Chapter 2
Regulation of Carbohydrate Metabolism, Lipid Metabolism, and Protein Metabolism by AMPK

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Contents

Abstract This chapter summarizes AMPK function in the regulation of substrate and energy metabolism with the main emphasis on carbohydrate and lipid metabolism, protein turnover, mitochondrial biogenesis, and whole-body energy homeostasis. AMPK acts as whole-body energy sensor and integrates different signaling pathway to meet both cellular and body energy requirements while inhibiting energy-consuming processes but also activating energy-producing ones. AMPK mainly promotes glucose and fatty acid catabolism, whereas it prevents protein, glycogen, and fatty acid synthesis.

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2.1 Historical Background

The AMP-activated protein kinase (AMPK) has an important place in the regulation of signaling pathways involved in energy and substrate metabolism. AMPK senses cellular energy status by monitoring ADP/ATP and AMP/ATP ratios and nutrient availability and regulates cellular events by stimulating ATP-generating cellular processes (such as glucose uptake, glycolysis, and fatty acid oxidation) while inhibiting ATP-consuming processes (such as fatty acid and protein synthesis) (Hardie et al. 2006) (Fig. 2.1). In order to adapt required energy demands, AMPK has acute effects on metabolic enzymes by direct phosphorylation as well as long-term action to change the transcriptional levels of metabolic proteins and enzymes.

The discovery of AMPK dates back to the 1970s and is clearly linked to lipid metabolism when the activity of Acetyl-CoA carboxylase (ACC) was shown to be regulated by phosphorylation and dephosphorylation reactions (Carlson and Kim 1973). Even if not yet identified, they partially purified the protein kinase responsible for ACC phosphorylation and called it ACC kinase. It was shown that ATP incorporation into liver-isolated ACC was correlated with its decreased carboxylase activity in fractions where the ACC kinase was present. ACC is a rate-limiting enzyme for fatty acid synthesis. Indeed, it carboxylates acetyl-CoA into malonyl-CoA, the first and regulatory step in fatty acid synthesis. Similar findings were simultaneously obtained with HMG-CoA reductase (HMGR), the rate-limiting enzyme of cholesterol biosynthesis pathway. HMGR was found to be negatively regulated by phosphorylation via a protein kinase present in liver cytosol (Beg et al. 1973). Inactivation of ACC and HMGR by their respective associated protein kinases and their reactivation by phosphatase treatment were confirmed later (Beg et al. 1979; Ingebritsen et al. 1981). ACC kinase and HMGR kinase were detected to be similarly positively regulated by cellular AMP levels and later on, in the late 1980s, it was find out that both enzymes were activated by the same protein kinase which has been called AMPK (Carling et al. 1987; Ferrer et al. 1985; Yeh et al. 1980; Munday et al. 1988; Carling et al. 1989).

AMPK is stimulated by AMP and inhibited by ATP, making it dependent on what is called the "adenylate energy charge," which is a monitor of the energetic level of the cell. Regulation of AMPK activity by cellular energy status makes AMPK a cellular fuel gauge and puts it into center for the coordination of cellular signaling events in different tissues. AMPK also regulates energy metabolism in the whole body via its action on hypothalamus in the brain as well as through the action of hormones and adipokines. The role of AMPK in the regulation of both cellular and whole-body energy metabolism is multifaceted and will be discussed under the

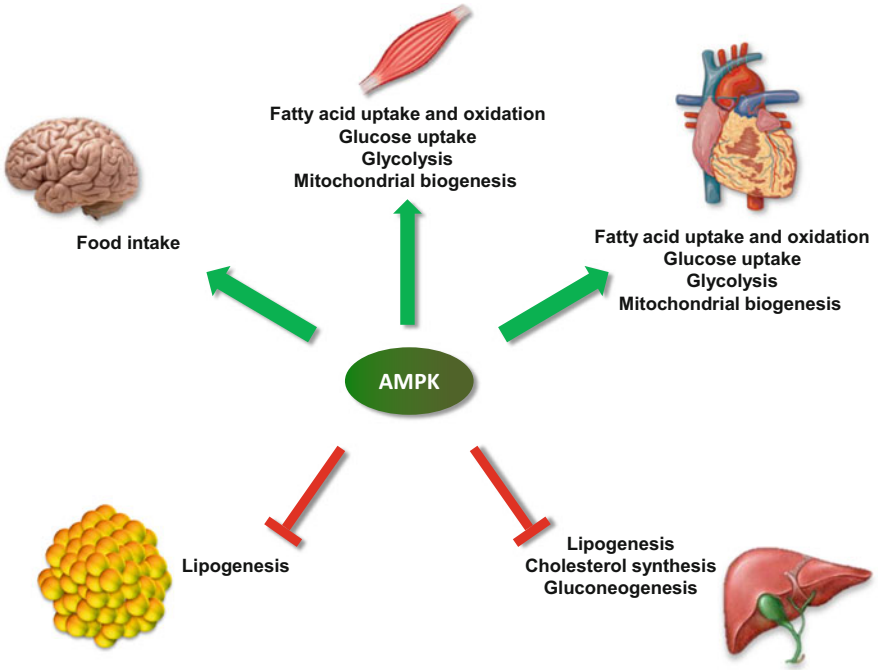

Fig. 2.1 AMPK regulates whole-body energy level. AMPK activation integrates different cellular functions to preserve energy while inhibiting energy-consuming processes and, conversely, activating energy-producing processes. Activation of AMPK by energy deprivation (fasting, exercise), by hormones, or pharmacologically leads to phosphorylation and (in)activation of numerous downstream targets in different tissues (see text for details). These actions of AMPK contribute to whole-body energy metabolism (see text for more details)

five main parts of this chapter as AMPK in carbohydrate and lipid metabolism, its role in whole-body insulin sensitivity, mitochondrial biogenesis, and protein turnover.

2.2 AMPK in Carbohydrate Metabolism

AMPK is ubiquitously expressed in the whole body and plays a vital role in substrate and energy metabolism through coordinating different cellular functions between different organs. Notably, AMPK activation is associated with whole-body insulin sensitivity. AMPK regulates carbohydrate metabolism by stimulating glucose uptake and glycolysis in insulin-sensitive tissues (heart, skeletal muscle, and adipose tissue) as well as inhibiting glucose production in liver. AMPK activation promotes cellular glucose uptake in an insulin-independent manner by translocation of glucose transporter 4 (GLUT4) to the plasma membrane as well as leading

increases in the expression levels of GLUT1 and 4. Historically, it has been shown that physiological activation of AMPK via exercise and/or pharmacological activation with 5-aminoimidazole-4-carboxamide ribonucleoside (AICAR) or antidiabetic drug metformin stimulates glucose uptake into muscles. Muscle glucose uptake caused by AICAR-mediated AMPK activation and contraction was not prevented by the phosphatidylinositol (PI) 3-kinase (PI3K) inhibitor wortmannin, indicating that AMPK acts on GLUT4 translocation and subsequent glucose uptake via a different mechanism than insulin signaling (Hayashi et al. 1998; Bergeron et al. 1999). Since muscle glucose uptake constitutes the important part of glucose clearance of the body, AMPK activation via exercise and contraction and AMPK-mediated muscle glucose uptake and glucose metabolism gain more importance for whole-body glucose clearance also during some pathophysiological conditions such as disease accompanied with insulin resistance. This makes AMPK an important target for the development of therapeutic approaches to treat diabetes and other insulin resistance-associated diseases. Therapeutic approaches targeting AMPK will be discussed further in this book.

2.2.1 Glucose Uptake

GLUT4 is mainly expressed in heart, skeletal muscle, and adipose tissue, and it plays important role in controlling the whole-body glucose homeostasis. In these tissues, extracellular glucose gradient and plasma membrane, GLUT4 levels are the main rate-limiting steps for glucose uptake. Insulin, muscle contractions, and exercise stimulate translocation of GLUT4-containing vesicles to plasma membrane and thereby facilitate glucose entry. Many studies have been performed using AICAR as pharmacological AMPK activator. AICAR-mediated muscle glucose uptake requires AMPKα2 but not AMPKα1 (Jorgensen et al. 2004a). In LKB1-deficient mouse muscles, basal activity of AMPKα2 is reduced and both muscle contraction and AICAR are neither able to increase the basal activity of AMPK nor able to stimulate glucose uptake, indicating the dependence of AMPK activation to LKB1 (Sakamoto et al. 2005). However, genetic evidences linking AMPK activation observed during muscle exercise to glucose uptake are still conflicting and partially inconclusive. Contraction-mediated glucose uptake is seriously impaired in muscle of double AMPKβ1/β2-deficient mice (O'Neill et al. 2011), whereas deletion of both AMPKα1 and AMPKα2 isoforms has almost no impact (Lantier et al. 2014). Concerning the heart, both electrical stimulation and pharmacological activation of AMPK in cardiomyocytes result in increase in glucose uptake (Habets et al. 2009; Zarrinpashneh et al. 2006). Paradoxically, increased workload in a model of ex vivo perfused working heart increases glucose utilization without any modification in AMP/ATP ratio and AMPK activity but is associated with Akt signaling and increased glycolysis (Beauloye et al. 2002). However, exercise increases cardiac AMPK activity and glucose uptake (Coven et al. 2003), but this could be linked to a β-adrenergic response (An et al. 2005). In the heart, AMPK-

dependent increase in glucose uptake is also linked to energetic stress situations like myocardial ischemia (Zarrinpashneh et al. 2006). In adipocytes, AMPK has been proposed to participate in the stimulation of glucose uptake mediated by adiponectin (Wu et al. 2003).

GLUT4 translocation is a complex process involving intracellular sorting of GLUT4 storing vesicles, transport of these vesicles to plasma membrane along with cytoskeletal proteins, docking, tethering, and fusion with the plasma membrane. The molecular mechanism responsible for GLUT4 translocation upon insulin stimulation has been well described (Rowland et al. 2011). Binding of insulin to its membrane receptor, which is an integral protein in cellular membranes, activates its tyrosine kinase activity, subsequently leading to tyrosine phosphorylation of insulin receptor substrate proteins (Fig. 2.2). This is followed by the recruitment and activation of PI3K, which results in the generation of second messenger PI-3,4,5-triphosphate (PIP3). PIP3 triggers the activation of Akt (also known as protein kinase B) through the action of two distinct upstream mediators, 3-phosphoinositide-dependent protein kinase-1 (PDK-1) and the mammalian target of rapamycin (mTOR) complex 2 (Destefano and Jacinto 2013; Manning and Cantley 2007). Akt substrate of 160 kDa (AS160, also known as TBC1D4) and TBC1D1 were identified as Akt target proteins. These targets are GTPase activating

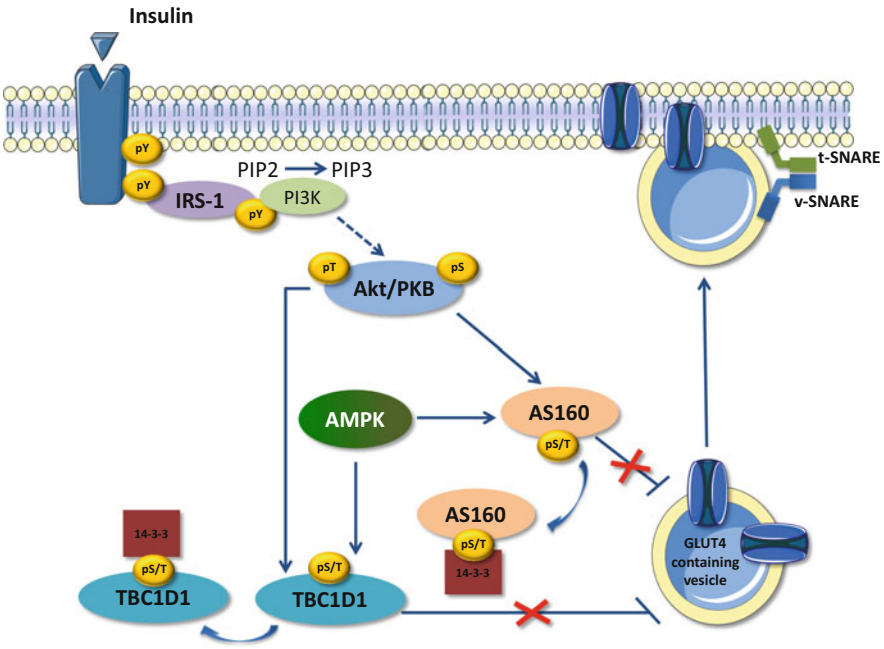

Fig. 2.2 Activation of AMPK increases glucose uptake independently of insulin signaling. AMPK mimics insulin by directly targeting AS160 and TBC1D1. Phosphorylation and inhibition of AS160 and TBC1D1 by AMPK result in translocation of GLUT4-containing vesicles to plasma membrane and concomitant glucose uptake

proteins (GAPs) for Rab, a small G protein known to be involved in vesicle formation, movement, and fusion (Zerial and McBride 2001). AS160 was first discovered in 3T3-L1 adipocytes as a downstream target of Akt under insulin stimulation (Kane et al. 2002; Sano et al. 2003). Afterward, many groups showed that activation of AMPK, either via contraction or AICAR, also promotes AS160 phosphorylation and leads to GLUT4 translocation and subsequent glucose uptake into muscle and adipose tissue (Kane et al. 2002; Sano et al. 2003; Bruss et al. 2005). Both AMPK and Akt phosphorylate several residues of AS160. A number of phosphorylation sites including Ser-588 and Thr-642 are common, others being specific to each stimulating pathway (Kramer et al. 2006). TBC1D1 is similarly phosphorylated by insulin and AMPK activators (Middelbeek et al. 2013; Pehmoller et al. 2009). Some of the phosphorylation sites in AS160 and TBC1D1 are responsible for their binding to 14-3-3 protein and their dissociation from GLUT4 storage vesicles, allowing translocation (Geraghty et al. 2007; Chen et al. 2008). It has to be mentioned that AMPK and insulin can also interact with one another to overstimulate glucose uptake independently of Akt/AS160 (Ginion et al. 2011). Fusion of GLUT4-containing vesicles with the plasma membrane requires a complex formation between target membrane-soluble *N*-ethylmaleimide-sensitive factor attachment protein receptors (t-SNAREs) and vesicle-associated SNAREs (v-SNAREs) (Sadler et al. 2015). Vesicle-associated membrane proteins (VAMPs) are subfamily of v-SNARES. Different VAMPs have been shown to be regulated in response to insulin and AMPK activators in cardiomyocytes (Schwenk et al. 2010). Besides GLUT4, muscle contraction also stimulates VAMP2, VAMP5, and VAMP7 translocation to cell membrane (Rose et al. 2009).

In addition to the acute regulation of glucose uptake, AMPK-mediated transcriptional regulation of skeletal muscle GLUT4 contributes to the regulation of whole-body insulin sensitivity by exercise in human and animal models (Holmes and Dohm 2004). The molecular mechanisms of this increase in GLUT4 transcription involve the phosphorylation of both peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1α) and histone deacetylase (HDAC) 5 (McGee et al. 2008; McGee and Hargreaves 2004). The phosphorylation of HDAC5 on Serines 259 and 498 by AMPK was shown to be sufficient to induce GLUT4 transcription (McGee et al. 2008). AMPK can directly interact and phosphorylate PGC-1α in vitro (Canto et al. 2009). Furthermore, AMPK activation has been shown to induce activation of two transcription factors, GLUT4 enhancer factor (GEF) and myocyte enhancer factor (MEF2), both responsible for GLUT4 expression (Holmes et al. 2005; Jager et al. 2007).

2.2.2 Glycolysis

Once glucose has been taken into the cell by GLUT4, it is rapidly phosphorylated into glucose-6 phosphate (G6P) by hexokinase II. G6P is converted to fructose

6-phosphate by glucose 6-phosphate isomerase and then to fructose 1,6-bisphosphate by phosphofructokinase 1 (PFK1). PFK1 is allosterically activated by increased energy deficit (AMP levels), as well as by fructose-2,6-bisphosphate (Fru-2,6-P_2) which is synthesized by 6-phosphofructokinase-2 (PFK2). PFK-2 is activated upon phosphorylation by AMPK and promotes glycolysis in the ischemic heart (Marsin et al. 2000), in the activated monocytes (Marsin et al. 2002), and in hypoxic cancer cells (Bando et al. 2005).

2.2.3 Glycogen Metabolism

Glycogen levels are dynamically regulated as a function of both glycogenesis (glycogen production) and glycogenolysis (glycogen breakdown) in tissues like liver and muscle. Glycogen levels constitute an important portion of energy source for muscle energy requirements during contraction and exercise. Glycogen synthase (GS), the enzyme responsible for glycogenesis, is allosterically regulated by G6P levels but can be also regulated by phosphorylation. It has been shown that AMPK phosphorylates and inhibits GS (Jorgensen et al. 2004b; Halse et al. 2003). The relationship between glycogen and AMPK is even more complex knowing that AMPKβ subunits contain a carbohydrate-binding module (CBM) that targets AMPK to glycogen, connecting the protein kinase close to its substrate GS (Polekhina et al. 2003; Koay et al. 2010). Autophosphorylation of AMPKβ on Thr-148 located at proximity of the CBM affects its ability to bind carbohydrates (Oligschlaeger et al. 2015).

2.2.4 Gluconeogenesis

Blood glucose is crucial for many cells and its concentration stays in a narrow range. Lower blood glucose levels (hypoglycemia) can be detrimental for brain, whereas high blood glucose levels (hyperglycemia) can lead to insulin resistance-associated diseases. Therefore, maintaining blood glucose levels is essential and liver plays a key role by regulating glucose production either via glycogenolysis or gluconeogenesis, in response to hormones (such as insulin and glucagon) and energy status. Metformin decreases high blood glucose levels by preventing hepatic glucose production (An and He 2016). Primary findings revealed that this action partly includes AMPK activation (Shaw et al. 2005). However, controversy came later with the nice study of Foretz and colleagues showing that metformin action on gluconeogenesis similarly occurs in the absence of LKB1/AMPK (Foretz et al. 2010). Nevertheless, AMPK activation with other drugs was also shown to partly block hepatic glucose production (Guo et al. 2016).

2.3 AMPK in Lipid Metabolism

Skeletal muscle contraction and exercise lead to AMPK activation and thereby promote fatty acid uptake and oxidation into insulin-sensitive tissues mainly in muscle (skeletal and heart muscle) and adipose tissue while inhibiting lipid synthesis (lipogenesis) in liver. Adipose tissue is the main lipid storage place in human body. Accumulation of lipids other than in adipose tissue contributes to lipid-induced insulin resistance and associated diseases, which will be further discussed in this book. Lipid metabolism starts with the entry of fatty acids into cells. Depending on the cellular energy status, fatty acids taken up across the plasma membrane are converted into fatty acyl-CoAs and either directed to mitochondria for β-oxidation or stored as lipids in lipogenic tissues such as adipose tissue and liver (Bickerton et al. 2007; Glatz et al. 2010).

2.3.1 Fatty Acid Uptake

Transportation of long-chain fatty acids (LCFA) into cells requires protein type transporters. Fatty acid transport proteins (FATP1–6), plasma membrane associated fatty-acid binding protein (FABPpm), and fatty acid translocase CD36 are mostly expressed fatty acid transporters in different type of tissues (Glatz et al. 2010; Coburn et al. 2000; Luiken et al. 2003). LCFA uptake is mediated either by one or by the cooperation of more fatty acid transporters. CD36 which is present both intracellularly and also on plasma membrane is crucial for LCFA uptake in response to both insulin and muscle contraction in heart and skeletal muscle (Luiken et al. 2002; Koonen et al. 2005). In myocytes, both exercise and pharmacological activation of AMPK stimulate translocation of intracellularly stored CD36 to plasma membrane in a way similar to that of insulin signaling (Kola et al. 2008). Similarly to GLUT4 translocation, this action also requires phosphorylation and inactivation of AS160 by AMPK (Samovski et al. 2012). AMPK-mediated long-chain fatty acid uptake depends on the plasma membrane CD36 levels (Habets et al. 2007) and signals through activation of the LKB1/AMPK pathway (Habets et al. 2009).

2.3.2 Lipid Synthesis

In the historical background of this chapter, we already focused on the primordial negative regulation of AMPK on ACC and HMGR, the rate-limiting steps of fatty acid and cholesterol synthesis, respectively (Carling et al. 1987; Ferrer et al. 1985; Yeh et al. 1980; Munday et al. 1988; Carling et al. 1989). However, regulation of lipid synthesis by AMPK is multifaceted and targets several other central elements

of this metabolic process. AMPK can act via the regulation of sterol regulatory element-binding protein-1 (SREBP-1) (Li et al. 2011). SREBPs are a family of transcription factors, which regulate the expression of enzymes required for endogenous cholesterol, fatty acid (FA), triacylglycerol, and phospholipid synthesis (Eberle et al. 2004). Activation of AMPK in liver and adipocytes inhibits lipogenesis by downregulating fatty acid synthase (FAS) activity through decreased SREBP-1 gene expressions (Madsen et al. 2015). It is interesting to note that adiponectin suppresses hepatic fatty acid synthesis through suppression of SREBP1c expression in an AdipoR1/LKB1/AMPK-dependent pathway (Awazawa et al. 2009).

Triacylglycerol (TAG) synthesis (esterification) and its counterpart, breakdown of lipids (lipolysis), are dynamic processes involved in the regulation of lipid levels in tissues like adipose tissue, liver, and skeletal muscle. Glycerol-3-phosphate acyltransferase (GPAT) is a rate-limiting enzyme for the synthesis of lysophosphatidic acid, the first step in TAG formation, and it is mainly expressed in adipose tissue and liver and, to a lesser extent, in skeletal muscle (Takeuchi and Reue 2009). It has been shown that GPAT can be targeted and inhibited by AMPK (Muoio et al. 1999).

2.3.3 Acetyl-CoA Carboxylase and Fatty Acid Oxidation

As mentioned previously, ACC phosphorylation/inhibition by AMPK leads to a decreased production of malonyl-CoA and subsequent inhibition of fatty acid synthesis. On the other hand, malonyl-CoA acts as an inhibitor of carnitine palmitoyl-CoA transferase-1 (CPT-1), a rate-limiting enzyme for mitochondrial fatty acid β-oxidation (Bruce et al. 2009; Nada et al. 1995). CPT-1 is located on the outer mitochondrial membrane and catalyzes the transfer of acyl moiety of LCFA-CoAs to carnitine and facilitates transport of LCFA-CoAs across the inner mitochondrial membrane. Indeed, the mitochondrial inner membrane is not permeable to acyl-CoA molecules. Following the phosphorylation and subsequent inhibition of ACC by AMPK, a fall in malonyl-CoA levels releases the inhibitory effect of malonyl-CoA on CPT-1, which results in the entry of long-chain fatty acyl-CoAs in mitochondria for β-oxidation. This release of inhibition increases the rate of β-oxidation, elevating ATP production (Fig. 2.3).

Two isoforms of ACC coexist in mammals. ACC1 and ACC2 are expressed in adipose tissue, brain, and liver, while ACC2 is predominantly expressed in heart and skeletal muscle (Kreuz et al. 2009). ACC2 has 146 residues longer in the NH_2 terminus and is located on the outer membrane of mitochondria. AMPK activation phosphorylates and inactivates ACC1 on Ser-79 and ACC2 on Ser-221 (Abu-Elheiga et al. 1995). The fate of malonyl-CoA depends on its location and production, either via ACC1 or ACC2. Studies with whole-body or tissue-specific knockout mice for ACC1 and ACC2, or using other genetic approaches, showed that malonyl-CoA produced by ACC2 is involved in the regulation of fatty acid

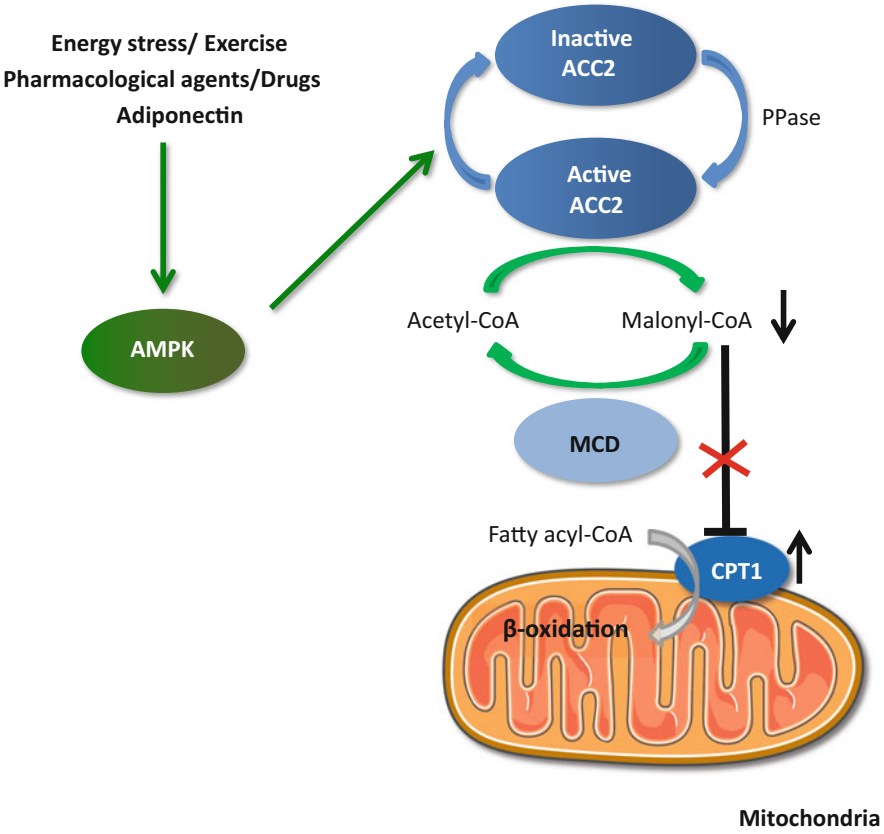

Fig. 2.3 Activation of AMPK increases fatty acid oxidation. Energy stress and pharmacological activation of AMPK increase tissue-specific ACC2 phosphorylation, which decreases malonyl-CoA production, removing its inhibitory action on CPT-1 and promoting fatty acid efflux into mitochondria for β-oxidation

oxidation, whereas malonyl-CoA produced by ACC1 is directed to fatty acid synthesis (Hardie and Pan 2002). These findings suggest that the activation of AMPK via exercise or other cellular stresses promotes fatty acid oxidation by phosphorylation and inactivation of ACC2, whereas inhibition of fatty acid synthesis is accomplished by inhibition of ACC1.

Accumulation of fatty acids outside of adipose tissues is one of the leading causes of insulin resistance and associated metabolic diseases. ACC phosphorylation by AMPK promotes lipid oxidation and thereby reduces lipid stores in muscle and liver. This action of AMPK can be counted as insulin-sensitizing effect contributing to whole-body insulin sensitivity (see next paragraph) (Awazawa et al. 2009; Yamauchi et al. 2002).

2.4 AMPK, Insulin Sensitivity, and Whole-Body Energy Balance

AMPK contributes to whole-body insulin sensitivity and energy balance either via acute phosphorylation and thereby regulation of metabolic enzymes activity or modulation of their transcriptional expression in the long term, in order to adapt gene expression to energy demands. There is a direct link between AMPK and its insulin-sensitizing effect on insulin signaling. Prolonged insulin stimulation is negatively regulated by activation of a negative feedback loop, which phosphorylates IRS-1 on Ser-636/639 and inhibits insulin signaling. By blocking this negative feedback loop, AMPK activation results in a stimulation of insulin signaling in insulin-resistant cardiomyocytes (Ginion et al. 2011). AMPK activation was also shown to increase the phosphorylation of insulin receptor substrate-1 (IRS-1) at Ser-789, which is associated with increased PI3K activity (Jakobsen et al. 2001). Furthermore, AMPK phosphorylation of IR residue Tyr-1162 is also associated with increased insulin sensitivity (Chopra et al. 2012). Finally, AMPK activation increases insulin sensitivity in muscle with a putative role of AS160 in this phenomenon (Kjobsted et al. 2015).

AMPK is also involved in the regulation of hypothalamic control of food intake and energy expenditure (Morton et al. 2006). Hypothalamus controls food intake and energy balance by modifying the synthesis of neuropeptides in response to changes in peripheral signals such as glucose levels and insulin or adipokines (Lage et al. 2008). When energy intake exceeds the energy expenditure, the expression of orexigenic (feeding promoting) neuropeptides such as AgRP and NPY decreases in contrast to the expression of anorexigenic (feeding inhibiting) neuropeptides, such as CART and POMC (Lage et al. 2008). Activity of AMPK in hypothalamus is controlled by hormonal (insulin or adipokines) and nutrient-derived anorexigenic and orexigenic signals. It has been shown that the expression of a dominant-negative form of AMPK in the hypothalamus is sufficient to reduce food intake and body weight, whereas constitutively active AMPK increases both (Minokoshi et al. 2004). Both glucose and insulin are anorexigenic signals able to inhibit AMPK activity in the hypothalamus (Minokoshi et al. 2004). Adipokines like leptin and ghrelin play an important role in hypothalamic control. Leptin regulates appetite, food intake, energy expenditure, and neuroendocrine function (Watanobe 2002). Anorexigenic effects of leptin exerted in the hypothalamus–sympathetic nervous system axis require inhibition of hypothalamic AMPK activity and thereby inhibit food intake and regulate body weight (Minokoshi et al. 2004). Similarly, orexigenic effect of ghrelin is mediated by the activation of hypothalamic AMPK (Kola et al. 2008). In summary, AMPK activation in hypothalamus in response to low leptin and high ghrelin levels leads to increased appetite.

Adiponectin is an antidiabetic adipokine. It exerts its antidiabetic properties through activation of AMPK, thereby increasing glucose utilization and fatty acid oxidation in muscle while decreasing gluconeogenesis in the liver and decreasing glucose levels in vivo (Wu et al. 2003; Yamauchi et al. 2002). Mechanistically,

AMPK activation by adiponectin is suggested to occur through the increased AMP levels sourced by the activity of FAS. FAS consumes a lot of ATP and subsequently produces AMP. FAS is suggested to act downstream of adiponectin receptors and therefore adiponectin increases the formation of fatty acyl-CoA derivatives and activates AMPK via the formation of AMP by this process in adipocytes (Liu et al. 2010).

2.5 AMPK and Mitochondrial Biogenesis

AMPK activation is associated with increased mitochondrial biogenesis, namely, growth and division of mitochondria. Factors activating AMPK such as exercise, caloric restriction, and oxidative stress have also an impact on mitochondrial biogenesis. Mitochondrial biogenesis is shown to fail in skeletal muscles of mice expressing a dominant-negative form of AMPK (Zong et al. 2002). AMPK-mediated mitochondrial gene expression involves activation of the peroxisome proliferator-activated receptors (PPARs) and PGC-1α (Jager et al. 2007; Suwa et al. 2003; Terada et al. 2002; Lee et al. 2006). PPAR-α activation is responsible for the upregulation of mitochondrial β-oxidation enzymes. PGC-1α is associated with increases in energy expenditure such as mitochondrial respiration and biogenesis as well as uptake of energy substrates (Wu et al. 1999; Lehman et al. 2000). PGC-1α exerts these effects by binding and co-activating other transcriptional factor and/or nuclear receptors to increase their expression such as ERRα, NRF1 and NRF2, and MEF2 and PPARα (Handschin and Spiegelman 2006; Vega et al. 2000). AMPK can activate PGC-1α by phosphorylation or increase its expression (Jager et al. 2007). AMPK also activates PGC-1α through its deacetylation via SIRT1, and PGC-1α deacetylation is associated with the induction of its target genes such as CPT1, pyruvate dehydrogenase kinase 4 (PDK4), or GLUT4 (Canto et al. 2009).

2.6 AMPK in Protein Turnover

Inasmuch as AMPK is a sensor promoting a global energy-saving program, it was rather logical to hypothesize that its activation should shutdown protein synthesis, a known energy-consuming pathway. This paradigm has been concomitantly established in hepatocytes (Krause et al. 2002; Horman et al. 2002; Dubbelhuis and Meijer 2002) and skeletal muscle (Bolster et al. 2002). AMPK activation leads to the inhibition of two important pathways regulating the initiation and the elongation steps of protein synthesis (Fig. 2.4). The first involves the inhibition of the mammalian target of rapamycin complex 1 (mTORC1), which is responsible for the stimulation of the p70 ribosomal S6 protein kinase (p70S6K) and of the eukaryotic initiation factor 4E (eIF4E) (Krause et al. 2002; Bolster et al. 2002).

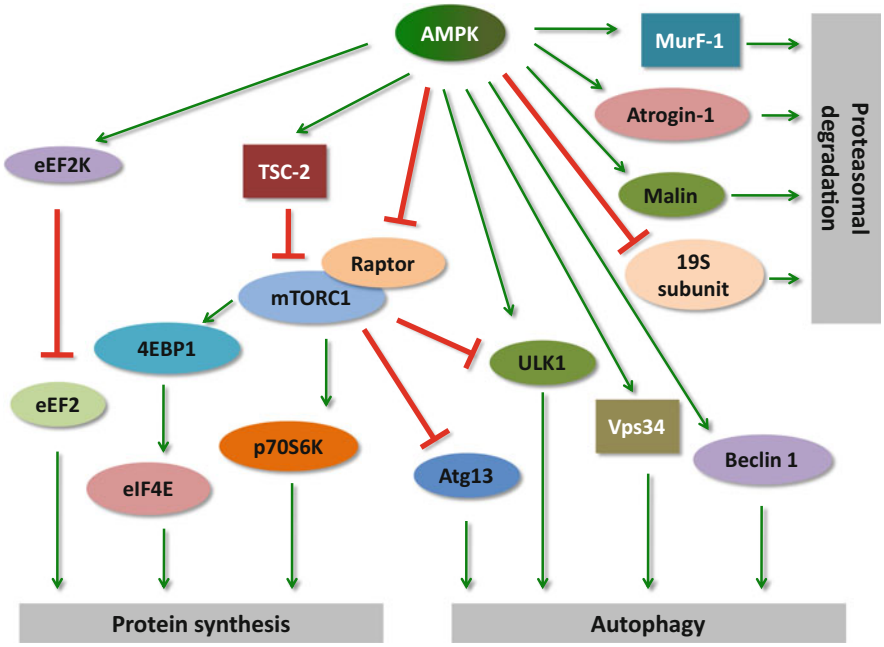

Fig. 2.4 AMPK involvement in protein turnover. This scheme represents the main downstream targets of AMPK involved in the regulation of protein synthesis, autophagy and ubiquitin-mediated proteasomal degradation (see text for more details)

Once activated by mTORC1, p70S6K phosphorylates the S6 ribosomal protein involved in the translation of 5′TOP mRNAs encoding for ribosomal proteins and translation factors. On the other side, phosphorylation of eIF4E binding protein 1 (4EBP1) by mTORC1 releases its binding partner eIF4E, which is then able to bind the mRNA cap and initiate protein synthesis. In summary, inhibition of mTORC1 by AMPK concomitantly reduces translation factor and ribosomal content as well as decreased initiation of translation. The second pathway targeted by AMPK concerns the inhibition of the eukaryotic elongation factor 2 (eEF2) implicated in the control of peptide chain elongation (Horman et al. 2002). It was rapidly established that the regulation of mTORC1 and eEF2 pathways by AMPK is indirect. Indeed, eEF2 inactivation by AMPK is mediated by the regulation of its upstream kinase called eEF2 kinase (eEF2K). AMPK phosphorylates and activates eEF2K, which, then, can phosphorylate eEF2 on an inhibitory site (Browne et al. 2004). In parallel, AMPK inhibits mTORC1 by acting on two of its partners, Raptor (Gwinn et al. 2008) and tuberous sclerosis complex 2 (TSC2) (Inoki et al. 2003). TSC2 is the GTPase-activating protein (GAP) of the small G protein Rheb involved in the activation of mTORC1. AMPK phosphorylates and activates TSC2 promoting the formation of the GDP-bound inactive state of Rheb responsible for mTORC1 inactivation (Inoki et al. 2003). Raptor makes part of the heterotrimeric central core of the mTORC1 with mTOR and mLST8. Raptor is an

essential regulatory element of mTORC1 involved in the interaction with accessory binding partners and in the recruitment of mTOR downstream substrates (Dunlop and Tee 2013). AMPK-mediated phosphorylation of Raptor leads to its binding with 14-3-3 and subsequent mTORC1 inhibition (Gwinn et al. 2008). Recent salient discoveries revealed that regulation of mTORC1 by AMPK is even more complex and involved the interaction of AMPK with Axin. Such Axin/AMPK complex is formed under energetic stress and is recruited to cytoplasmic surface of lysosomes allowing activated AMPK to target Raptor and TSC2 (Zhang et al. 2013, 2014; Bar-Peled and Sabatini 2014).

AMPK not only regulates protein synthesis but also promotes protein degradation. First, AMPK activation switches on autophagy. Autophagy was firstly documented by the Nobel laureate Christian De Duve (De Duve and Wattiaux 1966) and means "self-eating" in Greek. Autophagy is the catabolic process by which macromolecules and organelles are sequestered by specific double-layer membrane structures called autophagosomes and digested after fusion with lysosomes. Autophagy allows breakdown and recycling of intracellular components to promote cell survival under energetic stress. AMPK enhances autophagy via its inhibitory action on mTORC1. Indeed, under high-energy conditions, activated mTORC1 phosphorylates and inhibits early autophagic mediators, including ULK1 and Atg13, involved in autophagosome formation (Jung et al. 2010; Tan and Miyamoto 2016). In addition, AMPK directly promotes autophagic process by phosphorylating and activating ULK1 (Kim et al. 2011; Egan et al. 2011). More recently, it has been shown that AMPK phosphorylates two other autophagic promoters, the class III phosphatidylinositol-3 kinase called Vps34 and its partner Beclin 1 (Kim et al. 2013).

Besides autophagy, AMPK also regulates protein turnover by acting on the ubiquitin-proteasome system (UPS) (Ronnebaum et al. 2014). Protein degradation by UPS is an energy-consuming mechanism, which requires approximately 150 molecules of ATP per protein molecule (Peth et al. 2013). It is then reasonable to imagine that AMPK should block such ATP-consuming process. In line with this hypothesis, it has been shown that AMPK activation inhibits proteasome activity in endothelial cells (Wang et al. 2009). The molecular mechanism proposed to explain this inhibition includes the AMPK-dependent regulation (via O-GlcNAcylation process) of the 19S subunit of the proteasome (Xu et al. 2012). AMPK has been also found to interact with PSMD11, a component of the 19S subunit (Moreno et al. 2009). Even if UPS is energy consuming, the specific and UPS-dependent degradation of particular proteins could be energetically advantageous in particular circumstances. In this context, AMPK activation has been found to promote UPS process. AMPK activation results in the increase in expression of the E3 ubiquitin ligases called MuRF1 and Atrogin-1 in muscle and cardiac tissues via the regulation of different transcription factors (FoxO and MEF2) (Krawiec et al. 2007; Tong et al. 2009; Baskin and Taegtmeyer 2011). MurF1 and Atrogin-1 mediates muscle atrophy via myofibrillar protein ubiquitination. Such atrophic program is proposed to participate in the anti-hypertrophic action of AMPK. In a similar way, inhibition of glycogen synthesis by AMPK implicates a complex called Laforin/Malin where

Malin is an E3 ubiquitin ligase, which, when activated, degrades enzymes involved in glycogen formation (Solaz-Fuster et al. 2008). Other similar AMPK-dependent activation of E3 ubiquitin ligase can be found in the literature and occur in the regulation of plasma membrane transporters and channels (Bhalla et al. 2006; Alzamora et al. 2010).

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