, Roorda B, Clapham JC, Abuin A, Thomason-Hughes M *et al*. Improved glucose homeostasis in mice overexpressing human UCP3: a role for AMP-kinase? *Int J Obes Relat Metab Disord* 2004; **28**: 824–828.