MINI-REVIEW

LKB1/AMPK/mTOR Signaling Pathway in Non-small-cell Lung Cancer

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Abstract

   Links between cancer and metabolism have been suggested for a long time but compelling evidence for this hypothesis came from the recent molecular characterization of the LKB1/AMPK signaling pathway as a tumor suppressor axis. Besides the discovery of somatic mutations in the LKB1 gene in certain type of cancers, a critical emerging point was that the LKB1/AMPK axis remains generally functional and could be stimulated by pharmacological molecules such as metformin in cancer cells. In addition, AMPK plays a central role in the control of cell growth, proliferation and autophagy through the regulation of mTOR activity, which is consistently deregulated in cancer cells. Targeting of AMPK/mTOR is thus an attractive strategy in the development of therapeutic agents against non-small-cell lung cancer (NSCLC). In this review, the LKB1/AMPK/mTOR signaling pathway is described, highlighting its protective role, and opportunities for therapeutic intervention, and clinical trials in NSCLC.

Keywords: LKB1 - AMPK - mTOR - NSCLC - therapeutic target

Introduction

   Lung cancer is the most commonly diagnosed cancer as well as the leading cause of cancer death in males globally (Jemal et al., 2011). Even in the females, it is the fourth most commonly diagnosed cancer and the second leading cause of cancer death (Jemal et al., 2011). Regarding to histological cell type, non-small-cell lung cancer (NSCLC) including squamous carcinoma, adenocarcinoma and large cell carcinoma represents ~80-87% of all lung cancer cases (Khan et al., 2012). Current approach for the treatment of NSCLC consists of surgical resection, platinum-based chemotherapy, radiation therapy, and targeted therapy. Unfortunately, the prognosis of patients with NSCLC (5-year overall survival rate of 15%) has not dramatically improved in the past 30 years (Jemal et al., 2010) despite the use of these approaches.

   AMP-activated protein kinase (AMPK) is a sensor of energy status that maintains cellular energy homeostasis (Hardie, 2011). It arose very early during eukaryotic evolution, and its ancestral role may have been in the response to starvation. Although best known for its effects on metabolism, AMPK has many other functions, including regulation of mitochondrial biogenesis and disposal, autophagy, cell polarity, and cell growth and proliferation (Hardie, 2011). Both tumor cells and viruses establish mechanisms to down-regulate AMPK, allowing them to escape its restraining influences on growth.

   The discovery that the serine/threonine kinase LKB1 (Liver Kinase B1; also known as Serine/Threonine Kinase 11 - STK11), a known tumor suppressor, was the major upstream kinase required for activation of AMP in response to metabolic stress introduced for the first time a link between AMPK and cancer (Hawley et al., 2003; Woods et al., 2003). LKB1 had been originally identified as the tumor suppressor responsible for an inherited susceptibility to cancer, Peutz-Jeghers syndrome (Hemminki et al., 1998; Jenne et al., 1998). Humans with Peutz-Jeghers syndrome are heterozygous for loss-of-function mutations in the LKB1 gene (STK11). As expected for a tumor suppressor, the STK11 gene is also frequently mutated in spontaneous cancers, including ~30% of NSCLC (Sanchez-Cespedes et al., 2002; Ji et al., 2007). Does activation of AMPK explain the tumor suppressor effects of LKB1? Although there is no formal genetic proof of this as yet, it does seem likely to be the case, because of the 14 protein kinases known to be downstream from LKB1 (the α1 and α2 isoforms of AMPK, and the 12 AMPK-related kinases), AMPK is the only one known to cause inhibition of biosynthesis and cell growth, and cell cycle arrest. It was found that diabetics that had been treated with metformin, which is an AMPK-activating drug, had a significantly lower incidence of cancer than those on other treatments (Evans et al., 2005). More importantly, treatment of a tumor-prone mouse model with three different activators of AMPK—i.e., metformin, phenformin, or A-769662—significantly delayed tumor development (Huang et al., 2008). In recent

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years, more extensive researches were focus on the role of AMPK in tumors. This article will thus review the recent progresses of AMPK in NSCLC.

LKB1/AMPK/mTOR Signaling Pathway

AMPK is a heterotrimeric serine/threonine kinase constituted of a catalytic α subunit and two regulatory subunits (β and γ). Following an increase in cellular AMP/ATP ratio, AMP binding causes an allosteric change of AMPKγ conformation, thus exposing AMPKα Thr172 residue for phosphorylation by LKB1, which markedly activates AMPK. After activation, AMPK controls multiple direct targets involved in metabolic pathways, such as glycolysis (e.g., phosphofructo-kinase 2), fatty acid and cholesterol synthesis (e.g., acetyl-CoA carboxylase 1 [ACC1] and HMG-CoA reductase) (Shackelford and Shaw, 2009). Overall, AMPK activation leads to energy preservation for cell survival at the expense of growth and proliferation (Hardie, 2007).

In addition, AMPK plays a central role in the control of cell growth, proliferation and autophagy through the regulation of mTOR activity, which is consistently deregulated in cancer cells (Chapuis et al., 2010). mTOR is a central integrator of nutrient and growth factor inputs that controls cell growth in all eukaryotes and is deregulated in most human cancers (Guertin and Sabatini, 2007). mTOR is found in two biochemically and functionally discrete signaling complexes, mTOR complex 1 (mTORC1) and mTORC2 (Wullschleger et al., 2006). mTORC1 includes raptor (regulatory-associated protein of mTOR), which acts as a scaffold to recruit downstream substrates such as eukaryotic Initiating Factor 4E Binding Protein 1 (4E-BP1) and ribosomal S6 kinase (p70S6K1) that contribute to mTORC1-dependent regulation of protein translation (Holz et al., 2005). mTORC1 controls the translation of a number of cell growth regulators, including cyclin D1, hypoxia inducible factor 1α (HIF-1α), and c-myc, which in turn promote processes including cell cycle progression, cell growth and angiogenesis, all of which can become deregulated during tumorigenesis (Guertin and Sabatini, 2007). mTORC1 is nutrient-sensitive and acutely inhibited by rapamycin, though studies reveal that rapamycin does not fully suppress mTORC1 activity in many cell types (Choo et al., 2008; Feldman et al., 2009). In contrast, the role of the mTORC2 complex, which is based on the interaction between rictor (rapamycin-insensitive companion of mTOR) and mTOR (Jacinto et al., 2004), has only recently emerged in cancer cell biology and is mainly related to the control of Akt S473 phosphorylation and the control of SGK activity (Guertin et al., 2009).

Cancer genetics and Drosophila genetics led to the discovery of upstream components of mTORC1 including the tuberous sclerosis complex 2 (TSC2) tumor suppressor and its obligate partner TSC1 (Shaw and Cantley, 2006). TSC2 inhibits mTORC1 indirectly via regulation of the small GTPase Ras homologue enriched in brain (Rheb), such that loss of TSC1 or TSC2 leads to hyperactivation of mTORC1 (Huang and Manning, 2008). And when levels of ATP, glucose or oxygen are low, AMPK directly phosphorylates TSC2 on conserved serine sites (Inoki
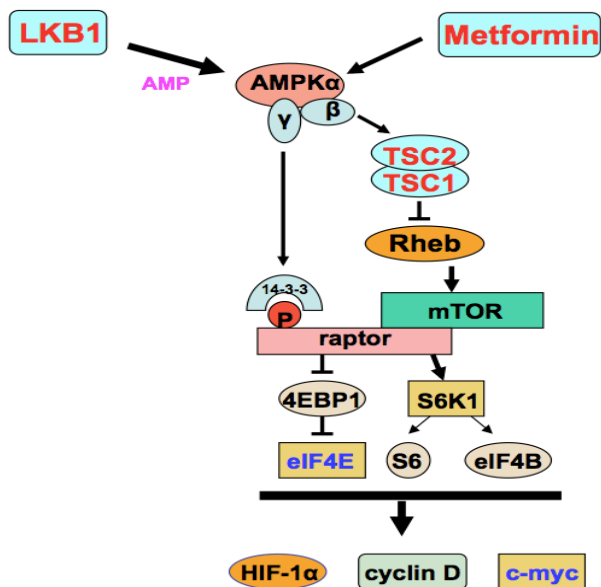

Figure 1. The LKB1/AMPK/mTORC1-dependent Regulation of Protein Translation. LKB1 is a master kinase controlling 14 substrates, including AMPK. Following AMP binding to γ-subunit, AMPKα catalytic site is activated through LKB1-mediated T172 phosphorylation. AMPK activation directly phosphorylates both TSC2 and raptor to inhibit mTORC1 activity by a dual mechanism, and mTORC1 controls the translation of a number of cell growth regulators

et al., 2003; Shaw et al., 2004; Liu et al., 2006). While TSC2 is clearly a central receiver of inputs that regulate mTORC1, cells lacking TSC2 still partially suppress mTORC1 following AMPK activation (Hahn-Windgassen et al., 2005; Gwinn et al., 2008). In agreement with these data, raptor has been identified as a direct substrate of AMPK in vivo. Phosphorylation of two conserved serines in raptor by AMPK induced binding to 14-3-3 and resulted in suppression of mTORC1 kinase activity (Gwinn et al., 2008). Phosphorylation of raptor was shown to be required for downregulation of mTOR and efficient G2/M cell cycle arrest following AMPK activation (Gwinn et al., 2008). Taken together, the current data indicate that energy stress results in LKB1-dependent activation of AMPK, which directly phosphorylates both TSC2 and raptor to inhibit mTORC1 activity by a dual mechanism, although it remains possible that additional substrates of AMPK contribute to the regulation of mTOR (Figure 1). Importantly, mTORC1 is currently the only signaling pathway downstream of LKB1 that has been shown to be deregulated in tumors arising in humans and mouse models of both Peutz-Jeghers syndrome (Shaw et al., 2004; Shackelford et al., 2009) and NSCLC (Shaw and Cantley, 2006; Ji et al., 2007).

AMPK Signaling Pathway in Tumors

Although there is therefore evidence that AMPK might provide protection against the development of tumors, as with any genuine tumor suppressor there is likely to be selection for loss of AMPK function in established tumors. Indeed, in a study of breast cancer, using immunohistochemistry with phospho-specific

antibodies against Thr172 on AMPK and Ser80 on ACC1, it was shown that AMPK activation appeared to be down-regulated (in the tumor compared with normal epithelium) in 90% of 350 cases. The mechanism underlying this down-regulation in breast cancer remains uncertain, but one simple explanation would be the loss of LKB1, which would prevent AMPK activation in response to metabolic stress (Hawley et al., 2003). Another mechanism for down-regulation of AMPK has been suggested in skin cancer cells (Zheng et al., 2009). A single point mutation in the proto-oncogene B-Raf (V600E, causing constitutive activation) occurs in up to half of all malignant melanomas. In melanoma cell lines carrying this mutation, LKB1 was found to be phosphorylated at two C-terminal sites by kinases acting downstream from B-Raf, and it was proposed that this interferes with the ability of LKB1 to phosphorylate and activate AMPK (Zheng et al., 2009).

Another mechanism is suggested by previous findings that phosphorylation of the α1 subunit of AMPK at Ser485 (equivalent to Ser491 on α2) by Akt (protein kinase B) inhibits the subsequent phosphorylation at Thr172—and consequent activation—by LKB1 (Horman et al., 2006). Akt is activated in many tumor cells due to either activating mutations in phosphatidylinositol (PI) 3-kinase (which generates PI-3,4,5-trisphosphate [PIP3], the activating signal for Akt) or loss of the lipid phosphatase PTEN (which breaks down PIP3). Phosphorylation of Ser485 would down-regulate AMPK in tumors containing hyper-activated Akt. Interestingly, this mechanism has been demonstrated to operate in human hepatoma cells infected with hepatitis C virus (HCV) (Mankouri et al., 2010). Tumorigenesis and viral infection bear certain analogies: In both cases, abnormal genes (activation of an oncogene or loss of a tumor suppressor in the first, insertion of the viral genome in the second) have taken over normal cellular functions and switched the cell from a quiescent state to one where there is active biosynthesis. The RNA genome of HCV encodes 10 viral proteins made by cleavage of a single polyprotein, and the virus also has a lipid envelope. Thus, replication of the virus in liver cells will require rapid protein and lipid synthesis and increase ATP turn-over, which would be expected to activate AMPK (which would in turn down-regulate protein and lipid synthesis). However, when HCV-infected cells were studied, it was found that phosphorylation of AMPK at Thr172 was reduced compared with uninfected controls. It was already known that one of the viral proteins (NS5A) binds and activates PI 3-kinase, thus switching on the Akt pathway (Street et al., 2004). Activation of Akt in virally infected cells was associated with phosphorylation of AMPK-α1 at the Akt site, Ser485 (Mankouri et al., 2010). To confirm that this was responsible for the down-regulation of Thr172 phosphorylation by the virus, the host cells were transiently transfected using DNAs encoding either wild-type α1, a potentially phospho-mimetic S485D mutant, or a nonphosphorylatable S485A mutant. Only in cells expressing the S485A mutant did the virus fail to replicate, suggesting that phosphorylation of Ser485 on AMPK-α1 is necessary for viral replication. Interestingly, it was also found that this mechanism for down-regulating AMPK could be overcome by treating

cells with metformin (Mankouri et al., 2010). This not only suggests that metformin could be a new treatment for chronic HCV infection, but also gives hope that metformin could be used to reverse AMPK down-regulation in tumors in which Akt is hyperactivated. Another intriguing feature of these results is that two of the complications of chronic HCV infection in humans are known to be hepatic steatosis (fatty liver) and hepatocellular carcinoma. Both might be expected to occur in cells in which AMPK was down-regulated, since AMPK switches off fatty acid and triglyceride synthesis, while, as discussed above, down-regulation of AMPK may be a prerequisite for rapid tumor growth.

LKB1/AMPK/mTOR in NSCLC

We will thereafter focus on recent breakthrough in the exploration of LKB1/AMPK/mTOR as a target in NSCLC. These explorations mostly focus on radiotherapy, traditional or potential chemotherapy drugs, and metabolism related proteins, all of which can activate AMPK.

Expression of Proteins in the AMPK Pathway

Meera and colleagues found that patients with recurrence of NSCLC had downregulation of markers in the AMPK signaling pathway, as indicated by decreased levels of total AMPK and pTSC2 and increased acetyl-CoA (normally inhibited by AMPK) (Nanjundan et al., 2010). And in stage III/IV patients, downregulation of pLKB1 was significantly associated with shorter cause-specific survival (Nanjundan et al., 2010). These findings are consistent with previous studies that inactivating mutations of LKB1 are seen more frequently in smokers and poorly differentiated NSCLC tumors (Matsumoto et al., 2007) and are associated with a shorter latency, more frequent metastasis, and accelerated pulmonary tumorigenesis (Ji et al., 2007). Recently, William et al. found that pAMPK expression levels were significantly higher in never smokers versus former smokers versus current smokers in surgically resected NSCLC (William et al., 2012). A positive pAMPK expression was associated with increased overall survival (OS) and recurrence-free survival (RFS) (William et al., 2012). And OS and RFS were statistically superior in pAMPK-positive than in pAMPK-negative patients with adenocarcinoma (median OS: 5.6 and 4.2 years, median RFS: 5.0 and 2.4 years, respectively), whereas they were similar in those patients with squamous cell carcinoma (William et al., 2012). These results indicated that high pAMPK expression levels are associated with increased survival in patients with NSCLC, especially those with adenocarcinoma. At this point, the biological significance of pAMPK expression will require further studies in cell lines and animal models to better understand the impact of AMPK activation in NSCLC.

Radiotherapy

Radiotherapy is one of the main therapeutic modalities in NSCLC. A previous study showed that p53-null cells

fail to arrest in response to AMPK stimulation by AICAR or glucose deprivation (Jones et al., 2005), indicating an association between AMPK and p53 and the cell cycle. Therefore, Toran et al. explored the regulation of AMPK by ionizing radiation (IR) and its role as a target for radiosensitization of NSCLC cells. The study had following results: (1) IR induced a robust activation of AMPK in NSCLC cells, independent of LKB1, (2) AMPK regulates IR induction of p53 and p21waf/cip, (3) AMPK modifies IR-induced G2/M checkpoint, (4) AMPK inhibition blocked IR induction of p53 and p21waf/cip as well as the IR-induced G2/M arrest, and (5) metformin significantly enhanced the IR activation of AMPK, and reduced surviving fraction of cells after 2 Gy (SF2) further (Sanli et al., 2010). And recently, they reported that lovastatin, the 3-hydroxy-3-methylgutaryl-CoA reductase inhibitor, inhibits survival and induces radiosensitization of NSCLC cells through induction of apoptosis, which may be partly mediated by activation of the AMPK signaling pathway (Sanli et al., 2011). A recent research examined the chronic modultion of expression and activity of AMPK/mTOR pathway by IR alone in xenograft models of NSCLC. This study demonstrated that irradiated tumors showed a sustained expression and activation of the AMPK-p53/p21cip1/p27kip1 but inhibition of the activity of the mTOR-4EBP1 pathway (Storozhuk et al., 2012). These studies showed evidence of involvement of AMPK in the IR-induced checkpoint control and clonogenic survival. Future studies should examine whether further modulation of the AMPK/mTOR pathway by novel therapeutics can sensitize NSCLC to radiation.

Traditional Chemotherapy Drugs

A recent study found that the anti-tumor effects of pemetrexed may play partly through AMPK/mTOR pathway. In this research, pemetrexed stimulation of AMPKα T172 phosphorylation was not detected in H460 cells, primarily because this residue was already hyperphosphorylated in untreated cells (Rothbart et al., 2010). However, several observations support the concept that AMPK was activated by pemetrexed: (1) the direct AMPK target ACC was hyperphosphorylated at S79, (2) eukaryotic elongation factor 2 (eEF2), the substrate for the direct AMPK target eEF2 kinase, was also hyperphosphorylated at T56 after pemetrexed treatment, and (3) S6K1, the downstream target of mTORC1, was hypophosphorylated at T389 (Rothbart et al., 2010). These findings have indicated that AMPK activation by pemetrexed inhibits mTORC1-dependent and -independent processes that control translation and lipid metabolism, identifying pemetrexed as a targeted therapeutic agent for AMPK/mTORC1 pathway that differs significantly from rapamycin analogs.

Potential Chemotherapy Drugs

Phosphatidylinositol ether lipid analogues (PIAs) were designed to target the pleckstrin homology domain of the serine/threonine kinase, Akt. Recently, Regan et

al. reported that PIAs activate AMPK in a CaMKKβ-dependent but LKB1-independent manner in LKB1-mutant NSCLC cells. Treatment of LKB1-mutant NSCLC xenografts with PIA decreased tumor volume by ~50% and activated AMPK (Memmott et al., 2008). These findings demonstrated that the anti-tumor effect of PIAs is exerted partly through AMPK pathway.

Recently, Han and colleagues reported that rosiglitazone, a synthetic ligand for PPARγ, suppressed NSCLC cell growth through PPARγ-independent signal pathways (Han and Roman, 2006). They got the following results: (1) rosiglitazone induced the phosphorylation of AMPKα protein in a dose- and time-dependent manner, (2) rosiglitazone had no effects on LKB1, (3) rosiglitazone decreased the phosphorylation of p70S6K protein in a dose- and time-dependent manner, (4) AMPK siRNA significantly abrogated rosiglitazone-reduced cell proliferation, (5) rapamycin reduced NSCLC cell growth and further enhanced cell growth inhibition in the presence of rosiglitazone(Han and Roman, 2006). This study revealed that the effect of rosiglitazone suppress NSCLC cell growth, which is exerted partly through AMPK/mTOR/p70S6K signaling pathway.

A previous research had proposed the anti-growth properties of chrysin against NSCLC cells (Wang et al., 2007). Recently, Shao and colleagues reported that the activation of AMPK may contribute to chrysin induced growth inhibition and apoptosis in cultured NSCLC cells (Shao et al., 2012). Their Western-blots results demonstrated a significant AMPK activation after chrysin treatment in A549 cells, and inhibition of AMPK diminished chrysin-induced cell growth inhibition and apoptosis (Shao et al., 2012). Chrysin also inhibited the activation of mTOR, and knocking-down of AMPK by shRNA almost reversed this effect. Further, both AICAR and A-769662 inhibited A549 cell growth and mTOR activation, while promoting cell death, and knocking-down of AMPK almost reversed these effects. These results have suggested that chrysin via activates AMPK to inhibit mTOR activation, which might be responsible for growth inhibition and/or apoptosis in NSCLC cells.

Twist1 is highly expressed in primary and metastatic NSCLC, and its expression promotes resistance to apoptosis when NSCLC cells are challenged with cisplatin (Wang et al., 2004). Jin and colleagues thus investigated the underlying mechanism initiated by silencing of Twist1 that sensitizes NSCLC cells to cisplatin (Jin et al., 2012). Silencing of Twist1 triggered ATP depletion, leading to AMPK-activated mTOR inhibition in NSCLC cells. AMPK-induced mTOR inhibition, in turn, resulted in downregulation of S6K1 activity. Downregulation of mTOR/S6K1 reduced Mcl-1 protein expression, consequently promoting sensitization to cisplatin. These findings highlight a novel mechanism of sensitization to cisplatin-induced cell death linking Twist1 to the AMPK/mTOR pathway and provide a rationale for the use of Twist1 as a promising therapeutic target.

Metabolism related proteins

Recently, Han and colleagues showed that fibronectin,

a matrix glycoprotein highly expressed in tobacco-related lung disease, stimulates NSCLC cell growth and survival (Han et al., 2006). Fibronectin inhibits the mRNA and protein expression of LKB1 as well as the phosphorylation of AMPKα. In addition, treatment with fibronectin induced the phosphorylation of p70S6K and 4E-BP1 (Han et al., 2006). They further showed that AICAR abrogated not only the effect of fibronectin on reduction of AMPK but also the fibronectin-induced phosphorylation of p70S6K, suggesting a cross-talk between the AMPK and mTOR in mediating the effect of fibronectin in stimulation of cell growth (Han et al., 2006).

Survivin is a member of the inhibitor of apoptosis protein (IAP) family that inhibits the execution of apoptosis (Tamm et al., 1998). Recent evidence has suggested that mTOR induces apoptosis by inhibiting survivin expression (Vaira et al., 2007). A recent study found that deguelin induces apoptosis in NSCLC cell lines by suppressing survivin expression. And the inhibition of survivin protein synthesis by deguelin is through the AMPK/mTOR pathway. The NSCLC cells overexpressing activated AMPK by adenoviral vector or AICAR showed marked decreases in the levels of phosphorylated (activated) p70S6K (pp70S6K), p4E-BP1, and survivin. Further, deguelin-induced decreases in the levels of p70S6K and p4E-BP1, as well as survivin protein expression, were dramatically restored in the NSCLC cells by pretreatment with the AMPK inhibitor compound C or si-AMPKα1/2 siRNA. Moreover, knockout of TSC2 completely blocked the effect of deguelin on survivin expression and phosphorylation of mTOR, p70S6K, and S6, demonstrating the importance of the TSC2/mTORC pathway in the deguelin-mediated survivin expression by activating AMPK (Jin et al., 2007).

Recently, mitochondria have emerged as effective target for anti-cancer therapy (Don and Hogg, 2004). Leucine zipper/EF hand-containing transmembrane-1 (LETM1) is a mitochondrial inner membrane protein that was first identified in Wolf-Hirschhorn syndrome, and was deleted in nearly all patients with the syndrome (Rauch et al., 2001). A recently research demonstrated that adenovirus-LETM1 suppressed NSCLC cell growth. They obtained the following results: LEMT1 overexpression (1) reduced mitochondrial ATP production and increased the expression of pAMPK, (2) significantly decreased phospho-mTOR at Ser 2448 expression level, (3) caused G1/S phase cell cycle arrest, (4) induced apoptosis both in vitro and in vivo, and (5) suppressed NSCLC growth and progression (Hwang et al., 2010). These results have strongly demonstrated that the overexpression of LETM1 alter NSCLC cell growth may act through the AMPK/mTOR signaling pathway.

The orphan nuclear receptor TR3 (NR41A and Nur77) is overexpressed in most lung cancer patients and is a negative prognostic factor for patient survival (Zhang, 2007). The prosurvival activity of TR3 was due, in part, to formation of a p300/TR3/specificity protein 1 (Sp1) complex bound to GC-rich promoter regions of survivin and other Sp-regulated genes (mechanism 1) (Lee et al., 2010). In a recent study, another TR3-dependent pro-oncogenic pathway was identified in NSCLC cells.

Inactivated TR3 by either siTR3 or DIM-C-pPhOH, an inhibitor of TR3, both inhibited NSCLC cell growth and induced apoptosis (Lee et al., 2012). In p53 wild-type A549 and H460 cells, siTR3 or DIM-C-pPhOH respectively inhibited the mTORC1 pathway, and this was due to activation of p53 and induction of the p53-responsive gene sestrin 2, which subsequently activated the mTORC1 inhibitor AMPKα (mechanism 2) (Lee et al., 2012). Thus, both siTR3 and DIM-C-pPhOH decreased or deactivated TR3, respectively, to inhibit growth and survival of NSCLC cells by inhibition of the mTORC1 pathway via p53/sestrin-dependent activation of AMPKα. This study revealed that the p53/AMPK/mTOR signaling play an important role in inhibition of growth and survival of NSCLC cells.

Conclusions

The LKB1/AMPK/mTOR signaling pathway has been extensively studied in metabolic disorders and recent evidences suggest its implication in cancer cell biology. Somatic mutations in the STK11 gene coding for the LKB1 serine/threonine kinase are detected in lung and uterine cervix cancers, emphasizing LKB1 as a strong tumor suppressor gene. Moreover, pharmacological activation of the LKB1/AMPK axis using metformin, AICAR or the A-769662 compound induces in most studies a dramatic suppression of cancer cell growth, demonstrating that the reinforcement of the tumor suppressive functions of LKB1/AMPK is a valuable therapeutic strategy for cancers.

However, AMPK agonists have different molecular targets and probably display off-target effects, and thus the interpretation of their molecular consequences turns out to be difficult. Moreover, the AMPK substrates are multiple, acting on glucose, fatty-acids and proteins metabolism and the exact AMPK-dependent pathways responsible for tumor suppression remain to be elucidated. Nevertheless, most studies have focused on the AMPK/TSC/mTOR pathway and the subsequent control of oncogenic protein translation to explain the tumor suppressive functions of AMPK activating molecules.

The impact of LKB1/AMPK modulations in NSCLC is barely studied and efforts have to be done to elucidate the potential of AMPK agonists as a new perspective for therapy in those patients, particularly in a clinical trial setting. The development of new molecules stimulating AMPK function, following an empirical or a systematic screening, is a critical step toward that goal as well.

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