Mechanisms of AMPK in the maintenance of ATP balance during energy metabolism

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Abstract
AMP-activated protein kinase (AMPK) is a conserved sensor of cellular energy change and is activated by increased AMP/ATP and/or ADP/ATP ratios. AMPK maintains the energy balance by decreasing the ATP-consuming processes such as transcription of synthetic fat genes and rRNA, the translation of ribosomal proteins, synthesis of cholesterol and fatty acid, while the metabolic pathways such as glucose and fatty transport, fatty acid oxidation, autophagy, mitochondrial synthesis and oxidative metabolism are increased to preserve ATP during energy deficiency. Recent advance has demonstrated that AMPK activity has a close association with the initiation and progression in various cancers. Here we review the mechanisms that AMPK controls energy metabolism through regulating ATP synthesis and consumption, and further discuss the deregulation of AMPK in cancers.

Keywords: AMPK; ATP synthesis and consumption; energy metabolism

Introduction
Adenosine triphosphate (ATP), the direct energy source, contains two high-energy phosphate bonds that store and transmit chemical energy named as “molecular currency” in life activities. During energy demand, ATP is hydrolyzed to ADP thereby releasing large amounts of energy. Conversely, ADP returns to ATP after acquiring one additional phosphate bond. Most of the cells sustain intracellular ATP/ADP ratio at 10:1. The ATP synthesis is dependent on catabolic reactions, such as the oxidative phosphorylation of glucose and the canonical mitochondrial oxidation pathway from ATP synthetase. In this sense, the cellular metabolism has a tight relation with energy homeostasis through the balance of ATP levels.

In 1981, SNF1 protein kinase was identified as the energy regulator in yeast to adapt to glucose limitation and utilization of alternate carbon sources (Hedbacker and Carlson, 2008). In 1994, AMP-activated protein kinase (AMPK) was revealed as the mammalian ortholog of yeast SNF1 (Norata et al., 2010). AMPK exists as a heterotrimeric complex comprising the catalytic subunit α (α1 and α2), the regulatory subunit β (β1 and β2), and the noncatalytic subunit γ (γ1, γ2, and γ3) (Hardie and Alessi, 2013). The α subunit is responsible for transferring the phosphate of ATP to target proteins. AMPK can be phosphorylated in the α-subunit at Thr172, Thr258, and Ser485 sites. Among these sites, phosphorylation of Thr172 is the hallmark of AMPK activation, while the phosphorylation of Ser485 inhibits...
Thr172 phosphorylation (Hardie and Alessi, 2013). AMPK is directly activated by phosphorylation at Thr172 by upstream kinases, including LKB1, CaMKK, TAK1, and MLK3 (Luo et al., 2015). Some pharmacological agents such as metformin and AICAR can also induce Thr172 phosphorylation via upstream kinases. Importantly, AMPK activity is regulated by the relative levels of ATP and AMP, both of which competitively bind γ subunit. ATP binding to the γ subunit leads to closure of AMPK trimer and consequent inhibition of AMPK. In contrast, free AMP or ADP binding of γ subunit results in allosteric domain rearrangement, which in turn allows the phosphorylation of Thr172 by upstream kinases. Dephosphorylation by specific phosphatases is additionally inhibited in response to energy crisis such as hypoxia, ischemia, starvation, exercise, and stress (Ruderman et al., 2013) (Figure 1). Activated AMPK inhibits glycogen, fatty acid, and protein synthesis by targeting SREBP1c/ChREBP, TIF-1A, mTORC1, and ACC1 signaling pathways. It also enhances glucose/fatty uptake, mitochondrial metabolism, and cellular autophagy by phosphorylating GLUT4/CD36, PGC-1α/ SIRT, and ACC2, respectively.

All above mechanisms are commonly found in skeletal muscle cells and adipocytes. However, different cancer cells show aberrant energy use, presenting various p-AMPK levels and downstream signals, under energy stress. Here we will review the mechanisms of AMPK activation in response to excessive energy consumption and then discuss the possible metabolic mechanisms regulated by AMPK in cancers and cancer stem cells (CSCs).

**Effects of exercise and oxidative stress on AMPK activation**

ATP synthesis and catabolism are dynamic processes in the maintenance of cellular homeostasis. Regular exercise and oxidation stress have long been known to increase AMPK activation and affect ATP levels as consequence of low glucose, hypoxia, ischemia, and starvation. Studies with AMPK α1/α2 knockout in mice have demonstrated that exercise-induced activation of p-AMPK α1/2 and p-ACC2 increases downstream PGC1-α, FOXO1, PDK4, and HKII mRNA contents (Jorgensen et al., 2005; Jager et al., 2007; Jeong et al., 2012). Moreover, AMPK α2 isoform is notably more sensitive to ATP content than α1 isoform even under activation by AICAR (Jorgensen et al., 2005). Nevertheless, at low-intensity exercise, loss of AMPK α2 activity does not change respiratory quotient, oxygen consumption, and skeletal muscle fatty acid oxidation. Furthermore, AMPK α1/α2 double knockout mice unexpectedly presented impaired complex I with diminished ADP-stimulated mitochondrial respiration. Similarly, knockout mice lacking skeletal muscle AMPK β1/β2 have reduced oxidative capacity, contraction-stimulated glucose uptake and mitochondrial content (O’Neill et al., 2011). All these findings provide evidences that AMPK activity not only affects the proteins that regulate exercise-induced skeletal glucose uptake and fatty acid oxidation, but also controls metabolic adaptation through regulating mitochondrial oxidative capacity, substrate utilization, and mitochondrial content dependent on diverse isoforms.

In cancer cells (Queiroz et al., 2014), cardiomyocytes (Kar et al., 2015), and neurons (Ju et al., 2014), oxidative stress activates AMPK to increase glycolysis. Induction of physiological oxidative stress by H2O2 suggests that change in adenine nucleotides could be the major drivers of AMPK activation rather than direct modifications in the oxidative processes (Auciello et al., 2014), which are associated with apoptosis and cell cycle arrest (Queiroz et al., 2014). Comprehensive reviews described that AMPK activation can reprogram mitochondrial dysfunction ensuing oxidative stress by altering cellular redox status and antioxidant enzyme expression via changes in PFK2, FOXO3a, PGC1-α, and mTOR (Wu et al., 2014). Furthermore, once activated by falling energy status, AMPK shuts off ATP-consuming anabolic processes and switches on nutrient catabolic pathways, which promotes a series of metabolic responses to the decrease of ATP level.

**AMPK and glucose/fatty acid transport**

In energy oversupply conditions, like high glucose, AMPK activity was reported to promote glucose intake and glycolysis activity by activation of mTOR/S6 and MAPK
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pathways. Recent studies also indicated that visfatin and isoeugenol causes increased uptake of glucose in adipocytes and myocytes (Kim et al., 2016), in which AMPKα2 subunit promotes GLUT4 gene expression (Lee et al., 2015), consistent with earlier studies showing that AICAR/AMPK enhanced glucose intake in muscle (Sakoda et al., 2002). In addition, overexpression of HDAC5 represses GLUT4 gene expression, and AICAR/AMPKα2 phosphorylates HDAC5 at S259 and S498 reduces nuclear HDAC5 resulting in decrease of HDAC5 binding with the GLUT4 promoter thereby promoting GLUT4 gene expression (Li et al., 2008) (Figure 2). Interestingly, it was reported that increase in nuclear MEF2A content, Glut4 promoter-bound MEF2A and GLUT4 expression were observed in AMPKα2 overexpression (OE) mice training muscles, but not in AMPKα2 knockout (KO) mice muscle, revealing that AMPKα2 regulates GLUT4 gene expression by other way besides HDAC5 nuclear export (Gong et al., 2011). Thus, the mechanism of AICAR/AMPKα2 regulating GLUT4 gene expression is still unclear.

Not only GLUT4, but also the fatty acid transporter CD36 can be recruited to the plasma membrane to facilitate fatty acid uptake by activated AMPK thereby activating ACC2, decreasing malonyl CoA, and up-regulating the β-oxidation of long-chain fatty acids (Glatz et al., 2010). In skeletal muscle, the deregulated AMPK is accompanied by fatty accumulation and insulin resistance enhances fatty acid oxidation (Ruderman et al., 2013). McFarlan et al. (2012) found that CD36 has a key role in muscle fuel selection, exercise performance, and training-induced muscle to use fatty acid oxidation. Fatty acids binding to CD36 leads to increase of intracellular cAMP and Ca\(^{2+}\) and mediates the release of neurotransmitters in taste cells for perception of fat or for intestinal peptide secretion to improve lipid absorption (Dramane et al., 2012; Sundaresan et al., 2013). In addition, pharmacological activation of AMPK can increase glucose and fatty intake in skeleton muscle and adipose cells.

**AMPK and lipogenesis homeostasis**

**AMPK inactivates ACC1 to prevent fatty acid synthesis**

The main source of fatty acid synthesis is acetyl-CoA originated from the glucose catabolism. Intracellular acetyl-CoA is carboxylated to generate malonyl-CoA in a reaction catalyzed by ACC, a key enzyme of fatty acid synthesis. AMPK induces the inhibitory phosphorylation of ACC1, a subunit of ACC, causing a decrease of cellular malonyl-CoA levels and prevents fatty acid chain extension. When there is sufficient glucose or energy, the increased malonyl-CoA inhibits CPT-1, the main function of which is to transport free fatty acids into the mitochondria for β-oxidation. Thus, ACC phosphorylation by AMPK benefits the recovery of CPT-1 activity and free fatty acid oxidation. Furthermore, studies have demonstrated that the adipokine CTRP1 enhances ACC1 inactivation-induced fatty acid oxidation and dramatically promotes whole body energy expenditure in mice (Peterson et al., 2012). Hence, it would be interesting to explore whether AMPK regulates the expression, secretion and activity of CTRP1.

**AMPK inactivates ACC2 to promote fatty acid oxidation**

ACC2, also a subunit of the ACC, is mainly present in skeletal and cardiac muscle. In resting muscle, the activation of AMPK leads to the phosphorylation of ACC (S79 on ACC1 and S221 on ACC2), of which phosphorylation of ACC2 at S221 can inhibit ACC activity and malonyl-malonyl-CoA production, and thereby increase fatty acid oxidation. However, whether AMPK-dependent inhibitory phosphorylation of ACC2 plays a regulatory role on skeletal muscle fatty acid oxidation is presently under debate. In model systems, ACC2 knock-in mice were reported to be resistant to AICAR-elicted increases in skeletal muscle fatty acid oxidation with normal adiposity and liver lipids but enhanced contents of triacylglycerol and ceramide, which are associated with hyperinsulinaemia, glucose intolerance and insulin resistance (O’Neill et al., 2014). An early study suggested that palmitic acid-induced insulin resistance and fatty acid oxidation is not correlated with the phosphorylation of AMPK or ACC2 (Alkhateeb et al., 2011). However, recent studies have showed that the overexpression of adiponectin can increase the number of mitochondria and mitochondrial DNA content, as well as increase peroxisome PGC1-α and mitochondrial ATP synthesis. The increased PGC1-α and TFAM activate AMPK/ACC2 pathway, and then down-regulate genes involved int the control of fat metabolism, suggesting that adiponectin can inhibit the fat-

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**Figure 2** The way of AMPK in the regulation of GLUT4 gene expression. HDAC5 represses GLUT4 gene transcription; AICAR/AMPKα2 phosphorylates HDAC5 to reduces nuclear HDAC5, resulting in increase of GLUT4 gene expression.
induced decrease of mitochondrial biosynthesis via AMPK/ACC2 pathway. Thus, AMPK-mediated inactivation of ACC2 still can balance fatty acid content in skeletal muscle through intricate cross-talk among signaling pathways controlling fatty acid oxidation.

AMPK and cholesterol homeostasis

Exogenous cholesterol is obtained from food, while endogenous cholesterol is from hepatic biosynthesis. In the cytoplasm of liver cells, acetyl-CoA can be transformed into endogenous cholesterol by 26 steps. Among these conversions, HMG-CoA reductase (HMGCR) catalyzing HMG-CoA to mevalonate is the rate-limiting step. Studies showed that AMPK inhibits HMGCR activity by phosphorylating HMGCR at S872, which would impair the affinity for NADPH (Clarke and Hardie, 1990; Ivstvan et al., 2000). A protein phosphatase 2A (PP2A) can reactivate the HMGCR (Friesen and Rodwell, 2004). Recently, Fullerton et al. (2015) found that the activation of AMPK β1 in macrophages decreases cholesterol content and fatty acid and sterols synthesis and increases cholesterol efflux, which is associated with increased gene expression of ATP binding cassette transporters, Abcg1 and Abca1, implying that AMPK regulates cholesterol synthesis by multitudinous pathways. More interestingly, Habegger et al. (2012) found that AICAR/AMPK mediating membrane cholesterol decrease corrects GLUT4 deregulation induced by insulin, suggesting that AMPK-inhibited cholesterol synthesis helps GLUT4 translocation and enhances glucose intake.

AMPK and protein synthesis

Several studies show that AMPK inhibits mTOR activity by repressing the formation of mTORC1, mainly by affecting on the binding of TSC2/Rheb or Raptor, further inhibiting protein translation. Activated AMPK phosphorylates TSC2 at Ser1387 or Thr1271, results in constitutive GTPase complex of TSC2-1 to maintain the mTOR activating factor Rheb in the GDP binding status, resulting in the inactivation of mTORC1 (Huang and Manning, 2008). In cancer cells, hyper-activation of PI3K/AKT or RAS/RAF/ERK signals prevents the formation of TSC2/Rheb complex to upregulate mTORC1 (Martelli et al., 2011). In addition, AMPK can upregulate autophagy by phosphorylating Ser722/792 of Raptor, an essential component of mTORC1 (Gwinn et al., 2008). In contrast, AKT and RAS/RAF/ERK pathways increase mTOR activity via phosphorylation of other sites of Raptor, such as the Ser863 (Steelman et al., 2011). Moreover, we and other groups found that AMPK can inhibit mTOR kinase activity through directly phosphorylation of mTOR protein at Thr2446 site (Cheng et al., 2004). However, the cellular function of the phosphorylation of mTOR at Thr2446 by AMPK is still unclear.

AMPK and mitochondrial functions

As already noted, AMPK increases fatty acid oxidation by the down-regulation of malonyl-CoA formation. However, under conditions of long-term AMPK activation, AMPK also regulates fatty acid oxidation by stimulating PPArα and PGC-1α (Lee et al., 2006). In addition, AMPK regulates glucose intake and new mitochondria synthesis, which is fully dependent on PGC-1α in vivo or in vitro (Jager et al., 2011). The transcriptional activator PGC-1α, not only modulates the expression of mitochondrial proteins, but also co-regulates mitochondrial synthesis of NAD(+) deacetylase SIRT1 or SIRT2/5 (Aquilano et al., 2010). Moreover, in HepG2 cells, a study showed that AMPK activation promotes the increase of SIRT1-3 and SIRT6 expression, downregulates SIRT5, while PGC-1α could upregulate SIRT5, which is accompanied with increased ATP synthesis and oxygen consumption, but without alteration of mitochondrial synthesis. Furthermore, studies demonstrated that there is a signaling network among AMPK, sirtuins and PGC-1α. On one hand, AMPK upregulates SIRT1. Similarly, SIRT1 deacetylates AMPK and PGC-1α to facilitate the expression of mitochondrial genes (Huang et al., 2014). On the other hand, in the energy deprivation processes, like exercise, both of AMPK and SIRT2 can promote mitochondrial synthesis and oxidation to balance energy consumption by activating PGC-1α, which has a profound effect on obesity, type II diabetes and other metabolic disorders.

AMPK and autophagy

ULK is the mammalian homologous protein of autophagy-related protein Atg1 described initially in yeast (Egan et al., 2011). A number of studies have showed that ULK serves as a positive regulatory protein kinase of autophagy body formation and forms an intracellular complex with mAtg13-FIP200 (Jung et al., 2009). AMPK regulates ULK activity by two mechanisms. First, mTORC1 phosphorylates ULK1 leading to dissociation of ULK1-mAtg13-FIP200 complex, which is inactive. Since AMPK inhibits mTORC1, the ULK complex remains active and can induce autophagy. The non-phosphorylated ULK and mAtg13 phosphorylate FIP200, and Atg13 in turn activates ULK to promote autophagy. Second, AMPK/ULK1 promotes mitochondria autophagy by enhancing the accumulation of autophagy specificity protein p62 (Egan et al., 2011). AMPK can also directly phosphorylate ULK1 at the Ser-317, 777, 555, and 673 sites to promote autophagy under glucose starvation and oxidative stress (Roach, 2011; Tian et al., 2015). In non-
starved conditions, activated mTORC1 can prevent the interaction of AMPK withULK1 by phosphorylating ULK1 at Ser-757 site and consequently prevent autophagic inducing activity. Though autophagy can avoid the energy crisis by hypoxia or oxidative stress by fully breaking down the damaged organelles and proteins, cells also take advantages of decomposed organelles components and de novo form new proteins or membrane structure to maintain metabolic fitness.

**AMPK and transcription factors**

**SREBP-1c**

SREBP-1c is a transcription factor that regulates the transcription of SRE1 containing genes, which controls sterol synthesis by mediating transcription of genes involved in fatty acid and sterol synthesis (Burg and Espenshade, 2011). SREBP-1 precursor protein is inserted into the endoplasmic reticulum and transported to the Golgi. It is then processed to the mature protein, which translocates to the nucleus and binds to SRE1 gene promoter. Sterol synthesis in turn inhibits the cleavage of SREBP1 precursor protein, forming a negative feedback loop to balance intracellular sterol content. SREBP-1c induces cholesterol synthesis by promoting the gene transcription of ATP-citrate lyase (ACL), acetyl-CoA synthetase (ACS), acetyl-CoA carboxylase (ACC), fatty acid synthase (FAS), stearoyl-CoA desaturase-1 (SCD1), and glycerol-3-phosphate acyltransferase (GPAT). In hepatocytes activated AMPK phosphorylates Ser372 of SREBP-1c and suppresses lipogenesis by preventing its cleavage and nuclear translocation (Li et al., 2011).

**ChREBP**

ChREBP, a bZIP transcription factor involved in fatty gene expression, like L-Type Pyruvate Kinase (L-PK), ACC, and FAS by forming a heterodimeric complex with Max-like protein X (Mlx), which directly binds to carbohydrate response element (Chore) (Clarke and Hardie, 1990; Burg and Espenshade, 2011). ChREBP is also a transcriptional inducer of glycolytic, gluconeogenesis, and de novo lipogenesis enzymes through regulation of PPARγ promoters (Witte et al., 2015). ChREBP modulation of hepatic expression of lipogenic gene fatty acid synthases is associated with increased H3K4 methylation and histone H3/H4 acetylation (Suzuki et al., 2015). Intriguingly, using a truncated ChREBP consisting of the C-terminal region, Kawaguchi et al. (2002) found that AMPK specifically phosphorylates ChREBP-Ser568, which results in the inactivation of its DNA binding activity and loss of fatty acid sensitivity. Recently, it was reported that glucose stimulates ChREBPα activity, which in turn increases ChREBPβ transcriptional and translational expression of adipocytes (Zhang et al., 2015). Moreover, ChREBP regulates GLUT5 mRNA to mediate glucose intake in adipocytes (Egan et al., 2014).

**HIF-1**

AMPK promotes ATP production via enhancement of hypoxia-inducible factor 1 (HIF-1). In human cancer cells, HIF-1 was reported to suppress fatty acid beta-oxidation through medium- and long-chain acyl-CoA dehydrogenases, and promote glycolysis by controlling the level of reactive oxygen species (Zhang, 2015). Recent studies have revealed that AMPK triggers cytosolic shutting of HDAC5 and enhances HIF-1α stabilization and nuclear accumulation (Gong et al., 2011). Seo reported that HDAC 4/5 could promote the transactivation of HIF-1 (Seo et al., 2009). Thus, the transcription factor HIF-1 is up-regulated by AMPK.

**TIF-1A**

Transcription initiation factor 1A (TIF-1A) is the RNA polymerase 1 (Pol I)-associated transcription factor and initiates transcription process by recruiting Pol I to the promoters of rRNA genes (rDNA) through the interaction with the TBP-containing promoter selectivity factor SL1 (Marin-Aguilar et al., 2017). Certain conditions, including stress and nutrient starvation, down-regulate transcription of rDNA. Hoppe et al. (2009) found that AMPK phosphorylates TIF-1A at Ser-635, which disrupts the interaction of TIF-1A with SL1, and consequently impairs the recruitment of Pol I to the rDNA promoter and transcription complex formation. Moreover, AMPK downstream factor, mTOR, inactivates TIF-1A by hyperphosphorylation at Ser44 and Ser199 (Mayer et al., 2004). Therefore, AMPK can regulate the expression of numerous genes.

**ATP and cancers**

Due to rapid growth and proliferation, large amounts of energy demand are required for cancer cells. Another metabolism for cancer cells to obtain energy is through aerobic glycolysis, which is called Warburg effect. Epidemiological investigations also suggest that there is an association between dietary fat intake and cancer risk (Willett et al., 1998). High glucose leads to high miR-451 expression to shut off AMPK activity leading to inhibition of cell migration and elevation of cell proliferation (Bronisz et al., 2015). AMPK, as a cellular fuel sensor, is able to suppress ATP-consuming anabolic processes and stimulate catabolism and ATP generation. Recently, ATP deregulation has been reported related to tumor growth. It was found that extracellular ATP in cancer cells can be internalized by macropinocytosis and caveolae-/clathrin-mediated
ecdyosmot, leading to ATP concentration increase by 1000 times higher than those in normal tissues (Qian et al., 2014, 2016). Evidences indicated that extracellular ATP accumulation increases glycogen stores, cytosolic Ca$^{2+}$ and Bcl-2/ Bax and mitochondrial biosynthesis, and plays a pivotal role in resistance to chemotherapy, as found in colon cancer (Zhou et al., 2012), cell survival (lung cancer) (Song et al., 2016), and metastases (prostate cancer, through activating Rho GTPase and MMPs) (Zhang et al., 2010). Low glucose stress was found to cause cellular NADH/NAD$^+$ redox imbalance, which contributes to the increase of glycolytic ATP production but decrease of mitochondrial-derived ATP generation for mitochondrial respiration in colonic epithelial cancer cells (Circu et al., 2017). All above shows that the ATP disorders have a close association with the progression of cancer cells.

Recently, ATP citrate lyase (ACL), an important enzyme involved in lipid biogenesis linked with glucose metabolism, was reported as a promising target for cancer prevention and treatment. The ACL is responsible for catalyzing the conversion of citrate and CoA into acetyl-CoA and oxaloacetate, which are the sources of lipogenesis and cholesterogenesis, along with the hydrolysis of ATP (Sun et al., 2010). Hanai et al. (2012) indicated that ACL deficiency is correlated with MET, differentiation and apoptosis in NSCLC (A549), leading to the inhibition of tumor growth in vivo. Clinically, ACL was also found to be upregulated and associated with local tumor stage, suggesting a prognostic value on NSCLC (Csanadi et al., 2015). It is therefore possible that the ATP concentration can significantly affect the biological behaviors of tumors.

ATP and cancer stem cells

Interestingly, ATP has also been reported to affect the cancer stem cells (CSCs), which are the progenitor cancer cells with mesenchymal features characterized by self-renewal potential, clonogenic properties, and genomic instability (Peitzsch et al., 2017). In glioblastoma cells, ATP reduces tumor sphere growth and the expression of glioma cancer stem cell markers, such as CD133, Oct-4 and Nanog, suggesting extracellular ATP affects CSC biology by purinergic system (Ledur et al., 2012). Even the ATP-binding cassette transporter may be regulated by c-Myc silencing in CD133(+) colon CSCs, and enhance the sensitivity of CSC to chemotherapy (Zhang et al., 2016). Moreover, studies have shown that the ACL knockdown reduces snail expression, EMT and cancer stemness independent on Ras-MAPK signaling (Hanai et al., 2013). However, the roles of ATP in the regulation of quiescence and self-renewal of CSCs are still unclear and warrant further investigation.

Conclusion

ATP depletion is not only due to exercise-induced energy demands, but also storage as fatty, cholesterol, glycogen, and proteins, especially in liver. Conversely, the catabolism of these nutrients may provide enough energy for cell survival in hostile environment. AMPK mostly promotes ATP production by increasing nutrient catabolism through regulation of key enzymes at the protein regulation level, whereas conserving ATP by switching off biosynthetic pathways mainly on related gene transcription level (Figure 3). Moreover, recent studies reveal that AMPK could keep ATP balance via regulation of the cell cycle and neuronal membrane excitability (Hardie and Alessi, 2013). ATP also regulates cancer cell growth, survival, apoptosis, and chemoresistance. All these suggest that AMPK would be an efficient therapeutic target for the modulation of ATP level under oxidation stress with multiple pathways that still are under further researches.

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