The dark face of AMPK as an essential tumor promoter

Sang-Min Jeon1,* and Nissim Hay2
1Research Oncology; Genentech, Inc.; South San Francisco, CA USA; 2Department of Biochemistry and Molecular Genetics; College of Medicine; University of Illinois at Chicago; Chicago, IL USA

Numerous studies have shown that supraphysiological activation of AMPK could inhibit tumor growth. On the other hand, accumulating data also suggest that AMPK activity is required for tumor growth and migration. These findings suggest that physiological activation of AMPK is critical for tumor growth/migration, possibly through maintenance of ATP levels. Our recent study provides the first evidence that the maintenance of cellular NADPH homeostasis is the predominant mechanism by which AMPK promotes tumor cell survival and solid tumor formation. We showed that AMPK activation is required to maintain intracellular NADPH levels through the activation of fatty acid oxidation (FAO) or the inhibition of fatty acid synthesis (FAS) during glucose deprivation or matrix detachment respectively. Through these processes AMPK activation inhibits the rise in reactive oxygen species (ROS) levels and promotes metabolic adaptation in response to metabolic stress. This finding also provides a new therapeutic opportunity through targeting metabolic adaptation of cancer cells, either alone or in combination with conventional anti-cancer drugs that cause metabolic stress.

Introduction

AMP-activated protein kinase (AMPK) plays a pivotal role in the regulation of energy homeostasis at both the cellular and organismal levels. Diverse stress conditions, such as nutrient starvation or hypoxia, that increase AMP, ADP, Ca2+ and reactive oxygen species (ROS) levels have been shown to activate AMPK (Fig. 1, and reviewed in ref. 1). AMPK exists as a heterotrimer consisting of an α-catalytic subunit and β, γ-regulatory subunits, and the phosphorylation of T172 in the α-catalytic subunit is a critical event for the full activation of AMPK under these conditions. Two major upstream kinases are responsible for the phosphorylation of the catalytic subunit: the liver kinase B1 (LKB1) and Ca2+/calmodulin-dependent protein kinase kinase 2 (CaMKK2)2-6 (Fig. 1). LKB1 is responsible for the activation of AMPK during energy stress when intracellular ATP levels are reduced and ADP and AMP levels are elevated. Thus, the LKB1-AMPK pathway has a major role in the regulation of metabolic adaptation during energy stress conditions. CaMKK2 activity is usually elevated when intracellular Ca2+ levels are elevated, and thus can activate AMPK regardless of the energy status of the cells. However, the physiological conditions in which the CaMKK2-AMPK axis plays a major role remain to be elucidated. In addition to AMP, ADP and Ca2+, recent studies also have identified reactive oxygen species (ROS) as another upstream activators of AMPK.7-11 Although ROS can increase the phosphorylation of T172, it was not yet determined which upstream kinases (or phosphatases) are responsible for this increase. Moreover, there is a debate whether ROS can activate AMPK directly through the oxidation of cysteine residues in AMPK, or indirectly through the increase of AMP, ADP or Ca2+ levels.7,8,10-12 Once activated, AMPK maintains energy balance through the activation of catabolism to increase ATP production and through the inhibition of anabolism.

**Keywords:** AMPK, LKB1, CaMKK2, ACC, NADPH, ROS, fatty acids, metabolic stress, cancer

Submitted: 07/28/12
Revised: 10/22/12
Accepted: 10/24/12
http://dx.doi.org/10.4161/cl.22651

*Correspondence to: Sang-Min Jeon; Email: jeon.sangmin@gene.com

Addendum to: Jeon SM, Chandelier NS, Hay N. AMPK regulates NADPH homeostasis to promote tumour cell survival during energy stress. Nature 2012; 485:661-5; PMID:22660331; http://dx.doi.org/10.1038/nature11066.
The Emerging Evidences for the Pro-Tumorigenic Role of AMPK

Despite the concept that AMPK hyper-activation is anti-tumorigenic, there are multiple observations that indicate that physiological AMPK activation is pro-tumorigenic (summarized in Table 1). Using an established model of glioblastoma, it was shown that AMPK is strongly activated during the early stages of solid tumor formation. This finding supports the notion that physiological activation of AMPK could be important for tumorigenesis. Consistently, it has been shown that LKB1-null mouse embryo fibroblasts (MEFs) are resistant to oncogene-induced anchorage-independent growth and that oncogene-transformed AMPKα1/α2-null (AMPKα-KO) MEFs are sensitive to anoikis and are severely impaired in their ability to form tumors in vivo. The silencing of AMPK in pancreatic cancer cells impairs both their ability to grow in an anchorage-independent manner and to form tumors in vivo.

Moreover, it has been shown that the LKB1-AMPK signaling pathway is required for glioma cell survival and spheroid migration in low-glucose conditions. The importance of AMPK activation for tumor cell growth, survival and migration has also been shown in prostate cancer. Unbiased RNAi screening identified that AMPKβ subunit is essential for prostate cancer cell survival. The same study found that the expression of AMPKβ subunit is highly elevated in metastatic prostate cancers when compared with primary prostate cancers. Interestingly, a critical role of the CaMKK2-AMPK axis to reduce ATP consumption through the phosphorylation of diverse substrates. Thus AMPK could restrain cell growth by inhibiting protein and fatty acid synthesis, while promoting cell survival mechanism through the elevation of mitochondrial metabolism and autophagy.

Because of these versatile and conflicting functions of AMPK in cell growth and survival, its role in cancer has been hotly debated. In this addendum, we briefly summarize recent literatures supporting the pro-tumorigenic role of AMPK and highlight our recent findings connecting AMPK and NADPH homeostasis as the potential mechanisms to explain those previous observations. Further, we discuss possible scenarios that can resolve the LKB1-AMPK paradox in cancer and potential applications of this finding to cancer therapy.

Figure 1. The mechanisms by which AMPK regulate NADPH homeostasis during energy stress. When glucose is available, NADPH is generated by the PPP and mitochondrial metabolism. NADPH is consumed in FAS and in regeneration of GSH to detoxify ROS. Energy stress conditions, such as glucose deprivation or matrix detachment, increase AMPK activation. The inhibition of AMPK by CaMKK2 could be important for tumorigenesis. Consistently, it has been shown that LKB1-null mouse embryo fibroblasts (MEFs) are resistant to oncogene-induced anchorage-independent growth and that oncogene-transformed AMPKα1/α2-null (AMPKα-KO) MEFs are sensitive to anoikis and are severely impaired in their ability to form tumors in vivo.
through inhibition of mammalian target of rapamycin complex 1 (mTORC1) or activation of p53.13,34 These previous studies suggested that AMPK promotes cell survival by conserving ATP levels during metabolic stress through the inhibition of ATP consuming processes or the activation of ATP producing processes, although there is no direct experimental evidence to support this view.

Our recent study unraveled a new function of AMPK in NADPH homeostasis, which is required to prevent and for the Kinase Suppressor of Ras 2 (KSR2)-induced anoikis resistance and anchorage-independent growth of cancer cells.33

### The Mechanisms by Which AMPK Activation Promotes Tumorigenesis: The Redox Connections

Previous studies suggested that the LKB1-AMPK pathway promotes cell survival during glucose deprivation, in part, through inhibition of mammalian target of rapamycin complex 1 (mTORC1) or activation of p53.13,34 These previous studies suggested that AMPK promotes cell survival by conserving ATP levels during metabolic stress through the inhibition of ATP consuming processes or the activation of ATP producing processes, although there is no direct experimental evidence to support this view.

Our recent study unraveled a new function of AMPK in NADPH homeostasis, which is required to prevent...
oxidative stress and promote cancer cell survival under metabolic stress conditions.\(^{35}\) (Fig. 1). NADPH is consumed and required for FAO, and for the maintenance of reduced glutathione, which is required to detoxify \(\text{H}_2\text{O}_2\) (Fig. 1). We showed that AMPK maintains NADPH homeostasis through the regulation of fatty acid metabolism by phosphorylating and inactivating acetyl-CoA carboxylase 1 (ACC1) and ACC2.\(^{35}\) ACC1 and ACC2, which are the major targets of AMPK in the regulation of FAS and FAO, convert acetyl-CoA to malonyl-CoA\(^{36}\) (Fig. 1). Malonyl-CoA is not only a precursor for FAS, but is also an allosteric inhibitor of carnitine palmitoyl transferase 1 (CPT1). CPT1 is associated with the outer mitochondrial membrane and transfers long-chain fatty acids from the cytosol into the mitochondrial matrix for FAO. ACC1 and ACC2 might have overlapping function. However, malonyl-CoA generated by ACC1, which is localized to the cytosol is largely channeled to FAS.\(^{37}\) On the other hand, malonyl-CoA generated by ACC2, which is localized to the outer mitochondrial membrane and in close proximity to CPT1, inhibits CPT1 and consequently FAO\(^{38}\) (Fig. 1). Since FAO fuels mitochondrial metabolism and increases TCA cycle metabolites, FAO could increase NADPH production through malic enzyme 1 (ME1) and isocitrate dehydrogenase 1 (IDH1) by converting malate and isocitrate to pyruvate (PY) and \(\alpha\)-ketoglutarate (\(\alpha\)-KG) respectively (Fig. 1).

In our study, we used two different conditions for metabolic stress, glucose deprivation and matrix detachment, which are both associated with solid tumor microenvironment.\(^{35,39}\) When glucose uptake is decreased, both glycolysis and the pentose phosphate pathway (PPP) can be inhibited (Fig. 1). The PPP is the major pathway that generates NADPH via glucose-6-phosphate dehydrogenase (G6PD) and 6-phosphogluconate dehydrogenase (6PGD). As a consequence of metabolic stress conditions when glucose availability is decreased in LKB1 deficient cancer cells, we showed that NADPH production is decreased from PPP and consequently \(\text{H}_2\text{O}_2\) levels are elevated, which is the main cause of cell death.\(^{35}\) However, the concurrent activation of LKB1-AMPK pathway under these conditions increases NADPH production and \(\text{H}_2\text{O}_2\) detoxification via inhibition of ACC2 and the increase of FAO.\(^{35}\) Only ACC2 inhibition and the induction of FAO—not ACC1 and FAO inhibition—is required for cell survival under glucose deprivation because FAS inhibition is occurring regardless of ACC1 or ACC2 status in response to glucose deprivation.\(^{35}\) This is consistent with the previous finding showing that in the absence of glucose, the activation of AMPK and FAO could promote the survival of cancer cells displaying hyperactive Akt.\(^{39}\) This is also consistent with the recent study showing that AMPK is essential for Myc-driven tumorigenesis through promoting mitochondrial respiration,\(^{32}\) further underscoring the importance of the AMPK-induced mitochondrial metabolism in tumorigenesis.

On the other hand, during matrix detachment, we found that the inhibition of FAS and therefore the inhibition of NADPH consumption by ACC1 inhibition is the predominant mechanism by which AMPK sustains NADPH levels and prevents oxidative stress\(^{35}\) (Fig. 1). Importantly, we found that even in the absence of LKB1, AMPK can be significantly activated during matrix detachment in a CAMKK2-dependent manner\(^{35}\) (Fig. 1). The mechanism by which the CAMKK2-AMPK axis is activated during matrix detachment is not known, but this activation of AMPK is not sufficient to fully protect the cells from oxidative stress induced by matrix detachment. The importance of AMPK activation in reducing oxidative stress during tumorigenesis was underscored by the observations that antioxidant treatment in LKB1- or AMPK-deficient cells could restore anchorage-independent growth of these cells. Consistently the inhibition of ACC1 or ACC2 could restore anchorage-independent growth and solid tumor formation of AMPK-deficient cells in vivo.\(^{35}\)

Collectively, our study demonstrates that NADPH and ROS maintenance by ACC inhibition is a major mechanism by which AMPK promotes cancer cell survival during energy stress, anchorage-independent growth and solid tumor formation. Further, the study established that in addition to ATP, NADPH maintenance is an important function of AMPK activation. It appears that in cancer cells, which are exposed to energy stress, the maintenance of NADPH is the predominant mechanism by which AMPK activation promotes cell survival.

Understanding the Previous Findings in the Context of AMPK-NADPH Paradigm

Our findings could explain several aspects regarding the role of the LKB1-AMPK pathway in cancer raised by previous studies, and which are not fully understood. For example, our results may explain why patients with Peutz-Jeghers syndrome, who have an inherited deficiency of LKB1, and most mouse models of LKB1 deficiency, develop only benign tumors.\(^{23}\) Although cells with LKB1 deficiency have an advantage in cell growth and proliferation as a result of mTORC1 activation, they cannot become fully malignant due to a disadvantage in cell survival during solid tumor formation, which involves matrix detachment and limited glucose supply. It would be, therefore, interesting to assess this possibility by crossing LKBI deficient mice with the mice overexpressing certain antioxidant genes such as catalase or the transcription factor NRF2, a master regulator of antioxidant enzymes and analyzing tumor development.\(^{40}\) In addition, our results could potentially explain why LKB1- or AMPK-deficient MEFs are resistant to both oncogene-induced anchorage-independent growth and tumor formation in vivo, and why AMPK is required for KSR2-mediated anoikis resistance and anchorage-independent growth.\(^{33-35}\) Interestingly, a recent study by Sorensen and colleagues also found that AMPK inhibits anoikis partially through the inhibition of mTORC1-mediated translation.\(^{25}\) This study adds additional mechanism for the protective role of AMPK during matrix detachment, although it is still possible that mTORC1 can regulate FAS and NADPH levels through regulation of sterol-regulatory-element-binding proteins 1 (SREBP1) that induces the expression of lipogenic enzymes.\(^{41,42}\) Likewise, this may also explain why Tsc2-null cells are hypersensitized to glucose deprivation.\(^{15,43}\) as mTORC1 hyperactivation accelerates FAS...
through its effect on SREBP1, which further increases NADPH consumption. Our results may also explain why Akt activation sensitizes cells to glucose deprivation and why FAO activation reverses this sensitization. Akt activation may sensitize cells to glucose deprivation because it inhibits AMPK or activates ATP-citrate lyase (ACLY), which in turn activates FAS and inhibits FAO, leading to NADPH depletion. Thus, FAO activation could promote cell survival under these conditions by increasing NADPH production. Similarly, this can also potentially explain why Myc-driven tumorigenesis requires AMPK-induced mitochondrial gene expression and mitochondrial metabolism. Enhancing mitochondrial metabolism by AMPK could increase NADPH production and provide potential benefits during Myc-driven tumorigenesis which is known to increase ROS levels. Finally, based on our findings showing that the CaMKK2-AMPK-NADPH axis plays a major role in cancer cell survival during matrix detachment, our study may explain why CaMKK2 is over-expressed in certain cancer and also may provide new mechanistic insights regarding the pro-tumorigenic role of the CaMKK2-AMPK pathway in prostate cancer migration and invasion.

The LKB1-AMPK Paradox: Unresolved Questions

Although somatic mutations in LKB1 are rare in most tumors, the mutations are prevalent in certain cancers, such as non-small cell lung carcinoma and cervical carcinoma. In mouse models, the deficiency in LKB1 accelerates Ras-induced lung tumorigenesis. Thus, one critical question is how the loss of function mutations in LKB1 occurs in these cancer cells, despite the disadvantages in metabolic adaptation. The simplest explanation would be that LKB1-deficiency could be pro-tumorigenic through the activation of mTORC1 or inactivation of other kinases downstream of LKB1 in a microenvironment where metabolic adaptation does not play a critical role. Indeed, it was recently shown that lung tumors are less hypoxic as compared with other solid tumors, suggesting that the LKB1-AMPK-mediated metabolic adaptation may not be critical for lung tumorigenesis. It is also possible that in these cases certain microenvironmental factors enable activation of AMPK through other upstream activators, such as CaMKK2, in the absence of LKB1. A more intriguing possibility is that LKB1 mutations could lead to cancer only if other occurring mutations could compensate for the loss of metabolic adaptation mediated by the LKB1-AMPK axis. Thus, it would be interesting to analyze genetic or epigenetic changes in these cancers to verify whether there are additional mutations that co-exist with LKB1 mutation, and that elicit protection from oxidative stress through alternative mechanisms. Finally, tracing metabolic fluxes redirected by genetic or epigenetic changes to compensate for the loss of LKB1 would be also important to resolve this issue.

Therapeutic Opportunity

Forced AMPK activation is being considered for cancer therapy as it was shown that it induces a cytostatic effect primarily through the inhibition of mTORC1. However, our results suggest that physiological activation of AMPK in cancer cells could promote their survival during two critical processes at the early stages of solid tumor formation. The metabolic adaptation mediated by AMPK activation could occur when cancer cells are exposed to an environment with limited nutrients and glucose and/or detachment from the matrix inside of a solid tumor, and when they migrate from the primary tumor and colonize in a secondary site during metastasis. Our results suggest that the combination of AMPK activators and potential ACC activators could eliminate the pro-survival effect of AMPK activation and would elicit cancer cell death during the two critical stages in cancer development. In addition, targeting metabolic adaptation could be a promising strategy if combined with conventional anti-cancer drugs that cause metabolic stress. Recently, it has been shown that anti-VEGF therapy in ovarian cancers induces oxygen and glucose deprivation and increases AMPK activity. Intriguingly, the AMPK activity as measured by p-ACC level is well correlated with the resistance to anti-VEGF therapy, while silencing AMPKα2 in ovarian cancer enhanced the therapeutic effect of anti-VEGF. Thus, it would be of importance to further assess the potential clinical benefits of this combination therapy. Further, as described above, analyzing specific compensatory genetic or epigenetic changes in LKB1-mutated cancers will help design new therapeutic strategies to treat those cancers.

References

1. Hardie DG, Ross FA, Hawley SA. AMPK: a nutrient and energy sensor that maintains energy homeostasis. Nat Rev Mol Cell Biol 2012; 13:251-62; PMID:22436748; http://dx.doi.org/10.1038/nrm3311.
2. Hawley SA, Boudeau J, Reid JL, Mustard KJ, Udd L, Makela TP, et al. Complexes between the LKB1 tumor suppressor, STRAD alpha/beta and MO25 alpha/beta are upstream kinases in the AMP-activated protein kinase cascade. J Biol Chem 2003; 278:23648-55; PMID:12849056; http://dx.doi.org/10.1074/jbc.M204177200.
3. Hawley SA, Pan DA, Mustard KJ, Ross L, Bain J, Edelman AM, et al. Calmodulin-dependent protein kinase kinase-beta is an alternative upstream kinase for AMP-activated protein kinase. Cell Metab 2005; 2:9-19; PMID:16054095; http://dx.doi.org/10.1016/j.cmet.2005.05.009.
4. Hurley RL, Anderson KA, Franzone JM, Kemp BE, Means AR, Witters LA. The Ca2+/calmodulin-dependent protein kinase beta is an alternative upstream kinase for AMP-activated protein kinase. J Biol Chem 2005; 280:29060-6; PMID:15980064; http://dx.doi.org/10.1074/jbc.M503824200.
5. Woods A, Dickerson K, Heath R, Hong SP, Momcilovic M, Johnstone SR, et al. Ca2+/calmodulin-dependent protein kinase beta acts upstream of AMP-activated protein kinase in mammalian cells. Cell Metab 2005; 2:21-33; PMID:16054096; http://dx.doi.org/10.1016/j.cmet.2005.06.005.
6. Shaw RJ, Kosmatka M, Bardeesy N, Hurley RL, Winters LA, DePinho RA, et al. The tumor suppressor LKB1 kinase directly activates AMP-activated protein kinase and regulates apoptosis in response to energy stress. Proc Natl Acad Sci U S A 2004; 101:3329-34; PMID:14985505; http://dx.doi.org/10.1073/pnas.0308061100.
7. Hawley SA, Ross FA, Chevzoff C, Green KA, Evans A, Fogarty S, et al. Use of cells expressing gamma subunit variants to identify diverse mechanisms of AMPK activation. Cell Metab 2010; 11:554-65; PMID:20519126; http://dx.doi.org/10.1016/j.cmet.2010.04.001.
8. Choi SL, Kim SJ, Lee KT, Kim J, Mu J, Burinbaum MJ, et al. The regulation of AMP-activated protein kinase by H(2)O(2). Biochem Biophys Res Commun 2001; 287:92-7; PMID:11354258; http://dx.doi.org/10.1006/bbrc.2001.5544.
9. Emerling BM, Weinberg S, Snyder C, Burgess Z, Murali GM, Voisard B, et al. Hypoxic activation of AMPK is dependent on mitochondrial ROS but independent of an increase in AMP/ATP ratio. Free Radic Biol Med 2009; 46:1386-91; PMID:19268526; http://dx.doi.org/10.1016/j.freeradbiomed.2009.02.019.
10. Mungan PT, Waypa GB, Jairamani A, Prakriya M, Dokic D, Ball MK, et al. Hypoxia triggers AMPK activation through reactive oxygen species-mediated activation of calcium release-activated calcium channels. Mol Cell Biol 2011; 31:3531-45; PMID:21670147; http://dx.doi.org/10.1128/MCB.00214-11.
Zmijewski JW, Banerjee S, Bae H, Friggeri A, Lazarowski ER, Abraham E. Exposure to hydrogen peroxide induces oxidation and activation of AMP-activated protein kinase. J Biol Chem 2010; 285:33154-64; PMID:20729205; http://dx.doi.org/10.1074/jbc.M110.143685.

Cardaci S, Filomeni G, Ciriole MR. Redox implications of AMPK-mediated signal transduction beyond energetic clues. J Cell Sci 2012; 125:2115-25; PMID:22619229; http://dx.doi.org/10.1242/jcs.095216.

Corradetti MN, Inoki K, Bardeesy N, DePinao RA, Guan KL. Regulation of the TSC pathway by LKB1: evidence of a molecular link between tuberous sclerosis complex and Fuzetti-Jeghers syndrome. Genes Dev 2004; 18:1533-58; PMID:1523735; http://dx.doi.org/10.1101/gad.1199104.

Egan DF, Shackelford DB, Mihaylova MM, Gelino MC, Lazarowski ER, Abraham E. Exposure to hydrogen peroxide induces oxidation and activation of AMP-activated protein kinase modifies 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 4 as an important regulator of prostate cancer cell survival. Cancer Discov 2012; 2:328-43; PMID:22576210; http://dx.doi.org/10.1158/2155-8290.CD-11-0234.

Goddleski J, Nowicki MO, Bronisz A, Nuovo G, Palazini J, De Luy L, et al. MicroRNA-451 regulates LKB1/AMPK signaling and allows adaptation to metabolic stress in glioma cells. Mol Cell 2010; 37:620-32; PMID:20227267; http://dx.doi.org/10.1016/j.molcel.2010.02.018.

Frigg DE, Howe MK, Wirtzmann BM, Brunner LA, Lack GW, et al. AMPK regulates the mTOR pathway by direct phosphorylation of Ulk1. Nat Cell Biol 2005; 7:631-7; PMID:15753721; http://dx.doi.org/10.1038/sj.onc.1205737.

Inoki K, Zhou Z, Guan KL. TSC2 mediates cellular energy response to control cell growth and survival. Cell 2003; 115:577-90; PMID:14651849; http://dx.doi.org/10.1016/S0092-8674(03)00929-2.

Kim J, Kundra M, Violett B, Guan KL. AMPK and AmpTOR regulate autophagy through direct phosphorylation of Ulk1. Nat Cell Biol 2011; 13:332-41; PMID:21258367; http://dx.doi.org/10.1038/ncb2352.

Merrill GF, Kurth EJ, Hardie DG, Winder WW. ACA riboose increases AMP-activated protein kinase, fatty acid oxidation, and glucose uptake in rat muscle. Am J Physiol 1997; 273:E1107-12; PMID:9090622.

Ng TL, Leprivier G, Robertson MD, Chow C, Ng KM, et al. LKB1/AMPK signaling and mitophagy connects energy sensing to mitophagy. J Cell Sci 2012; 125:2115-25; PMID:22619229; http://dx.doi.org/10.1242/jcs.095216.

Zhou G, Myers R, Li Y, Chen Y, Shen X, Fenyl-Melesy J, et al. Role of AMP-activated protein kinase in mechanism of metformin action. J Clin Invest 2001; 108:1167-74; PMID:11602624.

Buzza M, Zajeck B, DeGraffenried R, Harrazano S, Elstrom RL, et al. Glucose dependence of Akt-transformed cells can be reversed by pharmacologic activation of fatty acid beta-oxidation. Oncogene 2005; 24:4165-73; PMID:1580514; http://dx.doi.org/10.1038/sj.onc.1208622.

McFadden JW, Corl BA. Activation of AMP-activated protein kinase (AMPK) inhibits fatty acid synthesis in bovine mammary epithelial cells. Biochim Biophys Acta Commun 2009; 390:388-93; PMID:19747896; http://dx.doi.org/10.1016/j.bbr.2009.09.017.

Jiang T, et al. 5’-AMP-activated protein kinase activity is elevated early during primary brain tumor development in the rat. Int J Cancer 2011; 128:2230-9; PMID:20635388.

Bardeesy N, Sinha M, Hezel AF, Signoretti S, Jang T, et al. 5’-AMP-activated protein kinase (AMPK) is induced by low oxygen and glucose deprivation conditions found in solid-tumor microenvironments. Mol Cell Bioi 2006; 26:5336-47; PMID:16809770; http://dx.doi.org/10.1074/mcb.061066-006.

Ladourere KR, Amin K, Galaragam JM, Knapp M, Lu CS, Odedina J, et al. 5’-AMP-activated protein kinase (AMPK) is induced in low oxygen and glucose deprivation conditions found in solid-tumor microenvironments. Mol Cell Bioi 2006; 26:5336-47; PMID:16809770; http://dx.doi.org/10.1074/mcb.061066-006.

Ng TL, Leprivier G, Collaboration M, Martin MJ, Ladourere KR, et al. The AMPK stress response pathway mediates angiogenesis resistance through inhibition of mTOR and suppression of protein synthesis. Cell Death Differ 2012; 19:501-10; PMID:22141569; http://dx.doi.org/10.1038/cdd.2011.119.

Kato K, Ogura T, Kishimoto A, Minegishi Y, Nakajima N, Miyazaki M, et al. Critical roles of AMP-activated protein kinase in constitutive tolerance of cancer cells to nutrient deprivation and tumor formation. Oncogene 2002; 21:6808-90; PMID:12203120; http://dx.doi.org/10.1038/sj.onc.1205737.

Godlewski J, Nowicki MO, Bronisz A, Nuovo G, Palazini J, De Luy L, et al. MicroRNA-451 regulates AMPK activity and allows adaptation to metabolic stress in glioma cells. Mol Cell 2010; 37:620-32; PMID:20227267; http://dx.doi.org/10.1016/j.molcel.2010.02.018.

Frigo DE, Howe MK, Wirtzmann BM, Brunner LA, Lack GW, et al. AMPK regulates the mTOR pathway by direct phosphorylation of Ulk1. Nat Cell Biol 2005; 7:631-7; PMID:15753721; http://dx.doi.org/10.1038/sj.onc.1205737.

Laderoute KR, Amin K, Galaragam JM, Knapp M, Lu CS, Odedina J, et al. 5’-AMP-activated protein kinase (AMPK) is induced in low oxygen and glucose deprivation conditions found in solid-tumor microenvironments. Mol Cell Bioi 2006; 26:5336-47; PMID:16809770; http://dx.doi.org/10.1074/mcb.061066-006.

Ng TL, Leprivier G, Collaboration M, Martin MJ, Ladourere KR, et al. The AMPK stress response pathway mediates angiogenesis resistance through inhibition of mTOR and suppression of protein synthesis. Cell Death Differ 2012; 19:501-10; PMID:22141569; http://dx.doi.org/10.1038/cdd.2011.119.

Kato K, Ogura T, Kishimoto A, Minegishi Y, Nakajima N, Miyazaki M, et al. Critical roles of AMP-activated protein kinase in constitutive tolerance of cancer cells to nutrient deprivation and tumor formation. Oncogene 2002; 21:6808-90; PMID:12203120; http://dx.doi.org/10.1038/sj.onc.1205737.

Godlewski J, Nowicki MO, Bronisz A, Nuovo G, Palazini J, De Luy L, et al. MicroRNA-451 regulates AMPK activity and allows adaptation to metabolic stress in glioma cells. Mol Cell 2010; 37:620-32; PMID:20227267; http://dx.doi.org/10.1016/j.molcel.2010.02.018.

Frigo DE, Howe MK, Wirtzmann BM, Brunner LA, Lack GW, et al. AMPK regulates the mTOR pathway by direct phosphorylation of Ulk1. Nat Cell Biol 2005; 7:631-7; PMID:15753721; http://dx.doi.org/10.1038/sj.onc.1205737.

Laderoute KR, Amin K, Galaragam JM, Knapp M, Lu CS, Odedina J, et al. 5’-AMP-activated protein kinase (AMPK) is induced in low oxygen and glucose deprivation conditions found in solid-tumor microenvironments. Mol Cell Bioi 2006; 26:5336-47; PMID:16809770; http://dx.doi.org/10.1074/mcb.061066-006.

Ng TL, Leprivier G, Collaboration M, Martin MJ, Ladourere KR, et al. The AMPK stress response pathway mediates angiogenesis resistance through inhibition of mTOR and suppression of protein synthesis. Cell Death Differ 2012; 19:501-10; PMID:22141569; http://dx.doi.org/10.1038/cdd.2011.119.