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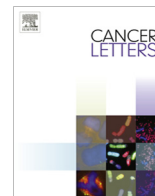
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Mini-review

The AMP-activated protein kinase (AMPK) and cancer: Many faces of a metabolic regulator



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ABSTRACT

The AMP-activated protein kinase (AMPK) is a central regulator of cellular metabolism and energy homeostasis in mammalian tissues. Pertinent to cancer biology is the fact that AMPK is situated in the center of a signaling network involving established tumor suppressors including LKB1, TSC2 and p53. However, recent research suggests that AMPK can exert pro- or anti-tumorigenic roles in cancer depending on context. Loss of AMPK activity has been observed in several tumor types, and can cooperate with oncogenic drivers to reprogram tumor cell metabolism and enhance cell growth and proliferation. However, AMPK activation can also provide a growth advantage to tumor cells by regulating cellular metabolic plasticity, thus providing tumor cells the flexibility to adapt to metabolic stress. Here we discuss the contextual nature of the “two faces” of AMPK in cancer, and discuss the rationale and context for employing AMPK activators versus inhibitors for cancer therapy.

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1. Introduction

The AMP-activated protein kinase (AMPK) is a heterotrimeric Ser/Thr kinase complex that functions as part of an evolutionarily conserved energy-sensing pathway. One unique feature of AMPK is its regulation by adenylate levels in the cell (i.e. ATP, ADP and AMP) [1]. AMP is a direct agonist of AMPK [2,3]. Stresses that stimulate ATP consumption or inhibit ATP production that result in an increased AMP:ATP ratio promote AMPK activation [4]. Glucose deprivation induces energetic stress in cells, and promotes phosphorylation of AMPK at Thr-172 in its activation loop. The activation of AMPK is tightly regulated and is dependent on both its phosphorylation by upstream kinases and its dephosphorylation by phosphatases [5]. Three upstream AMPK kinases have been identified to date: the tumor suppressor LKB1, calmodulin-dependent protein kinase kinase β (CamKK β), and TGF- β -activated kinase-1 (TAK1) [2]. Each upstream kinase activates AMPK in response to distinct stimuli, with LKB1 coupling energy levels to AMPK activation. For in-depth discussion of AMPK regulation, we refer readers to recent reviews [2,6]. From a metabolic standpoint, AMPK activation promotes net ATP conservation by activating pathways of catabolic metabolism and inhibiting anabolic

processes that consume ATP. The net result of AMPK activation is the conservation of cellular energy in order to avoid bioenergetic catastrophe and cell death.

From a signal transduction perspective, AMPK is situated at the center of a tumor suppressor network known to regulate cell growth and proliferation in response to stress. AMPK is regulated by phosphorylation by the tumor suppressor LKB1 [7,8]; likewise, the tumor suppressors TSC2 [9] and p53 [10] are downstream targets of AMPK activity. The proximity of AMPK to these established tumor suppressors implicate AMPK as a potential tumor suppressor. However, data from the Cancer Genome Atlas (TCGA) sequencing efforts indicate that mutations in AMPK subunits are relatively rare in cancer. Moreover, retaining AMPK activity and the ability to adapt to metabolic stress may function to promote tumor survival and growth. In this review, we will highlight the many faces of this metabolic sensor in cancer, and will discuss how AMPK may function to promote or antagonize tumor growth.

2. Deregulation of AMPK in cancer

2.1. Genomic disruption of AMPK

AMPK is rarely somatically mutated in human cancer and there is no evidence for a germline cancer predisposition syndrome involving AMPK subunits [11]. This may be due in part to redundancy in AMPK isoform expression. Humans harbor two genes for the α catalytic subunit (*prkaa1*, *prkaa2*), two β subunit genes

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(*prkab1*, *prkab2*) and three γ subunit genes (*prkag1*, *prkag2*, *prkag3*), and expression of these subunits varies between tissue types. Screening for AMPK mutations in a subset of TCGA datasets indicate that AMPK is mutated at low frequency in most tumor types [12–14], although the functional impact of these mutations has not been fully characterized. Expression levels of AMPK α subunits also vary between cancer subsets. AMPK loss alone is insufficient to initiate transformation of mouse embryonic fibroblasts (MEFs) [15], and spontaneous tumor formation in AMPK α -deficient mice has not yet been demonstrated, suggesting that AMPK loss is itself insufficient to drive tumorigenesis. However, we have recently shown that loss of AMPK can accelerate Myc-dependent lymphogenesis in mice [16], suggesting that loss of AMPK can cooperate with oncogenic drivers to promote tumorigenesis.

2.2. AMPK regulation by LKB1

STK11 encodes the liver kinase B1 (LKB1), a serine/threonine kinase that plays multifaceted roles in cell proliferation, polarity, metabolism, and survival [17]. AMPK is a downstream effector of LKB1 and carries out many of the key tumor suppressor functions of LKB1. These include inhibition of mTORC1 signaling by direct phosphorylation of TSC2 [9] or the mTORC1 regulatory subunit Raptor [18]. However, despite carrying out many major downstream functions of LKB1, AMPK can be phosphorylated by additional kinases (i.e. CAMKK β), and therefore may act independently of LKB1. Conversely, LKB1 phosphorylates a number of AMPK-related kinases in addition to AMPK α 1 and α 2 [19]. Thus, many of the phenotypes of LKB1-deficient tumors may not result from disrupted AMPK signaling. Recent studies have identified ROS as an upstream activator of AMPK, and this appears to be LKB1-independent [20,21]. Therefore AMPK and LKB1, although closely linked, display distinct differences in signaling that may account for divergent roles relating to tumorigenesis.

2.3. AMPK isoform specificity

To date, the differential expression of AMPK subunits in cancer has not been extensively investigated. However, there is some evidence that isoform-specific changes of AMPK subunits may occur. Phoenix *et al.* recently observed that AMPK α 2-null, but not AMPK α 1-null, MEFs display increased susceptibility to H-RasV12 transformation *in vitro* and tumor development as xenografts *in vivo* [22]. In primary breast cancer tissues, α 2 mRNA levels can be suppressed with no observable effects on α 1 subunit expression [23]. Similarly, forced expression of AMPK- β 1 has been shown to inhibit tumor cell growth [24]. These data suggest AMPK isoforms may differentially contribute to tumor cell growth and proliferation. Conditional animal models will help elucidate the role of individual AMPK α subunits in tumor development and progression.

2.4. Other pathways of AMPK regulation

Mechanisms of AMPK regulation independent of genomic alterations may also affect its activity in cancer. One such possible mechanism is AMPK regulation by microRNAs (miRNAs). The miRNA miR-451 was recently linked to control of LKB1-AMPK signaling within the context of glioma. Expression of miR-451 was shown to decrease in response to low cellular glucose levels, leading to modulation of LKB1/AMPK signaling in response to metabolic stress [25]. miR-451 targets expression of the LKB1 component MO25. Loss of miR-451 expression under low glucose levels promotes the stabilization of MO25 levels, leading to enhanced LKB1 expression and LKB1-dependent AMPK activation. miR-148b has been linked to suppression of AMPK α 1 expression, and its expression correlates with poor prognosis in pancreatic cancer

[26]. Many miRNAs can function as drivers of tumor growth, and it is tempting to speculate that miRNAs that target LKB1-AMPK signaling may promote dynamic transcriptional/translational regulation of this energy-sensitive pathway independent of genomic alterations.

Phosphatases and scaffold proteins for LKB1 and AMPK kinase complexes may also serve as regulators of AMPK kinase activity. For example, the phosphatase α -SNAP was identified as a negative regulator of AMPK activity [27]. Cells deficient for α -SNAP expression display constitutive AMPK activation in the absence of energetic stress. Similarly, the tumor suppressor folliculin (FLCN) and its interacting proteins FNIP1 and FNIP2 have been identified as AMPK binding proteins [28,29]. We have data indicating that loss of FLCN promotes constitutive AMPK activation regardless of cellular AMP levels, suggesting that FLCN is a negative regulator of AMPK activity [30]. Additional work will need to be performed to assess the impact of these AMPK regulators on tumor progression using established cancer models.

3. Gain versus loss of AMPK function: Benefits for tumor progression

Several studies have demonstrated that loss of AMPK activity can cooperate with oncogenes to promote tumor progression. One demonstration of AMPK inhibition in cancer is the suppression of LKB1 function by mutated B-RAF (V600E) in melanoma. Mutant B-RAF V600E promotes ERK and RSK-dependent phosphorylation of LKB1 in melanoma cells, resulting in AMPK inhibition [31]. Reversing this block in LKB1 signaling leads to the suppression of B-RAF V600E-mediated transformation [31]. Recently it has been shown that AMPK can also signal back to B-RAF to attenuate MEK-ERK signaling [32]. Inhibition of AMPK has also been observed in a PTEN-deficient model of thyroid cancer [33] and NSCLC cells expressing the mitochondrial HSP90 chaperone TRAP-1 [34].

Using a model of B cell lymphoma, we have shown that deletion of AMPK α 1 (the sole catalytic subunit in lymphocytes) synergizes with Myc to promote lymphomagenesis [16]. Whether these effects are restricted to Myc-driven hematological cancers remains to be determined. A recent study demonstrated that loss of AMPK in Myc-driven osteosarcoma (U2OS) cells results in increased cell death [35], indicating that the role of AMPK in Myc-driven tumorigenesis may be context dependent. However, these results may also suggest that AMPK loss provides a growth advantage to Myc-dependent tumors during tumor initiation and/or early progression, but that AMPK is required for the metabolic fitness of established tumor cells.

The ability to uncouple energy sensing by AMPK may prove beneficial as a means to avoid growth inhibition [34]. AMPK has been shown to inhibit cell proliferation through multiple mechanisms including stabilization of p53 [10,36] and regulation of the cyclin dependent kinase (CDK) inhibitors p21^{WAF1} and p27^{CIP1} [37]. It was recently shown that astrocytic tumors may rely upon AMPK-dependent control of the cell cycle (by phosphorylation of retinoblastoma) for initiation and progression [38]. In addition, identification of a novel AMPK substrate involved in mitosis completion (PPP1R12C) suggests that AMPK may coordinate nutrient status with mitosis completion, which may be important in some cancer cells [39].

Survival in the context of stress, such as hypoxia and nutrient deprivation, is advantageous to cancer cells. There is evidence to suggest that, depending on context, AMPK may exert either a positive or negative effect on cancer cell survival. Transformation by certain oncogenes, notably EN and H-RasV12, can promote defects in cellular responses to nutrient deprivation, which is characterized by decreased phospho-AMPK levels [40]. Conversely, activa-

tion of AMPK in cells in response to a broad range of stresses [41–43], and can provide cells with the metabolic flexibility to survive periods of stress. AMPK promotes this metabolic plasticity through multiple mechanisms including the induction of autophagy [30,44,45], promotion of fatty acid oxidation [46,47], and maintenance of intracellular NADPH levels to buffer cells from reactive oxygen species (ROS) [48]. Thus, engaging AMPK signaling may also aid tumor cell survival and provide a selective advantage to tumor cells. These pathways will be discussed at greater length in the following section.

4. AMPK and metabolic control

4.1. AMPK and metabolic adaptation

All proliferating cells need to balance nutrient availability and energy production with cell growth. During rapid cell division, cells must effectively double their protein, lipid and DNA content, while matching energy levels to biosynthetic need for survival [49]. Metabolic regulation is an important part of transformation and is now considered a hallmark of cancer [50]. For cancer cells to survive metabolic stress or conditions of nutrient withdrawal, they must be able to engage alternative metabolic pathways to maintain energetic balance. As mentioned, AMPK responds to changes in energy levels regulating both biosynthetic and energy-consuming processes [4]. Cells with a functional LKB1–AMPK pathway can survive metabolic stress, whereas cells lacking LKB1 or AMPK undergo programmed cell death, suggesting LKB1–AMPK signaling is critical for maintaining energetic homeostasis [9,25,41,51,52].

One way AMPK promotes energy homeostasis is through the direct regulation of metabolic enzymes by phosphorylation. AMPK inhibits fatty acid synthesis and stimulates lipid oxidation through the phosphorylation and inactivation of ACC1 [53] and ACC2 [54], respectively. In muscle tissue, AMPK has been shown act on glycolysis via phosphorylation of phosphofructokinase under ischemia in heart tissue [55], though a cancer-specific role for AMPK in stimulating glycolysis has yet to be demonstrated. As mentioned, AMPK also regulates autophagy, a catabolic process important for the maintenance of cellular energy and cell survival in starved cells [56]. AMPK-dependent phosphorylation of the ULK kinases directly induces autophagy in starved cells, resulting in the removal of damaged mitochondria through specific activation of “mitophagy” [44,45]. ULK kinases in turn can negatively regulate AMPK signaling through phosphorylation of AMPK subunits [57]. In situations of chronic nutrient starvation, AMPK can elicit changes in transcription through a number of mechanisms including phosphorylation of the transcriptional co-activator PGC1 α [58], the transcription factor FOXO3 [59], or the core histone H2B [41].

4.2. AMPK loss promotes tumor metabolism

An unexpected role for AMPK in regulating tumor metabolism was observed using AMPK α -deficient cell and animal models. We recently demonstrated that silencing AMPK promotes a metabolic shift characteristic of the Warburg effect in both transformed and non-transformed cells [16]. Silencing AMPK promotes increased glucose uptake, glycolytic flux, and flow of carbon into the tricarboxylic acid (TCA) cycle to fuel pathways of both ATP production and biosynthesis. Similarly, loss of LKB1 is sufficient to promote the Warburg effect in tumor cells [60]. Mechanistically, the pro-growth metabolic program promoted by loss of LKB1–AMPK signaling is mediated by the oxygen-sensitive transcription factor HIF-1 α . HIF-1 α protein levels are elevated in AMPK α -deficient cells under normoxia, leading to induction of a HIF-1 α -dependent transcriptional program that drives increased glycolysis under aerobic

conditions [16]. Lymphoma cells lacking AMPK activity display a reliance on HIF-1 α to maintain heightened glycolytic metabolism, and the growth of AMPK α 1-deficient Myc lymphomas *in vivo* is diminished when HIF-1 α stabilization is ablated. Thus, HIF-1 α acts as an essential mediator of the metabolic transformation mediated by AMPK loss.

In addition to its effects on glucose metabolism, AMPK loss can also promote unchecked mTORC1 activity [7,9]. Silencing AMPK while maintaining mTORC1 signaling may effectively bypass brakes on cellular metabolism, while supporting increased tumor cell growth via mTORC1 activity. Together, these results point to AMPK function as a “metabolic” tumor suppressor, limiting the growth of cancer cells by regulating Warburg metabolism and key biosynthetic pathways required to support unchecked proliferation.

While AMPK lies directly downstream of LKB1, it is important to note that the metabolic effects of LKB1 deficiency do not directly mirror those induced by AMPK loss. In addition to displaying enhanced glycolysis, LKB1-null cells display enhanced glutamine metabolism, primarily as an anaplerotic substrate to support the TCA cycle and oxidative phosphorylation (OXPHOS). Likewise, LKB1 and AMPK influence HIF-1 α protein expression through slightly different mechanisms. Silencing LKB1 promotes both increased transcription and translation of HIF-1 α , events which are sensitive to mTORC1 inhibition [60,61]. In contrast, loss of AMPK results in increased HIF-1 α protein levels with no discernable changes in HIF-1 α mRNA levels, while inhibiting mTORC1 has little effect on HIF-1 α protein levels when AMPK is silenced [16]. These data indicate that LKB1 exerts both AMPK-dependent and -independent mechanisms of metabolic regulation in tumor cells, and may impact mTOR signaling through other AMPK-related kinases such as MARK4 [62]. Regardless of mechanism, selection against AMPK activity appears to function as a key metabolic regulatory step during tumor initiation and progression, conferring a metabolic growth advantage to tumor cells.

5. Use of AMPK agonists

Interest in activating AMPK in tumors has flourished as more evidence has emerged supporting an anti-tumorigenic role for the kinase. Much work has been proposed using agonists of AMPK for cancer treatment, and the number of patents describing AMPK activators has rapidly increased [63]. The most convincing data to support the use of AMPK-activating compounds as anti-cancer agents has been through the use of the therapeutic biguanides: metformin and phenformin. The biguanide metformin is currently used to treat Type II diabetes. Metformin functionally inhibits complex I of the mitochondrial electron transport chain [64,65], leading to increases in intracellular ADP and AMP and indirect activation of AMPK. Growing interest in the LKB1–AMPK pathway in cancer prompted retrospective analysis of cancer incidence in patients with Type II diabetes. Several studies found that metformin treatment was associated with a significantly lower cancer incidence in patients relative to those using other medications to manage their diabetes [66,67]. Experimental evidence has also supported an anti-neoplastic effect for metformin. Treatment of animals harboring tumor xenografts with metformin or phenformin has been shown to delay tumor progression [68–71]. Other AMPK agonists, such as AICAR, salicylate and 2DG have also been shown to inhibit tumor cell proliferation *in vitro* [72–78], providing further rationale for use of these agents for cancer therapy.

Many AMPK agonists, including the biguanides, activate AMPK through indirect mechanisms. Thus, to truly assess the benefit of AMPK activation as a therapeutic option, direct AMPK activators are necessary. One compound known as A-769662 has been shown

to activate AMPK directly in cell free assays [79], making it a valuable tool to study AMPK-dependent cellular effects *in vitro* and *in vivo*. A-769662 has been shown to delay tumor onset in PTEN+/- mice [80], suggesting that A-769662 can exert anti-tumor effects *in vivo* within the context of PTEN loss (and the resultant increase in Akt and mTORC1 signaling). Similarly, another AMPK agonist, the PPAR γ active derivative OSU-53, has been shown to inhibit the growth of triple negative breast cancer *in vitro* and tumor xenografts [81].

As mentioned, the majority of evidence supporting the use of AMPK agonists as anti-cancer agents has been derived using compounds that do not directly activate AMPK, but do so indirectly through application of a metabolic stress. It stands to reason that these compounds will also elicit AMPK-independent cellular effects. AMPK-independent effects of metformin on cell growth have already been documented [82]. The efficacy of many of these agonists may be due to the fact that they induce metabolic stress in tumors, rather than any affect on AMPK activation. Tumor cells lacking LKB1 or AMPK undergo apoptosis at higher rates when subjected to energetic stress [16,41,51,60,83]. Shackelford et al. recently demonstrated that phenformin can act as a single agent to promote tumor cell apoptosis *in vivo* using a K-ras-driven lung cancer mouse model, but only in tumors lacking LKB1 expression [84]. These data support the idea that, upon application of a metabolic stress, LKB1-null cells cannot activate AMPK and have a reduced ability to survive disruption of mitochondrial function. In unpublished data from our laboratory, we find that compounds that cause a metabolic stress (phenformin, AICAR, salicylate, and 2DG) are considerably more effective at inducing cell death in tumor cells lacking AMPK catalytic activity. Thus, the use of biguanides may be most effective when used in combination with agents that inhibit, rather than activate, AMPK.

6. AMPK function in cancer: Is it all about context?

Given the tumor-suppressing and tumor-promoting capabilities of AMPK, assessing the role of AMPK in tumorigenesis clearly depends on context. A positive or negative role for AMPK in tumor growth could depend on the degree and/or mechanism of AMPK activation, the specific expression of AMPK isoforms, AMPK subcellular localization, the activity of other signaling networks in the cell, and extracellular environmental conditions. Loss of LKB1-AMPK signaling can clearly drive a proliferative and metabolic phenotype favorable for tumor cells when resources are plentiful. In this light, loss of LKB1-AMPK signaling can promote a pro-growth metabolic program in tumor cells (Fig. 1). Tumor cells lacking LKB1 or AMPK can gain enhanced mTOR activity, increases in HIF1 α -driven glucose and glutamine metabolism, and bypass metabolic checkpoints that normally restrict cell growth under low nutrient conditions. In this context, silencing AMPK signaling during transformation may provide tumor cells with a selective metabolic growth advantage, and be selected for during early tumorigenesis. Irreversible loss of AMPK brings with it the risk of losing metabolic plasticity and the ability to adapt to stressful growth conditions. As mentioned, tumor cells grown under chronic nutrient-restricted conditions develop resistance to metabolic stress in part by selecting for increased AMPK activity [40]. It remains to be determined whether increased AMPK activity is selected for during tumor progression, such as in metastatic or drug-resistant tumor populations.

Ultimately, for AMPK to be considered as a viable target for cancer treatment in a clinical setting, understanding the roles of AMPK in cancer development and progression is essential. Data highlighting roles for AMPK in cancer cell survival raises the caution that AMPK activation may not be beneficial, and in some cases could be pro-tumorigenic. Given these results, we argue that, in addition

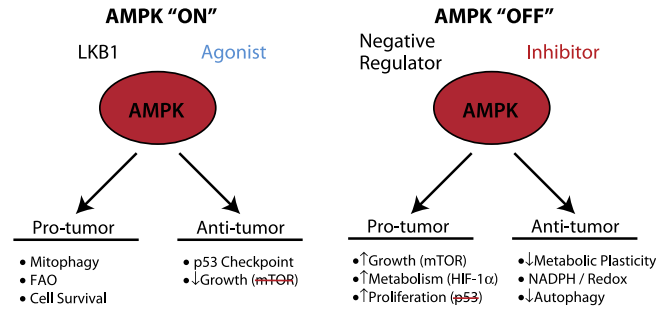


Fig. 1. AMPK can exert pro- or anti-tumor effects based on context. Activation of AMPK can exert pro-tumor effects under metabolic stress by engaging alternative metabolic pathways including mitophagy and fatty acid oxidation (FAO). However, activation of AMPK can inhibit cell growth by engaging p53-dependent cell cycle arrest and downregulation of mTORC1 activity. Inactivating AMPK may also promote pro- and anti-tumor responses. Loss of AMPK activity is associated with increased growth and proliferation (via elevated mTORC1 activity and reduced nutrient-sensitive p53 activation, respectively), and promotes pro-growth metabolism via HIF-1 α . Alternatively, lack of AMPK signaling may be exploited in an anti-tumor fashion, as the loss of AMPK-dependent metabolic plasticity disrupts energy homeostasis, NADPH/redox regulation, and impairs autophagy.

to AMPK agonists, AMPK inhibitors may have a place as anti-cancer therapeutics. The use of AMPK inhibitors, used alone or in conjunction with compounds that activate metabolic stress, may be effective in exploiting the altered metabolic demand of tumor cells.

Conflicts of interest

The authors have no conflicts of interest to declare.

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References

- [1] D.G. Hardie, D. Carling, S.J. Gamblin, AMP-activated protein kinase: also regulated by ADP?, *Trends Biochem. Sci.* 36 (2011) 470–477.
- [2] D.G. Hardie, F.A. Ross, S.A. Hawley, AMPK: a nutrient and energy sensor that maintains energy homeostasis, *Nat. Rev. Mol. Cell. Biol.* 13 (2012) 251–262.
- [3] D.G. Hardie, Minireview: the AMP-activated protein kinase cascade: the key sensor of cellular energy status, *Endocrinology* 144 (2003) 5179–5183.
- [4] D.G. Hardie, Sensing of energy and nutrients by AMP-activated protein kinase, *Am. J. Clin. Nutr.* 93 (2011) 891S–896S.
- [5] D.G. Hardie, AMP-activated protein kinase: an energy sensor that regulates all aspects of cell function, *Genes. Dev.* 25 (2011) 1895–1908.
- [6] D.G. Hardie, AMP-activated protein kinase: a cellular energy sensor with a key role in metabolic disorders and in cancer, *Biochem. Soc. Trans.* 39 (2011) 1–13.
- [7] R.J. Shaw, N. Bardeesy, B.D. Manning, L. Lopez, M. Kosmatka, R.A. DePinho, L.C. Cantley, The LKB1 tumor suppressor negatively regulates mTOR signaling, *Cancer Cell* 6 (2004) 91–99.
- [8] S.A. Hawley, J. Boudeau, J.L. Reid, K.J. Mustard, L. Udd, T.P. Makela, D.R. Alessi, D.G. Hardie, Complexes between the LKB1 tumor suppressor, STRAD α/β and MO25 α/β are upstream kinases in the AMP-activated protein kinase cascade, *J. Biol.* 2 (2003) 28.
- [9] K. Inoki, T. Zhu, K.L. Guan, TSC2 mediates cellular energy response to control cell growth and survival, *Cell* 115 (2003) 577–590.
- [10] R.G. Jones, D.R. Plas, S. Kubek, M. Buzzai, J. Mu, Y. Xu, M.J. Birnbaum, C.B. Thompson, AMP-activated protein kinase induces a p53-dependent metabolic checkpoint, *Mol. Cell* 18 (2005) 283–293.
- [11] J. Liang, G. Mills, AMPK: a contextual oncogene or tumor suppressor?, *Cancer Res* 73 (2013) 2929–2935.
- [12] N. Cancer Genome Atlas, Comprehensive molecular characterization of human colon and rectal cancer, *Nature* 487 (2012) 330–337.
- [13] N. Cancer Genome Atlas, Comprehensive molecular portraits of human breast tumours, *Nature* 490 (2012) 61–70.

- [14] N. Cancer Genome Atlas Research, Comprehensive genomic characterization of squamous cell lung cancers, *Nature* 489 (2012) 519–525.
- [15] K.R. Laderoute, K. Amin, J.M. Calaoagan, M. Knapp, T. Le, J. Orduna, M. Foretz, B. Viollet, 5'-AMP-activated protein kinase (AMPK) is induced by low-oxygen and glucose deprivation conditions found in solid-tumor microenvironments, *Mol. Cell Biol.* 26 (2006) 5336–5347.
- [16] B. Faubert, G. Boily, S. Izreig, T. Griss, B. Samborska, Z. Dong, F. Dupuy, C. Chambers, B.J. Fuerth, B. Viollet, O.A. Mamer, D. Avizonis, R.J. DeBerardinis, P.M. Siegel, R.G. Jones, AMPK is a negative regulator of the Warburg effect and suppresses tumor growth in vivo, *Cell Metab.* 17 (2013) 113–124.
- [17] D.R. Alessi, K. Sakamoto, J.R. Bayascas, LKB1-dependent signaling pathways, *Annu. Rev. Biochem.* 75 (2006) 137–163.
- [18] D.M. Gwinn, D.B. Shackelford, D.F. Egan, M.M. Mihaylova, A. Mery, D.S. Vasquez, B.E. Turk, R.J. Shaw, AMPK phosphorylation of raptor mediates a metabolic checkpoint, *Mol. Cell* 30 (2008) 214–226.
- [19] J.M. Lizcano, O. Goransson, R. Toth, M. Deak, N.A. Morrice, J. Boudeau, S.A. Hawley, L. Udd, T.P. Makela, D.G. Hardie, D.R. Alessi, LKB1 is a master kinase that activates 13 kinases of the AMPK subfamily, including MARK/PAR-1, *EMBO J.* 23 (2004) 833–843.
- [20] B.M. Emerling, F. Weinberg, C. Snyder, Z. Burgess, G.M. Mutlu, B. Viollet, G.R. Budinger, N.S. Chandel, Hypoxic activation of AMPK is dependent on mitochondrial ROS but independent of an increase in AMP/ATP ratio, *Free Radical Biol. Med.* 46 (2009) 1386–1391.
- [21] P.T. Mungai, G.B. Waypa, A. Jairaman, M. Prakriya, D. Dokic, M.K. Ball, P.T. Schumacker, Hypoxia triggers AMPK activation through reactive oxygen species-mediated activation of calcium release-activated calcium channels, *Mol. Cell Biol.* 31 (2011) 3531–3545.
- [22] K.N. Phoenix, C.V. Devarakonda, M.M. Fox, L.E. Stevens, K.P. Claffey, AMPK α 2 suppresses murine embryonic fibroblast transformation and tumorigenesis, *Genes Cancer* 3 (2012) 51–62.
- [23] M.M. Fox, K.N. Phoenix, S.G. Kopsiaftis, K.P. Claffey, AMP-activated protein kinase α 2 isoform suppression in primary breast cancer alters AMPK growth control and apoptotic signaling, *Genes Cancer* 4 (2013) 3–14.
- [24] J. Li, P. Jiang, M. Robinson, T.S. Lawrence, Y. Sun, AMPK- β 1 subunit is a p53-independent stress responsive protein that inhibits tumor cell growth upon forced expression, *Carcinogenesis* 24 (2003) 827–834.
- [25] J. Godlewski, M.O. Nowicki, A. Bronisz, G. Nuovo, J. Palatini, M. De Lay, J. Van Brocklyn, M.C. Ostrowski, E.A. Chiocca, S.E. Lawler, MicroRNA-451 regulates LKB1/AMPK signaling and allows adaptation to metabolic stress in glioma cells, *Mol. Cell* 37 (2010) 620–632.
- [26] G. Zhao, J.G. Zhang, Y. Liu, Q. Qin, B. Wang, K. Tian, L. Liu, X. Li, Y. Niu, S.C. Deng, C.Y. Wang, MiR-148b functions as a tumor suppressor in pancreatic cancer by targeting AMPK α 1, *Mol. Cancer Ther.* 12 (2013) 83–93.
- [27] L. Wang, D.L. Brautigam, α -SNAP inhibits AMPK signaling to reduce mitochondrial biogenesis and dephosphorylates Thr172 in AMPK α *in vitro*, *Nat. Commun.* 4 (2013) 1559.
- [28] M. Baba, S.B. Hong, N. Sharma, M.B. Warren, M.L. Nickerson, A. Iwamatsu, D. Esposito, W.K. Gillette, R.F. Hopkins 3rd, J.L. Hartley, M. Furihata, S. Oishi, W. Zhen, T.R. Burke Jr., W.M. Linehan, L.S. Schmidt, B. Zbar, Folliculin encoded by the BHD gene interacts with a binding protein, FNIP1, and AMPK, and is involved in AMPK and mTOR signaling, *Proc. Natl. Acad. Sci. USA* 103 (2006) 15552–15557.
- [29] R.S. Preston, A. Philp, T. Claessens, L. Gijzen, A.B. Dydensborg, E.A. Dunlop, K.T. Harper, T. Brinkhuizen, F.H. Menko, D.M. Davies, S.C. Land, A. Pause, K. Baar, M.A. van Steensel, A.R. Tee, Absence of the Birt-Hogg-Dube gene product is associated with increased hypoxia-inducible factor transcriptional activity and a loss of metabolic flexibility, *Oncogene* 30 (2011) 1159–1173.
- [30] M. Yan, M.C. Gingras, E. Dunlop, Y. Nouet, F. Dupuy, Z. Jalali, L. Chotard, E. Possik, B. Faubert, A.B. Dydensborg, S. Sabourin, D. Kharitidi, R. Preston, D.M. Davies, T. Roughhead, R.G. Jones, A. Pause, Loss of folliculin tumor suppressor drives AMPK-dependent metabolic transformation, *J. Clin. Invest.* (Under Review).
- [31] B. Zheng, J.H. Jeong, J.M. Asara, Y.Y. Yuan, S.R. Granter, L. Chin, L.C. Cantley, Oncogenic B-RAF negatively regulates the tumor suppressor LKB1 to promote melanoma cell proliferation, *Mol. Cell* 33 (2009) 237–247.
- [32] C.H. Shen, P. Yuan, R. Perez-Lorenzo, Y. Zhang, S.X. Lee, Y. Ou, J.M. Asara, L.C. Cantley, B. Zheng, Phosphorylation of BRAF by AMPK impairs BRAF-KSR1 association and cell proliferation, *Mol. Cell* 52 (2013) 161–172.
- [33] V.G. Antico Arciuch, M.A. Russo, K.S. Kang, A. Di Cristofano, Inhibition of AMPK and Krebs cycle gene expression drives metabolic remodeling of Pten-deficient preneoplastic thyroid cells, *Cancer Res.* 73 (2013) 5459–5472.
- [34] M.C. Caino, Y.C. Chae, V. Vaira, S. Ferrero, M. Nosotti, N.M. Martin, A. Weeraratna, M. O'Connell, D. Jernigan, A. Fatatis, L.R. Languino, S. Bosari, D.C. Altieri, Metabolic stress regulates cytoskeletal dynamics and metastasis of cancer cells, *J. Clin. Invest.* 123 (2013) 2907–2920.
- [35] L. Liu, J. Ulbrich, J. Muller, T. Wustefeld, L. Aeberhard, T.R. Kress, N. Muthalagu, L. Rycak, R. Rudalska, R. Moll, S. Kempa, L. Zender, M. Eilers, D.J. Murphy, Deregulated MYC expression induces dependence upon AMPK-related kinase 5, *Nature* 483 (2012) 608–612.
- [36] K. Imamura, T. Ogura, A. Kishimoto, M. Kaminishi, H. Esumi, Cell cycle regulation via p53 phosphorylation by a 5'-AMP activated protein kinase activator, 5-aminoimidazole-4-carboxamide-1- β -D-ribofuranoside, in a human hepatocellular carcinoma cell line, *Biochem. Biophys. Res. Commun.* 287 (2001) 562–567.
- [37] J. Liang, S.H. Shao, Z.X. Xu, B. Hennessy, Z. Ding, M. Larrea, S. Kondo, D.J. Dumont, J.U. Gutterman, C.L. Walker, J.M. Slingerland, G.B. Mills, The energy sensing LKB1–AMPK pathway regulates p27(kip1) phosphorylation mediating the decision to enter autophagy or apoptosis, *Nat. Cell Biol.* 9 (2007) 218–224.
- [38] M. Rios, M. Foretz, B. Viollet, A. Prieto, M. Fraga, J.A. Costoya, R. Senaris, AMPK activation by oncogenesis is required to maintain cancer cell proliferation in astrocytic tumors, *Cancer Res.* 73 (2013) 2628–2638.
- [39] M.R. Banko, J.J. Allen, B.E. Schaffer, E.W. Wilker, P. Tsou, J.L. White, J. Villen, B. Wang, S.R. Kim, K. Sakamoto, S.P. Gygi, L.C. Cantley, M.B. Yaffe, K.M. Shokat, A. Brunet, Chemical genetic screen for AMPK α 2 substrates uncovers a network of proteins involved in mitosis, *Mol. Cell* 44 (2011) 878–892.
- [40] G. Leprivier, M. Remke, B. Rotblat, A. Dubuc, A.R. Mateo, M. Kool, S. Agnihotri, A. El-Naggar, B. Yu, S.P. Somasekharan, B. Faubert, G. Bridon, C.E. Tognon, J. Mathers, R. Thomas, A. Li, A. Barokas, B. Kwok, M. Bowden, S. Smith, X. Wu, A. Korshunov, T. Hielscher, P.A. Northcott, J.D. Galpin, C.A. Ahern, Y. Wang, M.G. McCabe, V.P. Collins, R.G. Jones, M. Pollak, O. Delattre, M.E. Gleave, E. Jan, S.M. Pfister, C.G. Proud, W.B. Derry, M.D. Taylor, P.H. Sorensen, The eEF2 kinase confers resistance to nutrient deprivation by blocking translation elongation, *Cell* 153 (2013) 1064–1079.
- [41] D. Bungard, B.J. Fuerth, P.Y. Zeng, B. Faubert, N.L. Maas, B. Viollet, D. Carling, C.B. Thompson, R.G. Jones, S.L. Berger, Signaling kinase AMPK activates stress-promoted transcription via histone H2B phosphorylation, *Science* 329 (2010) 1201–1205.
- [42] D.E. Frigo, M.K. Howe, B.M. Wittmann, A.M. Brunner, I. Cushman, Q. Wang, M. Brown, A.R. Means, D.P. McDonnell, CaM kinase kinase β -mediated activation of the growth regulatory kinase AMPK is required for androgen-dependent migration of prostate cancer cells, *Cancer Res.* 71 (2011) 528–537.
- [43] H.U. Park, S. Suy, M. Danner, V. Dailey, Y. Zhang, H. Li, D.R. Hyde, B.T. Collins, G. Gagnon, B. Kallakury, D. Kumar, M.L. Brown, A. Fornace, A. Dritschilo, S.P. Collins, AMP-activated protein kinase promotes human prostate cancer cell growth and survival, *Mol. Cancer Ther.* 8 (2009) 733–741.
- [44] D.F. Egan, D.B. Shackelford, M.M. Mihaylova, S. Gelineo, R.A. Kohnz, W. Mair, D.S. Vasquez, A. Joshi, D.M. Gwinn, R. Taylor, J.M. Asara, J. Fitzpatrick, A. Dillin, B. Viollet, M. Kundu, M. Hansen, R.J. Shaw, Phosphorylation of ULK1 (hATG1) by AMP-activated protein kinase connects energy sensing to autophagy, *Science* 331 (2011) 456–461.
- [45] J. Kim, M. Kundu, B. Viollet, K.L. Guan, AMPK and mTOR regulate autophagy through direct phosphorylation of Ulk1, *Nat. Cell Biol.* 13 (2011) 132–141.
- [46] M. Buzzai, D.E. Bauer, R.G. Jones, R.J. DeBerardinis, G. Hatzivassiliou, R.L. Elstrom, C.B. Thompson, The glucose dependence of Akt-transformed cells can be reversed by pharmacologic activation of fatty acid β -oxidation, *Oncogene* 24 (2005) 4165–4173.
- [47] J.W. McFadden, B.A. Corl, Activation of AMP-activated protein kinase (AMPK) inhibits fatty acid synthesis in bovine mammary epithelial cells, *Biochem. Biophys. Res. Commun.* 390 (2009) 388–393.
- [48] S.M. Jeon, N.S. Chandel, N. Hay, AMPK regulates NADPH homeostasis to promote tumour cell survival during energy stress, *Nature* 485 (2012) 661–665.
- [49] M.G. Vander Heiden, L.C. Cantley, C.B. Thompson, Understanding the Warburg effect: the metabolic requirements of cell proliferation, *Science* 324 (2009) 1029–1033.
- [50] D. Hanahan, R.A. Weinberg, Hallmarks of cancer: the next generation, *Cell* 144 (2011) 646–674.
- [51] R.J. Shaw, M. Kosmatka, N. Bardeesy, R.L. Hurlley, L.A. Witters, R.A. DePinho, L.C. Cantley, The tumor suppressor LKB1 kinase directly activates AMP-activated kinase and regulates apoptosis in response to energy stress, *Proc. Natl. Acad. Sci. USA* 101 (2004) 3329–3335.
- [52] K. Kato, T. Ogura, A. Kishimoto, Y. Minegishi, N. Nakajima, M. Miyazaki, H. Esumi, Critical roles of AMP-activated protein kinase in constitutive tolerance of cancer cells to nutrient deprivation and tumor formation, *Oncogene* 21 (2002) 6082–6090.
- [53] S.P. Davies, A.T. Sim, D.G. Hardie, Location and function of three sites phosphorylated on rat acetyl-CoA carboxylase by the AMP-activated protein kinase, *Eur. J. Biochem.* 187 (1990) 183–190.
- [54] G.F. Merrill, E.J. Kurth, D.G. Hardie, W.W. Winder, AICA riboside increases AMP-activated protein kinase, fatty acid oxidation, and glucose uptake in rat muscle, *Am. J. Physiol.* 273 (1997) E1107–1112.
- [55] A.S. Marsin, L. Bertrand, M.H. Rider, J. Deprez, C. Beauloye, M.F. Vincent, G. Van den Berghe, D. Carling, L. Hue, Phosphorylation and activation of heart PFK-2 by AMPK has a role in the stimulation of glycolysis during ischaemia, *Current Biol.* – CB 10 (2000) 1247–1255.
- [56] J.J. Lum, D.E. Bauer, M. Kong, M.H. Harris, C. Li, T. Lindsten, C.B. Thompson, Growth factor regulation of autophagy and cell survival in the absence of apoptosis, *Cell* 120 (2005) 237–248.
- [57] A.S. Loffler, S. Alers, A.M. Dieterle, H. Keppeler, M. Franz-Wachtel, M. Kundu, D.G. Campbell, S. Wesselborg, D.R. Alessi, B. Stork, Ulk1-mediated phosphorylation of AMPK constitutes a negative regulatory feedback loop, *Autophagy* 7 (2011) 696–706.
- [58] S. Jager, C. Handschin, J. St-Pierre, B.M. Spiegelman, AMP-activated protein kinase (AMPK) action in skeletal muscle via direct phosphorylation of PGC-1 α , *Proc. Natl. Acad. Sci. USA* 104 (2007) 12017–12022.
- [59] E.L. Greer, P.R. Oskoui, M.R. Banko, J.M. Maniar, M.P. Gygi, S.P. Gygi, A. Brunet, The energy sensor AMP-activated protein kinase directly regulates the mammalian FOXO3 transcription factor, *J. Biol. Chem.* 282 (2007) 30107–30119.
- [60] B. Faubert, E.E. Vincent, T. Griss, R. Svensson, O.A. Mamer, D. Avizonis, D.B. Shackelford, R.J. Shaw, R.G. Jones, Loss of the tumor suppressor LKB1 promotes

- metabolic reprogramming of cancer cells via HIF-1 α , Proc. Natl. Acad. Sci. USA (in press).
- [61] D.B. Shackelford, D.S. Vasquez, J. Corbeil, S. Wu, M. Leblanc, C.L. Wu, D.R. Vera, R.J. Shaw, MTOR and HIF-1 α -mediated tumor metabolism in an LKB1 mouse model of Peutz–Jeghers syndrome, Proc. Natl. Acad. Sci. USA 106 (2009) 11137–11142.
- [62] L. Li, K.L. Guan, Microtubule-associated protein/microtubule affinity-regulating kinase 4 (MARK4) is a negative regulator of the mammalian target of rapamycin complex 1 (mTORC1), J. Biol. Chem. 288 (2013) 703–708.
- [63] F. Giordanetto, D. Karis, Direct AMP-activated protein kinase activators: a review of evidence from the patent literature, Expert Opin. Ther. Patents 22 (2012) 1467–1477.
- [64] M.R. Owen, E. Doran, A.P. Halestrap, Evidence that metformin exerts its anti-diabetic effects through inhibition of complex 1 of the mitochondrial respiratory chain, Biochem. J. 348 (Pt 3) (2000) 607–614.
- [65] M.Y. El-Mir, V. Nogueira, E. Fontaine, N. Averet, M. Rigoulet, X. Leverve, Dimethylbiguanide inhibits cell respiration via an indirect effect targeted on the respiratory chain complex I, J. Biol. Chem. 275 (2000) 223–228.
- [66] J.M. Evans, L.A. Donnelly, A.M. Emslie-Smith, D.R. Alessi, A.D. Morris, Metformin and reduced risk of cancer in diabetic patients, BMJ 330 (2005) 1304–1305.
- [67] A. Decensi, M. Puntoni, P. Goodwin, M. Cazzaniga, A. Gennari, B. Bonanni, S. Gandini, Metformin and cancer risk in diabetic patients: a systematic review and meta-analysis, Cancer Prev. Res. (Phila.) 3 (2010) 1451–1461.
- [68] M. Buzzai, R.G. Jones, R.K. Amaravadi, J.J. Lum, R.J. DeBerardinis, F. Zhao, B. Violette, C.B. Thompson, Systemic treatment with the antidiabetic drug metformin selectively impairs p53-deficient tumor cell growth, Cancer Res. 67 (2007) 6745–6752.
- [69] N. Wu, C. Gu, H. Gu, H. Hu, Y. Han, Q. Li, Metformin induces apoptosis of lung cancer cells through activating JNK/p38 MAPK pathway and GADD153, Neoplasma 58 (2011) 482–490.
- [70] M.V. Appleyard, K.E. Murray, P.J. Coates, S. Wullschleger, S.E. Bray, N.M. Kernohan, S. Fleming, D.R. Alessi, A.M. Thompson, Phenformin as prophylaxis and therapy in breast cancer xenografts, Br. J. Cancer 106 (2012) 1117–1122.
- [71] J.N. Kuznetsov, G.J. Leclerc, G.M. Leclerc, J.C. Barredo, AMPK and Akt determine apoptotic cell death following perturbations of one-carbon metabolism by regulating ER stress in acute lymphoblastic leukemia, Mol. Cancer Ther. 10 (2011) 437–447.
- [72] O.S. El-Masry, B.L. Brown, P.R. Dobson, Effects of activation of AMPK on human breast cancer cell lines with different genetic backgrounds, Oncol. Lett. 3 (2012) 224–228.
- [73] C. Rosilio, N. Lounnas, M. Nebout, V. Imbert, T. Hagenbeek, H. Spits, V. Asnafi, R. Pontier-Bres, J. Reverso, J.F. Michiels, I.B. Sahra, F. Bost, J.F. Peyron, The metabolic perturbators metformin, phenformin and AICAR interfere with the growth and survival of murine PTEN-deficient T cell lymphomas and human T-ALL/T-LL cancer cells, Cancer Lett. 336 (2013) 114–126.
- [74] D.J. Elder, A. Hague, D.J. Hicks, C. Paraskeva, Differential growth inhibition by the aspirin metabolite salicylate in human colorectal tumor cell lines: enhanced apoptosis in carcinoma and *in vitro*-transformed adenoma relative to adenoma relative to adenoma cell lines, Cancer Res. 56 (1996) 2273–2276.
- [75] L.X. Dong, L.L. Sun, X. Zhang, L. Pan, L.J. Lian, Z. Chen, D.S. Zhong, Negative regulation of mTOR activity by LKB1–AMPK signaling in non-small cell lung cancer cells, Acta Pharmacol. Sin. 34 (2013) 314–318.
- [76] E. Vakana, J.K. Altman, H. Glaser, N.J. Donato, L.C. Platanias, Antileukemic effects of AMPK activators on BCR–ABL-expressing cells, Blood 118 (2011) 6399–6402.
- [77] C. Petti, C. Vegetti, A. Molla, I. Bersani, L. Cleris, K.J. Mustard, F. Formelli, G.D. Hardie, M. Sensi, A. Anichini, AMPK activators inhibit the proliferation of human melanomas bearing the activated MAPK pathway, Melanoma Res. 22 (2012) 341–350.
- [78] F.V. Din, A. Valanciute, V.P. Houde, D. Zibrova, K.A. Green, K. Sakamoto, D.R. Alessi, M.G. Dunlop, Aspirin inhibits mTOR signaling, activates AMP-activated protein kinase, and induces autophagy in colorectal cancer cells, Gastroenterology 142 (2012) 1504–1515. e1503.
- [79] B. Cool, B. Zinker, W. Chiou, L. Kifle, N. Cao, M. Perham, R. Dickinson, A. Adler, G. Gagne, R. Iyengar, G. Zhao, K. Marsh, P. Kym, P. Jung, H.S. Camp, E. Frevort, Identification and characterization of a small molecule AMPK activator that treats key components of type 2 diabetes and the metabolic syndrome, Cell Metab. 3 (2006) 403–416.
- [80] X. Huang, S. Wullschleger, N. Shpiro, V.A. McGuire, K. Sakamoto, Y.L. Woods, W. McBurnie, S. Fleming, D.R. Alessi, Important role of the LKB1–AMPK pathway in suppressing tumorigenesis in PTEN-deficient mice, Biochem. J. 412 (2008) 211–221.
- [81] K.H. Lee, E.C. Hsu, J.H. Guh, H.C. Yang, D. Wang, S.K. Kulp, C.L. Shapiro, C.S. Chen, Targeting energy metabolic and oncogenic signaling pathways in triple-negative breast cancer by a novel adenosine monophosphate-activated protein kinase (AMPK) activator, J. Biol. Chem. 286 (2011) 39247–39258.
- [82] A. Kalender, A. Selvaraj, S.Y. Kim, P. Gulati, S. Brule, B. Violette, B.E. Kemp, N. Bardeesy, P. Dennis, J.J. Schlager, A. Marette, S.C. Kozma, G. Thomas, Metformin, independent of AMPK, inhibits mTORC1 in a rag GTPase-dependent manner, Cell Metab. 11 (2010) 390–401.
- [83] F. Dupuy, T. Griss, J. Blagih, G. Bridon, D. Avizonis, C. Ling, Z. Dong, D.R. Siwak, M.G. Annis, G.B. Mills, W.J. Muller, P.M. Siegel, R.G. Jones, LKB1 is a central regulator of tumor initiation and pro-growth metabolism in ErbB2-mediated breast cancer, Cancer Metab. 1 (2013) 18.
- [84] D.B. Shackelford, E. Abt, L. Gerken, D.S. Vasquez, A. Seki, M. Leblanc, L. Wei, M.C. Fishbein, J. Czernin, P.S. Mischel, R.J. Shaw, LKB1 inactivation dictates therapeutic response of non-small cell lung cancer to the metabolism drug phenformin, Cancer Cell 23 (2013) 143–158.