Review

Cancer Research

AMPK: A Contextual Oncogene or Tumor Suppressor?

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Abstract

The AMP-activated protein kinase (AMPK) functions to monitor and maintain energy homeostasis at the cellular and organism level. AMPK was perceived historically primarily as a component of the LKB1/STK11 tumor suppressor (LKB1 mutations cause the Peutz-Jegher cancer predisposition syndrome) cascade upstream of the TSC1/2/mTOR pathway and thus likely to be a tumor suppressor. However, AMPK has recently been shown to promote cancer cell survival in the face of extrinsic and intrinsic stressors including bioenergetic, growth factor, and oncogene stress compatible with studies showing that AMPK is required for oncogenic transformation. Thus, whether AMPK acts as a *bona fide* tumor suppressor or a contextual oncogene and, of particular importance, whether AMPK should be targeted for activation or inhibition during cancer therapy, is controversial and requires clarification. We aim to initiate discussions of these critical questions by reviewing the role of AMPK with an emphasis on cancer cell adaptation to microenvironment stress and therapeutic intervention. *Cancer Res; 73(10); 2929–35. ©2013 AACR.*

AMPK Regulation

The AMPK holoenzymes

Kinase-competent AMP-activated protein kinase (AMPK) complexes exist in mammalian cells as heterotrimers composed of one α catalytic and 2 β and γ regulatory subunits encoded by the *PRKAA1, PRKAA2, PRKAB1, PRKAB2, PRKAG1, PRKAG2,* and *PRKAG3* genes. To add to the complexity, multiple potentially functional splice variants have been identified. As a result, multiple AMPK isoenzyme complexes are likely present in any cell depending on the tissue and cell specificity of individual subunit expression.

Allosteric versus "agonistic" activation

AMPK is unique as a kinase in terms of functioning as a sensor of cellular energy levels. Mammalian AMPKγ has 3 CBS adenosine phosphate binding sites; ATP, ADP, and AMP compete for CBS1 and CBS3, whereas CBS4 is constitutively occupied by AMP independent of adenyl nucleotide concentrations. AMP/ADP binding promotes T-loop phosphorylation and allosteric activation of α subunits, whereas ATP binding inhibits the kinase complex (1). Thus, AMPK activation is regulated by adenylate energy charge rather than solely by relative levels of AMP and ATP as thought previously. Other metabolic intermediates including glycogen and NADH can bind AMPK complexes, but whether they alter AMPK activity remains undefined (2). In theory, any stimulus that alters cellular energy levels alters AMPK activation, including an increasing number of drugs and xenobiotics, such as paclitaxel, metformin, and resveratrol. However, it is important to make a clear distinction between the effects of energy stress and AMPK activation *per se* before any cellular outcome can be appropriately attributed to AMPK (3). As an example, metformin, which has been proposed to be an AMPK "agonist," has no direct effect on either AMPK or its upstream kinase LKB1 (4). Instead, metformin inhibits the mitochondrial electron transport chain complex I disrupting energy homeostasis (5) and also alters mTOR function independently of AMPK and TSC2 (6).

T-loop phosphorylation

AMPK activation requires phosphorylation at the conserved threonine residue (Thr172 in case of human and murine AMPKα2) within the activation loop (i.e., the T-loop) of the catalytic subunit. LKB1 is the primary kinase phosphorylating this site; however, depending on cellular and activation context, other kinases, including CaMKKβ and TAK1, can activate AMPK. AMPK activation can also be affected by Thr172 dephosphorylation, although the responsible phosphatase(s) awaits identification (1, 2). The relative contribution of Thr172 phosphorylation/dephosphorylation and allosteric activation of AMPK by nucleotide binding remains controversial.

AMPK and Cancer

AMPK and "stress management" in cancer cells

AMPK functions physiologically to allow cells to cope with stress, including metabolic, growth factor deprivation, and oncogenic stress (Fig. 1). AMPK activates catabolic and inhibits anabolic metabolism, a scenario that is not compatible with cell proliferation and is consistent with a tumor suppressor role. However, although AMPK, when highly activated, can potently inhibit cell proliferation and tumor growth, loss of AMPK is not sufficient to confer cell proliferation in the absence of adequate nutrients and growth factors, which is

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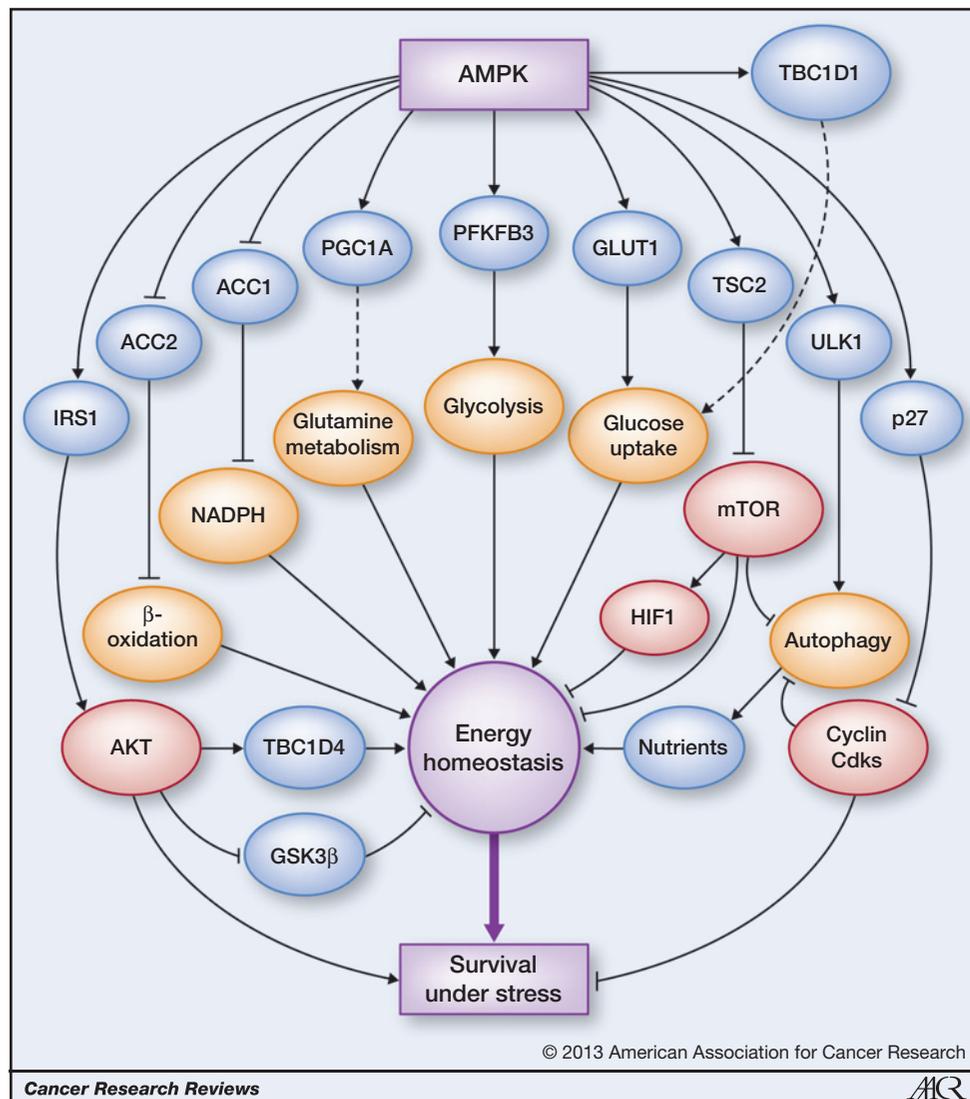American Association for **Cancer Research**   **2929**

Figure 1. AMPK promotes cell survival. Under conditions where growth factors, nutrients, oxygen, adhesion, and pH are unfavorable for cell proliferation, as well as under oncogenic stress induced by deregulated Ras and Myc oncogenes, AMPK can activate multiple pathways that maintain bioenergetic homeostasis to support cell survival. Which downstream processes manifest under basal conditions and in response to particular stress conditions as well as the functional outcomes are dependent on the cellular context and the duration and magnitude of the stress.

distinct from defects in genome surveillance genes that lead to cell division despite unrepaired DNA errors. Instead, loss of bioenergetic homeostasis leads to programmed cell death in cells lacking either LKB1 or AMPK but not normal cells identically stressed (7–10). Further, cells lacking AMPK are resistant to oncogenic transformation (11). We posit that AMPK may act as a conditional tumor suppressor or oncogene depending on the degree of AMPK activation, the particular AMPK isoforms present, and other processes activated in the cell (12). It is possible that modest activation of AMPK engages cell protective mechanisms resulting in oncogene-like activities, whereas increased magnitude or duration of stress could induce growth arrest or cell death exhibiting a tumor suppressor function.

AMPK-related kinases other than AMPK may mediate some of the tumor suppressor functions of LKB1

Germline mutations in *LKB1* are the cause of Peutz-Jegher cancer predisposition syndrome (PJS), a rare and dominantly inherited condition characterized primarily by benign intestinal hamartomatous polyps and mucocutaneous pigmentation associated with increased risk of developing malignant tumors of multiple lineages (13–16). Somatic *LKB1* mutations are found in lung and cervical cancer; epigenetic inactivation of *LKB1*, although rare, has been reported in sporadic papillary breast cancer. LKB1 haploinsufficiency ($LKB1^{+/-}$) in mice gives rise to phenotypes similar to human PJS with the formation of polyps in the gastrointestinal tract and increased frequency of liver, bone, and endometrial cancer (13). Thus, *LKB1* is a validated tumor suppressor gene.

In contrast with LKB1, AMPK α, β, and γ subunits are rarely (<3% for any subunit) somatically mutated in human cancers and indeed are amplified more frequently than mutated (cancergenome.nih.gov/), and there is no evidence for a germline cancer predisposition syndrome involving AMPK subunits. Complete loss of AMPK function is embryonically lethal in mice. Conditional AMPK knockout models have been created (17); however, the role of AMPK in tumorigenesis has not been

extensively studied in these models. Similar to *LKB1* deletion (14, 18), murine fibroblasts lacking both catalytic isoforms of AMPK are resistant to oncogenic transformation (11), which is consistent with AMPK and an intact energy-sensing mechanism being required during oncogenesis. Although loss of AMPK on its own is insufficient to provoke tumor formation in mice, inactivation of AMPKα1, the sole catalytic subunit in murine B-cell lineages, can accelerate *Myc*-driven lymphomagenesis (19). In contrast, deletion of the α2 but not the α1 subunit of AMPK increases susceptibility to H-RasV12–induced transformation in murine fibroblasts (20), raising an interesting possibility that distinct AMPK subunits contribute to tumor suppression independent of or in addition to the energy-sensing function of AMPK in particular contexts. Indeed AMPKα2 can regulate p53, mitosis, chromosome segregation, and cell division symmetry (21, 22). Further studies are needed to determine whether specific AMPK isoenzymes may exhibit independent oncogenic or tumor suppressive functions.

AMPK α, β, and γ subunit levels are elevated in 2% to 25% of human cancers (cancergenome.nih.gov/) and cancer cell lines (23–28). Data on AMPK and downstream substrate phosphorylation are variable (cancergenome.nih.gov/; refs. 23, 29) likely due to multiple factors, including tumor lineage, metabolic status, and challenges with preserving phosphoprotein levels in patient samples. Although AMPK activity would be predicted to decrease in tumor cells lacking functional LKB1, AMPK can be activated in a variety of cancer lines independent of LKB1, and high-level AMPK phosphorylation is present in lung cancer where loss of LKB1 is common (29), which may be mediated via alternative mechanisms of AMPK activation involving CAMKK2, TAK1, or unknown phosphatases. Although it remains unclear to what extent the energy-sensing function of AMPK contributes to the tumor suppressor function of LKB1, it is possible that modest AMPK activation in LKB1-deficient cells, which may be insufficient for growth inhibition, could be adequate for promoting cell survival (30) contributing to the apparent dichotomy of AMPK actions.

Aside from its role in energy sensing, LKB1, originally identified as one of the partitioning-defective proteins (PAR-4) in *Caenorhabditis elegans* (31), is essential for the establishment of cell polarity, a function that is potentially relevant to the tumor suppressor role of LKB1 (32). Under energy-replete conditions in *Drosophila*, dLKB1, but not dAMPKα (SNF1A), regulates polarity. However, upon nutrient deprivation, dAMPKα acts as a conditional regulator of cellular polarity. In support of a link between polarity and energy sensing, we have shown that Rab25, which is frequently amplified in human cancers and represents a key link between vesicle recycling and cellular polarity, is a potent regulator of energy balance in tumor cells (33, 34). We have recently reviewed the emerging evidence supporting the concept that polarity, vesicle recycling, and cellular metabolism are integrally linked and that deregulation of these mechanisms may contribute to tumorigenesis (35).

In addition to AMPK, LKB1 also phosphorylates and regulates 12 AMPK-related kinases (BRSK1/2, NuAK1/2, SIK1/2/3, MARK1/2/3/4, and SNRK; ref. 36). LKB1 contributes to maintenance of genomic stability and homeostasis of hematopoietic stem cells in a manner that is largely independent of AMPK

and mTORC1 (37). Thus, AMPK-related kinases rather than AMPK may mediate the tumor suppressor role of LKB1 (38, 39), although NuAK1 (also known as ARK5), NuAK2, SIK1, SIK2, and SIK3 have been linked to tumor formation, invasion, and metastasis (40–44).

AMPK and the p53 tumor suppressor

AMPK regulates p53 acetylation and phosphorylation (45, 46), again leading to the perception that AMPK functions as a tumor suppressor. However, AMPK-dependent p53 activation promotes cell survival while inhibiting cell proliferation, consistent with p53 acetylation being required for inhibition of cell proliferation but not apoptosis and being dispensable for the tumor suppressor function of p53 (47). AMPK α and β subunits are also regulated by acetylation in mammalian and yeast cells, respectively (48, 49), raising the possibility that common acetylation enzymes may target the AMPK–p53 complex. Because LKB1 and p53 mutations are not mutually exclusive in human cancer, these 2 pathways, although linked, could have independent contributions to tumor suppression. Future studies using genetically modified animal models will shed light on the interaction between AMPK and p53 and the impact on cellular outcome that is likely contextual and dependent on the degree and duration of AMPK action.

Are AMPK and AKT friends or foes?

The AMPK energy-sensing pathway and the phosphoinositide 3-kinase (PI3K)–AKT cascade converge on mTOR with opposing regulatory effects, with the effect of AMPK activation being dominant over AKT-dependent pathways (50); it is thus tempting to postulate that AMPK antagonizes the functional effects of AKT activation. This is indeed the case for TSC2 and FOXO3, which are phosphorylated by both AMPK and AKT at different sites with opposite effects on TSC2 activity and FOXO3 translocation, though not necessarily cellular outcome (36). Importantly, both AMPK and AKT have multiple substrates in addition to TSC2 and FOXO3. As many of the targets overlap (e.g., IRS1, TBC1D1, TBC1D4, PFKFB2, PFKFB3, TSC2, and p27Kip1), AMPK and AKT frequently function in concert, responding to distinct extracellular cues or physiologic conditions to coordinate bioenergetics and cell viability (1, 36, 51, 52). Furthermore, under glucose depletion, both AMPK and AKT are activated despite suppression of serum-stimulated activation of the mTOR cascade; however, rather than being antagonistic, both coordinately support cell survival (7, 53). The cooperation between AKT and AMPK is likely widespread given the multifaceted roles of AMPK and AKT in regulating glucose homeostasis.

AMPK in tumor formation, adaptation to adverse microenvironments, and resistance to therapy

The lack of genetic evidence for loss of AMPK function in cancer may rather suggest an essential role of AMPK in oncogenic transformation consistent with AMPK being a master sensor and regulator of cellular energy homeostasis, a prerequisite for survival and function of mammalian cells including cancer cells (Fig. 1). Because of adaptation to oncogene activation or loss of tumor suppressors that drive energy

demand/supply imbalance, cancer cells may exhibit increased reliance on adequate AMPK function, especially under the hypoxic and nutrient-deficient conditions that are typical of the tumor microenvironment. In solid tumors, AMPK activation is heterogenous, resembling that of hypoxia (11), where inducible AMPK activation could mediate a prosurvival role analogous to that of hypoxia-inducible factors (HIF). Cellular responses to hypoxia, including activation of AMPK or AMPK family kinases, also allow cells to tolerate nutrient starvation (25, 54). The prosurvival role of AMPK can, at least in part, be attributed to autophagy induction and the maintenance of proliferative quiescence (55–58), a concept that has been substantiated by *in vitro* and *in vivo* studies showing that AMPK activation and autophagy serve as protective mechanisms conferring resistance to growth factor deprivation and antiangiogenesis therapies (51, 52).

AMPK activation can confer on cancer cells the flexibility to use nutrient sources other than glucose. AMPK is a major regulator of fatty acid catabolism through phosphorylating and inactivating ACC1 and ACC2 that catalyze acetyl-CoA carboxylation to produce malonyl-CoA, a substrate for fatty acid biosynthesis. Malonyl-CoA potently inhibits CPT1, which mediates mitochondrial fatty acid uptake (36). Thus, AMPK promotes fatty acid transport into mitochondria and subsequent breakdown by β-oxidation. AMPK also upregulates CTP1C expression (9) and increases CPT1C levels in response to glucose starvation and hypoxia to facilitate fatty acid catabolism and ATP production (59). Silencing CPT1C increases sensitivity to rapamycin, hypoxia, and glucose restriction in multiple cancer lines and reduces xenograft tumor growth suggestive of a causal link. In addition, AMPK-dependent ACC1/2 inactivation increases NADPH levels due to decreases in consumption during fatty acid synthesis and increases in NADPH production through β-oxidation (30). AMPK also facilitates the use of fatty acids supplied by adjacent adipocytes in the tumor microenvironment (60). Thus, the cooperative effects of AMPK on ACC and CPT1 activity coordinately increase β-oxidation, ATP production, and NADPH levels, supplying the energy source and building blocks required for rapid cancer growth while increasing cell survival by providing protection from ROS production.

The amino acid proline becomes available from the breakdown of ECM during tumor invasion. The PRODH proline dehydrogenase mediates the first step of proline degradation, eventually leading to generation of glutamate fueling the tricarboxylic acid (TCA) cycle leading to ATP and ROS production. AMPK can upregulate PRODH in response to hypoxia and glucose deprivation. The resultant increases in bioenergetics and autophagy induced by ROS can then promote cell survival (61).

Furthermore, some cancer cells become reliant on mitochondrial glutaminolysis due to metabolic reprogramming during oncogenic transformation (62). AMPK plays a critical role in mitochondrial biogenesis. Both NuAK1 and AMPK are required for the expression of mitochondrial respiratory chain complexes that support use of glutamine as an energy source in MYC-overexpressing cancer cells, where depletion of either NuAK1 or AMPK causes apoptosis in a MYC-dependent man-

ner (63). Intriguingly, MYC overexpression induces NuAK1-dependent AMPK activation, placing NuAK1 upstream of AMPK in this setting (63). The mechanism underlying the cross-talk between NuAK1 and AMPK merits further investigation.

Interestingly, the budding yeast AMPK ortholog Snf1 mediates the expression of genes required for metabolism of nonglucose carbon sources through the oxidative phosphorylation pathway and for promoting filamentous growth, an invasive form of yeast growth induced by nutrient limitation (64). Thus, the ability of AMPK to confer metabolic plasticity in mammalian cells may be phylogenetically conserved (1). Indeed, mammalian AMPK associates with and phosphorylates histone H2B at the promoter and transcription regions of AMPK-dependent genes (9). Future studies are needed to dissect the respective role of cytoplasmic and nuclear AMPK in regulating substrate metabolism.

AMPK and the Warburg effect

The adaptive mechanisms described above require intact mitochondrial function, which may not be available to all cancer cells due to the complexity of tumor microenvironments, architectural heterogeneity, and genetic backgrounds. In several cancer lineages, genetic defects involving TCA enzymes (MERRF, SDH5, and FH) are associated with tumorigenesis, whereas oncogenic H-Ras transformation impairs mitochondrial function (51, 65). The affected cells are hence forced to rely on aerobic glycolysis with lactate production rather than oxidative phosphorylation to maintain ATP levels, as in the Warburg effect, a widespread phenotype of cancer cells. Interestingly, AMPK is required for apoptotic resistance conferred by FH deficiency (66). AMPK regulates glycolysis by phosphorylating and activating PFKFB3, one of the 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatases (PFKFB1∼4), as shown in monocytes (67). This increases the levels of fructose-2,6-bisphosphate, a potent allosteric activator of the rate-limiting glycolysis enzyme PFK1 (68). PFKFB3 is overexpressed in multiple cancer lineages, and its phosphorylation is increased significantly in human colon and breast cancer samples potentially as a consequence of AMPK activation (69). Various stress signals, including hypoxia and nutrient restriction, can drive PFKFB3 expression, and AMPK contributes to increasing PFKFB3 and glycolytic flux in response to lowered pH (70). In addition, PFKFB2, a phosphorylation target of both AKT and AMPK, is also overexpressed in human cancers. Thus, AKT and AMPK may promote glycolysis depending on cell context.

In addition to the role of AMPK in allowing cells to cope with stress, AMPK was recently shown to act as a negative regulator of the Warburg effect under nutrient rich and growth factor–replete conditions in the absence of evident energy imbalance (19). Although it is unclear whether AMPK activation in this setting (Eμ-*Myc* transgenic) is causally linked to the ability of cells to compensate for MYC overexpression as observed in human cancer cells (63), AMPK depletion further increases mTORC1 activation, HIF1 levels, and aerobic glycolysis in *Myc*-overexpressing cells (19). Notably, AMPK depletion led to increases in lactate production exceeding what would be solely explained by glucose uptake (19), suggesting the use of non-glucose carbon sources for anabolism, the maintenance of

bioenergetics, and lactate production. The role of lactate production by proliferating cancer cells, the centerpiece of the Warburg effect, remains poorly understood despite extensive studies. Indeed, the key glycolysis enzyme PFK1 is regulated by O-GlcNAcylation, which inhibits its kinase activity and is necessary for optimum tumor growth (71), suggesting that suppression of lactate-producing glycolysis can also confer survival and growth advantages to cancer cells depending on genetic background and cell contexts. It is unclear whether this process is regulated by AMPK; however, AMPK phosphorylates and inhibits GFAT1 (72), which catalyzes the first step of the hexosamine biosynthesis pathway that produces UDP-GlcNAc, an obligatory substrate of O-GlcNAc transferase. Further studies are needed to determine the role of AMPK-mediated GFAT1 phosphorylation on O-linked glycosylation, which could have a profound impact comparable with that of phosphorylation on proteins that function in response to nutrients and stress, including AMPK itself.

Concluding Remarks and Future Perspectives

Previous studies have focused on the role of AMPK in the LKB1–AMPK–TSC2–mTOR cascade and suppression of cell growth. Although additional aspects of AMPK function and regulatory mechanisms are likely to be identified in the near future, recent studies have begun to elucidate the contribution of the energy sensing function of AMPK, which promotes cell survival, in cancer cell adaptation to the adverse microenvironment present in tumors not only by energy conservation but also by facilitating switching to alternative nutrient sources. Because AMPK activation is readily reversible when conditions become favorable for tumor cell proliferation, we contend that the energy-sensing function of AMPK plays a conditional oncogenic role, which may confer a survival advantage under selection pressure, contributing to cancer cell evolution and the rise of progressive cell populations. Although emerging evidence continues to show seemingly conflicting roles of AMPK in controlling tumorigenesis as driven by different oncogenes including myc (19) and H-RasV12 (73), which highlights the importance of cellular and genetic contexts for AMPK function, most studies consistently show that AMPK promotes cancer cell survival under stress even when a tumor suppressor role has been proposed (19, 74). Thus, a logical implication of recent progress in this field is that inhibiting rather than activating AMPK may provide a therapeutic avenue for overcoming drug resistance, preventing metastasis, and eradicating residual disease, in which contexts eliminating surviving and dormant cancer cells becomes more desirable than inhibiting cell proliferation. Thus, high-

ly selective AMPK inhibitors, expected to disrupt AMPK-dependent mechanisms contributing to the maintenance of bioenergetic homeostasis (Fig. 1), will not only confer desirable tools to elicit the functional roles of AMPK in more clinically relevant settings but also provide a potential approach for cancer therapy. AMPK inhibition may lead to deregulation of the mTOR cascade, which could mitigate the effects of AMPK inhibitors. This concern could potentially be resolved via combination therapy with mTOR inhibitors, several of which are in clinical use. Furthermore, we predict that selective AMPK inhibitors will be most effective when AMPK is activated, a condition under which mTOR activation can be detrimental to cell survival (7, 75).

Instead of AMPK inhibitors, AMPK agonists are currently being pursued for cancer treatment. The antidiabetic agent metformin is perceived as a most promising candidate being tested for cancer treatment in several large-scale clinical trials. This approach is expected to mimic energy stress and cause growth arrest, as neither LKB1 nor AMPK is the direct target of metformin (4). Thus, it will be necessary to clearly distinguish functional outcomes of AMPK activation from the secondary consequences of metabolic stress or the effects of such therapeutic interventions on other cellular targets, including AMPK family members.

Full implementation of AMPK-targeted drugs into clinical management, however, will be dependent on an improved understanding of AMPK regulation as well as its roles in tumor progression. New studies are needed to further address the role of AMPK in tumorigenesis and to resolve the conundrum around whether and when AMPK acts in a tumor suppressive or an oncogenic role. Given the lack of evidence for loss of AMPK *per se* in human tumors, conditional knockout models and deletion of individual AMPK subunits in mice are required to elicit the potential use of AMPK and AMPK-targeted therapy. As indicated above, it will be critically important to assess the physiologic functions of AMPK and the interplay with AKT and PI3K in glucose, fatty acid metabolism, and cell survival in the context of clinical stage, treatment status, patient outcome, tumor type, and architecture.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: J. Liang, G.B. Mills
Writing, review, and/or revision of the manuscript: J. Liang, G.B. Mills

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