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Functional characterization of AMP-activated protein kinase signaling in tumorigenesis

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Abstract

AMP-activated protein kinase (AMPK) is a ubiquitously expressed metabolic sensor among various species. Specifically, cellular AMPK is phosphorylated and activated under certain stressful conditions, such as energy deprivation, in turn to activate diversified downstream substrates to modulate the adaptive changes and maintain metabolic homeostasis. Recently, emerging evidences have implicated the potential roles of AMPK signaling in tumor initiation and progression. Nevertheless, a comprehensive description on such topic is still in scarcity, especially in combination of its biochemical features with mouse modeling results to elucidate the physiological role of AMPK signaling in tumorigenesis. Hence, we performed this thorough review by summarizing the tumorigenic role of each component along the AMPK signaling, comprising of both its upstream and downstream effectors. Moreover, their functional interplay with the AMPK heterotrimer and exclusive efficacies in carcinogenesis were chiefly explained among genetically altered mice models. Importantly, the pharmaceutical investigations of AMPK relevant medications have also been highlighted. In summary, in this review, we not only elucidate the potential functions of AMPK signaling pathway in governing tumorigenesis, but also potentiate the future targeted strategy aiming for better treatment of aberrant metabolism-associated diseases, including cancer.

Keywords

AMPK; energy deprivation; kinase; LKB1; tumorigenesis; mouse models; metformin

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1. Introduction

AMP-activated protein kinase (AMPK) is an evolutionally conserved serine/threonine protein kinase across species from yeast to mammal. Biologically, AMPK is regarded as a central switch of metabolic pathways, and directly senses cellular stresses and energy deprivation [1]. AMPK is initially identified due to its regulatory roles in lipid metabolism and cholesterol balance. Subsequently, accumulating evidences have elucidated that its energy-sensing efficacy covers, including but not limited to glucose, lipid or protein metabolism, either by transiently altering the phosphorylation status of various downstream metabolic kinases or modulating the chronic, long-term adaptation through transcriptional intervention [2].

It is well characterized that adenosine triphosphate (ATP) is the direct source of energy of cells in physiological status, which is mainly produced by oxidative phosphorylation inside the mitochondria. In order to guarantee the metabolic homeostasis, intracellular levels of ATP have to be maintained in a narrow physiological range [3]. However, following the excessive consumption of ATP in certain physiopathological stresses, the cytoplasmic AMP/ATP ratio is accordingly elevated, and acts as a sensitive indicator of nutritional abnormality. Subsequently, the increased ratio of AMP/ATP, as a result of relatively lower glucose supply, prolonged exercises, ischemia, hypoxia as well as medications, will trigger the activating phosphorylation of AMPK. This AMP-involved AMPK phosphorylation mainly depends on its upstream protein kinases including liver kinase B1 (LKB1), Calcium/calmodulin-dependent protein kinase II (CaMKKII) and TGF-beta-activated kinase 1 (TAK1) [4]. The major biological function of activated AMPK is to synergistically stimulate catabolic reactions and inhibit anabolic metabolism to supplement the deficiencies in ATP amount in variously above-mentioned conditions [5].

Structurally, all eukaryotes feature heterotrimeric components of the AMPK complex, containing a catalytic subunit α and two regulatory subunits, β and γ, respectively [6]. More importantly, the phosphorylation of Thr172 in the α subunit is required for AMPK enzymatic activation. Specifically, there are four tandem repeats identified within the subunit γ, in which include two theoretical binding sites either for AMP or for ATP. Notably, adenosine diphosphate (ADP), an intermediate of ATP and AMP, directly interacts with the γ subunit, implying a critical role for ADP under stressful circumstances [7]. Hence, according to current research findings, there are three possible mechanisms that mediate AMPK activation following the binding of AMP or ADP to γ subunit. Firstly, a conformational change occurs after the AMP binding, which makes it relatively easier for the AMPK holo-complex to become a substrate of upstream kinases. Secondly, the dephosphorylation effect on Thr172 by protein phosphatase 2Cα (PP2Cα) is antagonized after AMP is in physical association with the γ subunit. Thirdly, the allosteric activation of AMPK by the interaction of AMP with the γ subunit has been recognized as an auxiliary effect of LKB1 or CaMKKII-mediated phosphorylation events [8, 9].

Physiologically, diversified AMPK isoforms, derivative from transcriptional splice variants, including α1, α2, β1, β2, γ1, γ2 and γ3, are closely linked to different composition of the AMPK holo-complex, tissue distribution, subcellular localization, AMP/ATP sensitivity,

downstream targets and upstream kinases [1]. Specifically, recent studies have elucidated that there are merely three distinct types of subunit assembly in human skeletal muscles (namely α2β2γ1, α2β2γ3 and α1β2γ1), rather than the 12 possible compositions theoretically. In contrast to subunit α1, complex constituted by subunit α2 is primarily anchored in cellular nucleus or cytoplasm, suggesting its dual functions of activating both transcriptional factors and cytoplasmic targets in these cellular compartments, respectively. Meanwhile, different isoforms of subunit α are specifically phosphorylated by their upstream kinases in a tissue-context-dependent manner. Taken together, different tissues prefer the specific AMPK complex, properly responding to systematic or cellular reactions through its own way to offer possible diversity in AMPK signaling pathway activation in different tissue or cellular contexts [10].

As a hallmark of cancer, the Warburg effect has primarily distinguished tumor cells from normal metabolism in healthy somatic cells. To this end, malignant cell has to remodel its metabolic pattern and therefore adapts to nutrient needs during rapid divisions, characterized by higher glycolysis rate and more production of lactates as well as macromolecules. TSC2, a well-known tumor suppressor, serving as a downstream effector of AMPK complex, connects AMPK-TSC2-mTOR as a pivotal pathway in cancer metabolism, which highlights the additional regulatory significance of AMPK besides its normal efficacy in energy homeostasis [11]. Moreover, in addition to the pivotal role of sensing energy or impacting cellular metabolism, AMPK could also module multiple cancer-associated pathways to play a potential role in tumorigenesis, including depressing inflammatory reactions and cell divisions, inducing cell cycle arrest, and facilitating the occurrence of apoptosis. In keeping with this notion, LKB1, the major AMPK upstream kinase, has also been identified to function as a tumor suppressor in various malignancies. Pathologically, mutation of LKB1 triggers carcinogenesis associated with the Peutz-Jeghers syndrome, predisposing patients to lung, liver as well as cervical cancers. Thus, all these evidences implicate that AMPK may similarly play a tumor suppressive role by governing the catabolic pathways, since synthesis of essential nutrients is the obligate step for cell growth and divisions [12].

Taken together, there is currently lacking of a comprehensive summary discussing the interplay between AMPK signaling and carcinoma, especially in combination with its biochemical behaviors with the wealthy mouse modeling studies in elucidating the potentially critical role of AMPK signaling pathway in tumorigenesis. Therefore, we're performing this review in order to summarize the tumorigenic role of each component within the AMPK pathway (Figure 1).

2. Functions of AMPK signaling components in tumorigenesis

2.1. AMPK isoforms

2.1.1. The α-subunit (α1, α2-catalytic subunits)—As stated above, the catalytic α-subunit of AMPK consists of two homogenous isoforms, AMPKα1 and AMPKα2, in which AMPKα1 is also termed "hepatic isoform" since it accounts for approximately 94% of catalytic activity of α-subunit in rat liver. On the contrary, AMPKα2 is most frequently expressed in skeletal muscles, with relatively lower levels of expression in liver and heart. Despite of their difference in tissue distribution and subcellular localization, both isoforms

have similar and mutual efficacies, especially in regulation of various aspects of tumorigenesis, such as angiogenesis, cell multiplicity and chemosensitivity (Table 1) [13].

Dysregulated AMPKα1/mTORC1 signaling axis has been verified via analyzing xenograft colon cancer in rodent models, in which the catalytic capability of AMPKα1 is greatly inhibited and consequently leads to activation on mTORC1 activity, following the attenuated inhibitory phosphorylation by AMPKα1 [14]. Reactivation of AMPKα1 could significantly decrease the proliferative ability of hepatocellular carcinoma cells [15]. Additionally, miR-301a-mediated depression of AMPKα1 is partially contributing to the chemoresistance of doxorubicin in osteosarcoma cells [16]. Nevertheless, different AMPKα1 functionality in tumorigenesis has been reported, revealing a versatile role of AMPKα1 that depends on tumor types and pathological phases. Notably, forced elevation of AMPKα1 expression exhibits potent impacts in triggering protective autophagy in chronic myelomonocytic leukemia cells, therefore enhancing its anti-apoptotic ability and longevity [17]. Similarly, amplified AMPKα1 expression has been also confirmed among cervical cancer, positively correlated to tumor progression and multiplicity. These mechanistic controversies implicate that AMPKα1 may also facilitate the survival of tumor cell under stressful circumstances, although there is lacking of enough evidence on how it works and how it distinguishes with physiological metabolic regulation *in vivo* [18].

Similar to AMPKα1, the actual role of AMPKα2 on carcinogenesis remains elusive according to current literatures. *Ampkα2*-knockout easily induces the malignant transformation among embryonic fibroblasts, implicating that AMPKα2 largely acts as a potentially vital suppressor of tumorigenesis (Table 1) [19]. Meanwhile, suppression of AMPKα2 isoform is commonly observed among murine models with breast cancer, resulting in repressed apoptosis and relieved tumor expansion among neoplastic cells [20]. Unlike AMPKα1, AMPKα2 is a favorable prognostic indicator amid cervical cancer patients, mainly due to its anti-tumor properties during cervical carcinogenesis [21]. Surprisingly, evidence from *in vitro* analysis has suggested that AMPKα2 serves as a strong promoter of vascular endothelial growth factor (VEGF) in glioblastoma, subsequently to stimulate its proliferative activity via increased blood supplies [22]. However, the physiological role of AMPKα2 in tumorigenesis and its relevance to VEGF expression warrants further investigations, especially *in vivo*.

2.1.2. The β-subunit (β1, β2-regulatory subunits)—As a regulatory subunit, AMPKβ, serving as a scaffold to anchor AMPKα and AMPKγ subunits, is essential for the assembly of AMPK complex. Additionally, the subcellular localization of AMPK trimer also largely depends on the activity of the β subunit. Conditional depletion of *Ampkβ* in transgenetic mice results in significant decrease of glucose uptake and adaptive alterations during exercises, suggesting the pivotal role of β-subunit in regulation of AMPK viability [23, 24]. Similar to the α subunit, there are two isomers of β subunit, AMPKβ1 and AMPKβ2, each with specific tissue distributions. Specifically, liver is the main habitat of AMPKβ1, while AMPKβ2 is primarily expressed in skeletal muscles [25].

Currently, evidences that discuss the oncogenic role of different AMPKβ isoforms remain inadequate, especially the *in vivo* results (Table 1). Notably, AMPKβ1 expression is

dramatically depressed within lung carcinoma cells, while its forcing expression could conversely inhibit the malignant proliferation via a p53 dependent [26] or independent manner [27]. Moreover, its anti-tumor efficacy has also been confirmed in advanced ovarian cancer, in which reduced AMPKβ1 level indicates more metastatic tendency and worse clinical stages [28]. However, some controversies have emerged concerning the physiological effect of AMPKβ in tumorigenesis. According to a report from Li *et al.*, higher expression of AMPKβ1 and AMPKβ2 were detected among human ovarian carcinoma, and further linked to poorer histological type and clinical stages [29]. These outcomes warrant us for the further investigations of the different roles of AMPKβ in tumorigenesis.

2.1.3. The γ-subunit (γ1, γ2, γ3-regulatory subunits)—Based on current knowledge, γ-subunit is a necessarily regulatory component of AMPK heterotrimer, since it directly senses and binds with cytoplasmic AMP/ADP in order to stimulate the enzymatic activity of AMPK. Structural analyses have identified three unique isoforms of γ-subunit, γ1, γ2 and γ3, in which γ1 is the most ubiquitously expressed isomer over the body. However, the other two subtypes, γ2 and γ3, have specific distributions and mainly exist in heart and skeletal muscles, respectively [30].

Consistent with the physiological role of AMPK, the expression of all three isotypes of γ-subunit could be elevated during the inhibition of the respiratory chain, while knockdown of γ-subunit displays unfavorable impacts on cell metabolism in rodent skeletal muscles (Table 1) [31]. Conversely, ectopic expression of the γ subunit may enhance the storage of glycogen, thus preventing cells from ischemic damage [32]. Furthermore, the γ1 isoform acts as a key factor in regulating erythrocyte membrane elasticity, and its deactivation triggers hemolytic anemia and splenomegaly in mouse models [33]. By far, the studies regarding tumorigenic role of AMPKγ remain inadequate, although it plays an inevitable role in AMPK activity. Clinically, missense mutation of AMPKγ1 has been observed in a small fraction of colorectal cancer specimens, indicating the potentially suppressive role of AMPKγ1 in tumorigenesis [34]. Meanwhile, amplification of AMPKγ2 is associated with better histological grade among ovarian cancer patients [29]. And also the identification of mutations in *PRKAG2*, which encodes the ubiquitously expressed γ2 subunit, characterized by increased unstimulated AMPK activity and resulting in heart muscle disease, provides an opportunity to investigate the metabolic consequences of AMPK activation in both mouse and man.

Hence, further in-depth evidence is urgently desired to clarify the physiological contribution of these γ isoforms to human diseases including cancer.

2.2. AMPK upstream regulators

2.2.1. LKB1—Liver kinase B1 (LKB1), also termed as serine/threonine kinase 11 (STK11), was initially discovered in the Peutz-Jeghers Syndrome due to its loss-of-function germline mutations, which features far-ranging hamartomas located in the entire gastrointestinal tract and with higher risk of transforming into invasive malignancies than sporadic polyps [35].

This enzyme remains structurally conserved across species, playing a vital role in mediating metabolic homeostasis, cell multiplicity, polarity and autophagic initiation [36].

LKB1 is ubiquitously detected inside versatile tissues and highest expression in embryonic digestive epithelium as well as testis, which gradually fades away along the process of cell maturity. Physiologically, LKB1 is predominantly anchored within cellular nucleus, owing to the presence of the nucleus localization region (NLS) inside its N-terminal domain [35]. More importantly, pseudokinase STRADα and scaffolding protein MO25 form a heterotrimer with LKB1, thus promoting the connection of exportins with LKB1, such that the holo-enzyme complex could be ultimately translocated into cytoplasm and act as a regulatory kinase to phosphorylate a spectrum of its downstream targets, including AMPK [37]. Moreover, the mitochondrial localization of LKB1 is proven to be pivotal for its role in modulating apoptosis [35]. These findings suggest that the cytoplasmic re-localization may be a prerequisite for LKB1 mediated biological behaviors.

Given its critical role in both metabolism and tumorigenesis, elucidating the regulatory network of LKB1 will greatly help us to understand its working mechanisms in suppressing tumorigenesis *in vivo* (Table 2). By far, AMPK is the most well-characterized substrate of LKB1, which is phosphorylated at the Thr172 residue of the catalytic subunit α to achieve enzymatic activation of AMPK [10]. LKB1 is the exclusive upstream activating kinase of AMPK following the energy deprivation in majority tissues, directly mediating AMPK-involved effects such as catabolic reactions and protective autophagy [38]. In support of this notion, genetic knockout of *Lkb1* in murine models almost completely silences the phosphorylation on Thr172 as well as AMPK downstream efficacies among embryonic fibroblasts, despite in the setting of AMPK agonists or other functional stimulators [39].

In addition to the classical LKB1/AMPK transduction, a total of 12 AMPK-related kinases are confirmative substrates of LKB1, including NUAKs, SIKs, BRSKs, MARKs, SNRK and MELK. Similarly, the phosphorylated T-loop by LKB1 is necessary to activate their kinase activities, whereas deficiency in LKB1-mediated phosphorylation event significantly restricts their physiological capabilities. Specifically, the LKB1/MARKs pathway has been characterized to regulate the intracellular microtubule dynamics, in addition to the myosin adjustment by LKB1/NUAKs and neuronal polarization by LKB1/BRSKs, all of which are physiologically reported to be responsible for regulating cell polarity, a critical process that runs a mock when cells undergo cellular transformation [35].

Meanwhile, LKB1 is capable of triggering transcriptional reprogramming via phosphorylation on remaining AMPK related substrates, in order to regulate cell adhesion, longevity and expansion [40]. On the other hand, the molecular basis that leads to LKB1 enzymatic activation remains to be rarely discussed. To this end, as mentioned above, the assembly of STRADα-MO25-LKB1 complex strongly stimulates the allosteric activation of LKB1. It is currently acknowledged that this effect is the core mechanism for activating LKB1, instead of other patterns of post-translational modifications such as phosphorylation [37]. Mechanistically, a recent study has reported that Skp2 directly polyubiquitinates LKB1, which facilitates the binding of LKB1 and MO25 and subsequently leads to the promotion of LKB1 kinase activity. As a result, *Skp2*-null mice display a significantly

lowered ability to maintain the completeness of LKB1 complex in response to cellular stresses. The interaction of Skp2/LKB1 is crucial for holo-enzyme complex assembly and LKB1 activation, no matter under physiological or stressful situations [41]. In addition to Skp2-meidated regulation of LKB1 mechanism, there are also several identified upstream kinases of LKB1, including PKA, ATM and PKC that target either Thr366 or Ser325 residue of LKB1 for phosphorylation in murine models. These activating phosphorylations successfully activate the LKB1-AMPK-mTOR pathway or other similar signaling to trigger appropriate reactions [35]. However, the intrinsic mechanism of these kinases especially their physiological roles in affecting the complex formation of STRADα-MO25-LKB1 remains undefined, thus further clarifications should be anticipated to better understand their physiological contribution and underlying molecular mechanisms in activating LKB1 in response to various experimental challenges.

During the past decades, LKB1 has been well-described as a tumor suppressor, since its loss-of-function mutation is commonly detected and believed to directly induce the oncogenesis in a wide range of malignancies [42]. Knockout mice models have been extensively applied to study the molecular basis of LKB1 associated carcinogenesis. Specifically, germline biallelic depletion of *Lkb1* induces embryonic lethality among engineering mice, while those characterized by heterozygous $Lkb1^{+/-}$ display multiple intestinal hamartomas, pathologically mimicking the alterations in the Peutz-Jeghers Syndrome (PJS) patients [43]. Following the selective knockout of both *Lkb1* alleles in lung tissue, development of adenocarcinoma, squamous and large cell carcinoma have been early aroused, especially the KRAS-driven lung malignancies [44]. Moreover, conditional depression of *Lkb1* in specific tissues has also led to occurrence of various cancers, including bone, prostate, pancreatic, breast as well as dermatological carcinomas [45]. Thus, these preclinical outcomes derived from genetically engineered mice have well verified and simulated the pathogenesis of human neoplasms, revealing an important role of LKB1 in clinical prognosis and potential treatment.

Clinically, analyses from human specimens have demonstrated that *LKB1* depletion is closely correlated to more malignant behavior in various cancers [46]. Mechanistically, the *LKB1* inactivation induced tumorigenesis is mainly attributed to metabolic reprogramming towards a more anabolic phenotype following the failure of the LKB1-AMPK pathway [47], Moreover, *LKB1* silencing contributes to the redox imbalance and resultant chemoresistance in non-small cell lung carcinoma [48]. The CCL2-mediated macrophage recruitment is enhanced in part due to the loss-of-function mutation on *LKB1*, which partially explains the development of endometrial cancer [49]. Besides, LKB1 could likewise affect epithelial mesenchymal transition [50], Hippo/YAP signaling [51], proinflammatory transduction [52] as well as TGF-β pathway [53] to function as a tumor suppressor in multiple neoplasms.

On the contrary, several studies have reached controversial results that LKB1 may also play a pro-oncogenic role during diversified tumorigenesis, especially under particular environments such as energy deficiency [35]. Specifically maintenance of LKB1 is essential for the viability of ovarian cancer spheroids *in vitro* [54]. Furthermore, some researches on lung malignancy reveal that hyper-expression of LKB1 helps stressful cells to survive glucose-starvation induced apoptosis, meanwhile frustrating the cytotoxic impact by

erlotinib [55]. These exceptional outcomes implicate that the functional range of LKB1 in tumorigenesis may be far beyond current cognition and depend on different cell types or developmental phases. Hence, more in-depth investigations are warranted to fully understand the physiological role of LKB1 in tumorigenesis.

2.2.2. CaMKK2—As a vital secondary messenger, Ca^{2+} and its signaling pathway have been verified to participate in various aspects of tumorigenesis, such as proliferation and malignant dissemination. Calmodulin could directly bind to calcium ions as their intracellular recipient, following the Ca^{2+} influx triggered by alterations on membrane potential. Consequently, the Ca^{2+}-calmodulin complex will stimulate the family of calcium/calmodulin-dependent protein kinase kinases, which consists of calcium/calmodulin-dependent protein kinase kinase 1 (CaMKK1) and kinase 2 (CaMKK2). It has been currently clarified that calcium/calmodulin-dependent protein kinase I (CaMKI) and kinase IV (CaMKIV) are major downstream targets of CaMKK2. More importantly, CaMKK2 also activates its downstream molecule AMPK under certain physiological circumstances, in order to maintain the metabolic balances [56].

Recently, Nelson *et al* has identified CaMKK2 as an androgen-responsive gene, and its elevation by androgens leads to largely expressed in prostate cancer cells, favoring the migration and distant metastasis of prostate cancer [57][58]. Specifically, AMPK is believed to be a major downstream target of CaMKK2-mediated the carcinogenic role of androgens. In keeping with this notion, inhibiting CaMKK2 could dramatically reduce the metastatic property of prostate cancer [59]. Furthermore, Massie *et al* and Shima *et al* consistently confirmed that the presence of CaMKK2 is positively correlated to advanced stages and negatively linked to survival prognosis among patients of prostate cancer [60, 61]. Moreover, results derived from xenograft mouse models revealed that CaMKK2 aberrantly reemerged in the androgen-responsive or castration-resistant prostate cancer (CRPC) tissues and involved in the androgen-stimulated pathogenesis as a hub protein [61]. They further demonstrated that CaMKK2 displayed a higher expression level in castration-resistant xenograft models, and depletion of *CaMKK2* could highly restrict the expression of downstream targets of androgen signaling. Nevertheless, in contrast to this finding, another group independently demonstrated that CaMKK2 significantly limited the transcriptional activity of AR in advanced CRPC as well as its proliferation, offering a controversial evidence of the potential role of CaMKK2 in CRPC development [61]. Thus, more investigations are still needed to clarify the physiological role of CaMKK2 in CRPC development (Table 2).

Similar to the prostate cancer setting, higher expression of CaMKK2 is observed in gastric cancer samples, leading to strengthen the gastric cancer cell proliferation and invasion by phosphorylating AMPK [62]. Therefore, by an overall consideration of prostate and gastric cancer, the CaMKK2-AMPK signaling axis may serve as an oncogenic pathway rather than the classically tumor-suppressive role of AMPK in most malignancies.

2.2.3. TAK1—Transforming growth factor-β activated kinase 1 (TAK1) is a member of MAP kinase kinase kinase (MAPKKK) family, regarded as a core effector in regulation of various cell behaviors including angiogenesis, inflammation, metabolism and carcinogenesis

[63]. TAK1 has been demonstrated as an upstream kinase of AMPK by directly phosphorylating its Thr172 residue. Furthermore, AMPK is also observed to reciprocally activate TAK1, compromising a feedback loop in mediating inflammatory signals [64]. Importantly, activation of the TAK1/AMPK signaling axis plays vital roles in preventing malignant expansion and inducing protective autophagy, irrespective of pancreatic cancer [65] or hepatocellular carcinoma [63]. As such, genetic depletion of *Tak1* in mouse models significantly promotes hepatic oncogenesis [66], while an elevation of apoptosis level is observed on KRAS-dependent colon cancer models, following the inhibited expression of TAK1 [67]. This paradox hints that the physiological function and downstream targets of TAK1 may vary among diverse malignancies, which warrant further in-depth investigation.

2.2.4. PKA—Protein kinase A (PKA) is a conserved hetero-tetramer kinase complex in mammalian cells, individually constituted by two catalytic subunits as well as two regulatory subunits. Structurally, there are totally four distinct isotypes of PKA with specific tissue distributions [68]. The intact heterotetrameric form arrests the biological function of PKA under physiological conditions. Once the intracellular cAMP level is elevated, this secondary messenger could directly bind the regulatory subunits of PKA to release its catalytic subunits, leading to phosphorylate their downstream targets for responding to cellular stresses [69]. Notably, the PKA catalytic subunit can interact with and directly phosphorylate AMPKα at the Ser173 residue, thus blocking its activating phosphorylation at Thr172 by other upstream kinases, such as LKB1. This PKA/AMPK regulatory pathway has been found to be involved in multiple cellular actions, especially in metabolic maintenance [70].

Given that AMPK is a well-known anti-oncogenic effector, the potentially tumorigenic role of PKA is therefore investigated. Experiments on murine models suggest that elevated PKA functionality significantly induces the malignant alteration of normal mammary epithelial cells, mechanistically through activating the Src pathway [71]. Meantime, the miR-33a/PDE8A/PKA signaling plays stimulatory role on glioma progression, in which the viability of PKA is regained following the inhibition on PDE8A activity by miR-33a [72]. Similar result is also observed in liver cancer cells, where PKA directly phosphorylates AMPK to reverse the cell cycle arrest [73]. Clinically, both regulatory subunits of PKA are overexpressed in thyroid carcinoma, correlating with stronger motility and proliferative ability [74].

On the other hand, novel studies have also demonstrated a possible tumor suppressive role of PKA among certain types of cancers. Surprisingly, PKA could activate AMPK to trigger cell cycle arrest and cellular apoptosis in myeloma, possibly through the phosphorylation on LKB1-Ser428 residue, which subsequently stimulates the AMPK activity [75]. Moreover, based on genetically modified mouse models, *Pka* knockout significantly accelerates the skin tumorigenesis via upregulation of transcriptional factors GLI1 and YAP1 [76]. Consistently, PKA activation is also effective to inverse the process of epithelial mesenchymal transition (EMT), thereby impeding the cancer initiation by targeting the histone demethylase PHF2 [77]. Taken together, these controversies reveal that the actual role of PKA in carcinogenesis remains obscure, even if in the same kind of human tissue

such as mammary epithelium, where AMPK-independent pathway may partially involve in this process.

2.2.5. GSK3—As a pivotal enzyme in glucose metabolism, glycogen synthase kinase 3 (GSK3) is ubiquitously expressed in mammals and widely involved in numerous regulatory pathways by targeting over one hundred substrates [78]. Identified as an upstream kinase of AMPK, GSK3 binds with AMPKβ prior phosphorylating the AMPKα, which facilitates AMPKα binding to phosphatases and therefore inactivates AMPK [79]. Currently, the biological impacts of GSK3 have been extensively unveiled on metabolic dysregulation, neurodegenerative disorders as well as neoplastic onset [80]. The oncogenic properties of GSK3 have been confirmed among prostate and colon cancer models, acting as a downstream target of androgen-dependent [81], and the Wnt pathway, respectively [82]. On the contrary, engineered mice with *Gsk3* depletion feature more aggressive phenotype of breast and skin cancer, which is attributed to stabilization of β-catenin and enhanced expression of c-Myc and survivin [80]. Hence, the physiological role and detailed molecular mechanisms of GSK3 in tumorigenesis await further investigation.

2.2.6. PP2A and PP2C—Phosphorylation is one of the most common forms of reversible protein post-translational modification, with up to 30% of all proteins being phosphorylated at any given time. To convert this process, the protein phosphatase is identified as an enzyme to remove the phosphate group from the phosphorylated amino acid residue of its substrate protein. Since around half of the intracellular serine/threonine kinase is controlled by Protein Phosphatase 2A (PP2A), which therefore modulates the major pathways of cell proliferation, metabolic homeostasis and cell survival [83]. Acting as a major antagonist of tumorigenic kinases, such as Akt, SRC and MEK, PP2A has been identified as a tumor suppressor in various malignancies, through decreasing cell proliferation, invasiveness and inducing apoptosis as well as senescence. Therefore, the inactivation of PP2A is commonly observed during neoplastic formation, and several explanatory mechanisms of which have been established in carcinogenesis, mainly including the elevated expression of PP2A inhibitors and genetic alterations on PP2A subunits [84].

Recently, the phosphorylation of AMPK has been observed largely inhibited by a ceramide-dependent activation of PP2A in the mice fed with high-fat diet [85]. Additionally, Park *et al* described a Ca^{2+}-involved interplay between PP2A and AMPK, where the inflow calcium ions directly connected with the binding sites of PP2A and promoted its physiological activity, resulting in the depression of AMPK phosphorylation [86].

Moreover, the physiological role of PP2C has been disclosed to maintain homeostasis in the case of cellular stresses, through repressing the stress-responding signals especially the relevant kinases such as ASK1, TAK1, MKK3, JNK and ATM [87]. Meanwhile, the interplay between PP2C and AMPK has also been gradually disclosed. Moreover, PPM1A and PPM1B, the members of PP2C which serving as metal-dependent (Mg^{2+} or Mn^{2+}) monomeric enzymes, were observed to involve TNF-α-mediated AMPK inactivation by dephosphorylating the AMPK Thr172 residue to trigger insulin resistance in skeletal muscle cells [88]. Likewise, PPM1D (WIP1) [89] and PPM1E [90] have been confirmed as upstream regulators of AMPKα, contributing to the participation of PP2C/AMPK pathway

in various pathological procedures, including degenerative disorders and malignant formations. Nevertheless, further evidences are still needed to clarify whether the remaining isoenzymes of PP2A or PP2C family could directly interact with and dephosphorylate AMPK.

2.2.7. USP10—The ubiquitin specific proteases (USPs) are essential members of human deubiquitinases (DUBs), mainly functioning to facilitate the cellular deubiquitination process and therefore participate in various biological behaviors such as tumorigenesis and adaptive reprogramming [91]. USP10, also termed as UBPO, has been identified as a subtype of the USP sub-family of DUBs, of which the catalytic region recognizes the targeted ubiquitin and both terminal domains assist its subcellular localization [92].

p53 is the classical downstream target of USP10, whose activation under stressful circumstances leads to deubiquitination on p53, therefore inducing its stability and nuclear localization [93]. Meanwhile, experimental results have further concluded that AMPK is a novel substrate of USP10 in murine models. Mechanistically, following the energy deprivation, USP10 largely deubiquitinates AMPKα so that its activating phosphorylation by LKB1 could be greatly enhanced. Reversely, AMPK could also phosphorylate USP10 Ser76 residue, both of which construct a feedforward loop and thus help the exhaustive cells to survive extreme environments [94].

Biologically, silenced *USP10* in lung cancer cells contributes to the elongated cell survival and depressed apoptosis, partially through deubiquitinating the mismatch repair protein MSH2 [95], or negatively modulating EIF4G1-mediated functions [96]. USP10 is also a proliferative inhibitor in pancreatic cancer, and negatively influenced by miR-191 [97]. Furthermore, USP10-mediated stabilization of SIRT6 attenuates the oncogenic effect of c-Myc activation and ultimately induces the neoplastic suppression investigated in a xenograft colon cancer model [98].

Clinically, relatively lower expression of USP10 is observed in gastric cancer specimens relative to the adjacent controls, and indicated the poor outcomes of the patients [92]. The USP10 responsible deubiquitination is able to stimulate the anti-oncogenic activity of p53 both in renal clear cell carcinoma [93] and colorectal cancer [99], highlighting the potential significance of USP10/p53 targeted cancer treatment. Although the majority of current viewpoints agree the tumor-inhibitory role of USP10, its possibly versatile functions require future in-depth studies.

2.2.8. LncRNA NBR2—Long non-coding RNA (LncRNA) is a subfamily of mammalian RNA featuring more than 200 constituted nucleotides. Since it is incapable of encoding functional proteins, this type of genomic product has long been recognized as transcriptional rubbish without actual cell merits [100]. Nevertheless, novel investigations have uncovered its core regulatory role on diverse processes, including cell multiplicity and neoplastic initiation [101].

Neighbor of BRCA1 gene 2 (NBR2) genetically locates alongside the well-known gene BRCA1, a frequently silenced tumoral suppressor in breast cancer and ovarian cancer [102].

It is experimentally verified that NBR2 tends to generate long non-coding RNA instead of parallel protein for exerting its biological impacts. Both in vivo and in vitro evidences have recently discovered a feed-forward loop of AMPK-LncRNA NBR2 axis under situations of chronic energy deprivation. After the initiation of AMPK activation by LKB1, the induced LncRNA NBR2 could directly bind to AMPKα and further stimulate the activation of AMPK as its novel upstream effector [103]. Mechanistically, the intensive rather than initiative functionality by LncRNA NBR2 seems to be a time-efficient manner for AMPK amplification especially under long-lasting starvation, the depletion of which significantly disrupts the signaling cascades of AMPK and ultimately leads to dysregulated cell cycle and apoptotic response. On the other hand, AMPK is probably not the only downstream target of LncRNA NBR2, since overexpressed LncRNA NBR2 remains effective in repressing cell proliferation despite of AMPK knockout [104].

Similar to its neighboring gene BRCA1, NBR2 is also believed to mainly serve tumor-inhibitory effect in several kinds of malignancies. Irrespective of in vivo (xenograft models) or in vitro (cell lines and clinical samples) experiments on renal and breast cancer, LncRNA NBR2 is greatly inhibited in contrast to adjacent controls, with involvement of AMPK and mTOR. Survival analysis of breast cancer has additionally revealed that the lower level LncRNA NBR2 has, the poorer prognosis patients will gain [104]. These results implicate that LncRNA NBR2 may be a novel therapeutic target although more in-depth investigations are still urgently needed, especially knockout evidences and mechanistical clarifications.

2.3. AMPK downstream substrates in tumorigenesis

2.3.1. AMPK downstream substrates in long-term transcriptional reprogramming

2.3.1.1. PGC1α: PPAR gamma co-activator 1α (PGC1α), as a transcriptional co-activator, regulates the faculty of genes involved in energy metabolism, and masters the regulation of mitochondrial biogenesis. Once activated, the ubiquitous expression of PGC1α interacts with certain transcriptional factors that correlate to metabolic regulation and cancer progression [105]. In detail, the N-terminal domain of PGC1α receives upstream activation signals and facilitates the formation of a transcriptional complex containing transcriptional factors and chromatin structure remodeling proteins such as p300 [106, 107]. Meantime, the C-terminal region of PGC1α helps to connect with vitamin D receptor (VDR), both of which accelerate the transcriptional initiation through an allosteric effect [108].

AMPK is a well-known upstream activator of PGC1α by phosphorylating its N-terminal residues. Cellular stresses that cause energy deprivation could easily induce the AMPK-PGC1α pathway activation to maintain internal homeostasis under physiological conditions, including exercises, fasting or hypothermy [109]. Mechanistically, PGC1α-involved adaptation is mainly achieved by a long-term transcriptional adjustment [105]. For instance, PGC1α responds to persistent endurance training by stimulating muscle-specific myocyte enhancer factor 2 (MEF2), which increases the oxidative capability of muscle fibers under stressful circumstances [110]. Meanwhile, the efficiency of oxidative phosphorylation is greatly improved inside mitochondria, owing to the activation of PGC1α as well as its subsequent co-activation of nuclear respiratory factor 1 (NRF1) [111].

Recently, the pathological linkage between PGC1α and neoplastic formation has drawn more attention due to the critical roles of PGC1α to make adaptive alterations on respiratory chain inside the cancer cell mitochondria [105]. Somatic depletion of *Pgc1α* significantly reduces the occurrence of colorectal and hepatic carcinoma among chemically induced mice (Table 3) [112]. Furthermore, aberrant positivity of PGC1α is detected in various cancer types with particular signal pathways. Specifically, Shiota *et al* stated that PGC1α could activate androgen receptor pathway to promote prostate cancer progression [113]. Moreover, PGC1α acts as a key downstream component of oncogene MITF, whose activation could largely boost the clearance of ROS inside melanoma cells and gear up the cancer metabolism and growth [114]. Taguchi *et al* reported that mutated p53 directly upregulated PGC1α level in a fraction of lung adenocarcinoma, resulting in tumor expansion and local progression [115]. Consequently, the above-mentioned evidences highlight the clinical potential of PGC1α as a therapeutic target among cancer sufferers.

2.3.1.2. FOXO3: With more than a hundred of members and evolutionarily conserved function, the forkhead-box family (FOX) plays key role in controlling cell fate, malignant transformation and internal metabolism [116]. FOXO3 is one of the four members (FOXO1, FOXO3, FOXO4 and FOXO6) of FOXO subfamily in mammals, which is ubiquitously expressed and serves as a transcriptional factor interacting with motif FHRE within target gene promoters [117]. Upstream signals ultimately lead to post-transcriptional modifications on FOXO3, including phosphorylation, acetylation and ubiquitination, in which six C-terminal residues of FOXO3 have been identified as phosphorylation sites by AMPK, including Thr179, Ser399, Ser413, Ser439, Ser555 and Ser588 [118]. Further studies have suggested that the AMPK-FOXO3 signaling exerts endurable and protective impact against skeletal atrophy [119] and keratinocytic senescence [120], mainly based on its transcriptional reprogramming. Additionally, its anti-tumor functionality has also been verified in breast and liver cancer *in vitro*, demonstrating a remarkable growth-inhibitory effect [121].

Besides its well-investigated role in aging-related and degenerative disorders, the physiological significance of FOXO3 in carcinogenesis has gradually surfaced. Germline knockout of both alleles (*Foxo3*$^{-/-}$) triggers a late onset of tumor phenotype among mouse models. And conditional depletion on somatic cells directly results in the formation of hemangiomas and lymphoblastic lymphomas, implying the probably inhibitory activity of FOXO3 in human cancers [122]. Mechanistically, recent studies have disclosed that FOXO3 inactivation is mainly attributed to network regulation by diversified oncogenic pathways. Specifically, FOXO3 is a downstream target and negatively regulated by the PI3K-Akt pathway, which leads to cell cycle arrest and apoptosis among thyroid, cervival and breast cancer. In addition, the Ras-MEK-ERK, IKK pathway and several micro-RNAs such as miR-183, miR-96 and miR-182 are also capable of promoting the degradation or restricting the expression level of FOXO3 in various cancers respectively [123].

So far, although the majority of reports have regarded FOXO3 as a tumor suppressor, its pro-tumoral action may also exist. Analyses from *in vivo* experiments implicate that a simultaneous activation of both FOXO3 and β-catenin effectively elongates the cell survival and expedites the distant dissemination among colorectal cancer xenografts in murine

models. Subsequent evidences from colon cancer shows a strong positive correlation between FOXO3 nuclear positivity with metastatic tendency and life expectancy among cancer patients [124]. Similarly, an oncogenic role of FOXO3 is also identified in breast cancer cells, straightly through upregulating the expression of metastatic promoters MMP-9 and MMP-13 *in vitro* and *in vivo* [125]. Hence, despite of the versatile functions that FOXO3 has involved in during cancer progression, more physiological evidences are still needed to clarify and consider its opposite role in tumorigenesis, especially for angiogenesis, metastasis, stemness maintenance and differentiation.

2.3.1.3. SREBP-1c: Sterol regulatory element binding protein (SREBP) is a transcriptional factor family involved in regulation of lipogenesis, in which SREBP-1c transcriptionally activates its downstream responsive genes in nucleus, promoting lipogenic activity in mammalian liver [126]. Specifically, the mature form of SREBP-1c moves towards nuclear genome and increases the expression of lipo-synthetic enzymes such as FASN and ACC. It has been discovered that AMPK serves as an upstream kinase of SREBP-1c by phosphorylating its Ser372 residue, leading to a significant reduction in SREBP-1c nuclear translocation and transcriptional activity, thereby resulting in attenuated lipo-synthetic ability among hepatic cells [127]. Hence, this behavior provides theoretical basis for AMPK agonists, including metformin and flavonoids, to be employed to cure fatty liver disorders.

Elevated lipogenesis is a metabolic hallmark of cancer cells, such that the oncogenic role of SREBP-1c has drawn much attention due to its predominant function in controlling lipid synthesis. Notably, the relevance of high-fat diet and tumorigenesis among breast, pancreas, prostate gland and endometrium has been clearly disclosed, which highlights the potential role of SREBP-1c on initiation of such malignancies. In terms of breast cancer development, the SREBP-1c-FASN axis is abnormally activated by oncoprotein HBXIP based on evidence from xenograft mice models [128]. *In vivo* and clinical experiments have respectively proven that SREBP-1c is a potent promoter of pancreatic cancer and its redundancy indicates worse prognosis (Table 3) [129]. Likewise, overexpression of SREBP-1c is ubiquitously detected in prostate cancer samples, and miR-185 and 342-mediated inhibition of SREBP-1c could greatly restrict the invasiveness and trigger apoptosis in prostate cancer cells [130]. Moreover, SREBP-1c-FASN has been recognized as a pivotal signaling that promotes the aggressive properties of endometrial carcinoma [131].

Sirtuin 1 (SIRT1), the most conserved NAD+-dependent protein deacetylase, has emerged as a key metabolic sensor, which activates SREBP-1c to facilitate its oncogenic properties during the malignant alteration of endometrium [132]. To this end, SREBP-1c does play a critical role in accelerating the metastasis of hepatocellular carcinoma due to its primary function to stimulate lipogenesis in liver [133]. Moreover, the correlations between SREBP-1c and neural oncogenesis have also been extensively investigated, in which aberrantly increased expression of SREBP-1c is found inside glioblastoma tissues, which positively relates to tumor growth and local spread by stimulating its downstream targets of ACC and FASN [134]. Additionally, upregulation of SOAT1 [135] and N-glycosylation of SCAP jointly contribute to SREBP-1c activation [136], while miR-132 suppressively targets SREBP-1c and diminishes its oncogenic properties in glioma cells [137]. In summary, based

on current literatures, SREBP-1c targeted therapy has a bright future among cancer patients, especially for those with lipid-induced malignancies.

2.3.1.4. H2B: H2B is one of the core histones in eukaryotic cells that compositely construct chromatin along with condensed nuclear DNA [138]. Consisting of methylation, acetylation, phosphorylation and ubiquitination of specific residues, post-translational modifications on histones have been considered as a vital form among all epigenetic activities, which is essential for gene transcription, adaptive remodeling of chromatin and DNA replication. Specifically, the monoubiquitinated modification of H2B is not only serving as an activator of gene expression, but also involves in multiple DNA-processing procedures such as DNA repair [139]. More interestingly, AMPK could directly phosphorylate H2B in the Ser36 residue, to facilitate the transcriptional role of H2B on chromatin. Once the Ser36 residue has been replaced by alanine, the transcriptional action linked to AMPK activation could be largely inhibited, revealing a central role of H2B phosphorylation on AMPK-dependent transcriptional reprogramming for cellular stresses [140].

H2B does involve in multiple neoplastic procedures following various post-transcriptional modifications, among which monoubiquitination is of the most importance and has received the maximum attentions on its tumorous activity [141]. According to the classical facts, the ubiqutination cascade of CDK9-WAC-RNF20/40 signaling plays a unique role in monoubiquitinating H2B on the Lys120 residue. On the contrary, the deubiqutinase USP22 antagonizes the ubiquitin ligase complex RNF20/40 on H2B monoubiquitination. Mechanistically, the enhanced transcriptional elongation by H2Bub1 effectively reduces the possibility of DNA misparing and malignant mutation, which has been therefore classified as a nuclear indicator of tumor suppression among diversified malignancies. Collectively, downregulation of the H2B monoubiquitination level by altering any component of the CDK9-WAC-RNF20/40 signaling could lead to an increased tendency of cancerous transformation *in vitro* or in mouse models.

On the other hand, phosphorylation on H2B has been certified as an alternative mechanism mediating tumor initiation. Phosphorylated Ser32 residue on H2B by ribosomal S6 kinase 2 (RSK2) facilitates transformation from the normal skin epidermal cells towards squamous carcinoma in a genetic knockout model [142]. Nevertheless, a relative dephosphorylation status of the H2B Ser23 residue occurs in prostate cancer cells compared to normal controls, which reveals that the actual role of H2B phosphorylation on tumorigenesis depends on phosphorylation sites and developmental stages of malignancies [143]. Thus, as a promising therapeutic target, the exact mechanisms of H2B modifications on tumor progression should be supplementarily explained by additional updates and literatures.

2.3.2. AMPK downstream substrates in acute adaptations of metabolism

2.3.2.1. ACC: As a pivotal enzyme mediating fatty acid oxidation, acetyl-CoA carboxylase (ACC), triggering the transformation of cellular acetyl-CoA into malonyl-CoA, is an endogenous inhibitor of carnitine palmitoyltransferase-1 (CPT1) in mammals. Biologically, CPT1 acts as a direct promoter of mitochondrial β-oxidation of cytoplasmic fatty acids, therefore, activation of ACC effectively decreases the rate of fatty acid oxidation.

Physiologically, ACC interchanges between its active and inactive form dependent on its dephosphorylation and phosphorylation status respectively. Two isoenzymes of ACC have been identified as ACC1 and ACC2, with a tissue-context expression manner, in which ACC2 has been elucidated as the major regulator of fatty acid oxidation in both cardiac and skeletal muscles, while similar function of ACC1 has been emphasized largely in renal tissue. Meanwhile, both isoenzymes during fatty acid oxidation share the functions in liver [144].

Mechanistically, AMPK could phosphorylate ACC1 on the Ser79 residue, resulting in the inhibition of enzymatic activity of ACC1 and subsequent to accelerate fatty acid oxidation in the setting of energy deprivation. Hence, ACC1, the downstream target of AMPK, primarily responds to metabolic stresses through adaptive adjustments instead of transcriptional alterations [145]. Similar to ACC1, AMPK is the major upstream kinase of ACC2 by phosphorylating its Ser212 residue to inhibit its physiological ability [146]. Moreover, PKA, as an alternative enzyme, could slightly deactivate ACC2 within cardiac muscles [147]. Collectively, all these evidence indicate that ACC2 is an acute adaptive responder under stressful conditions, with its vital role to regulate lipid synthesis inside the mitochondria.

Recently, accumulating investigations have also paid close attention to the actual role of ACC1 on carcinogenesis (Table 3), since elevated lipogenic activity is commonly occured in neoplastic cells. To this end, overexpression of phosphorylated ACC1 has been detected among diverse malignancies, including prostate cancer and breast cancer [148]. Furthermore, ACC1 is responsible for malignant transformation of skin epithelial cells, whose depletion greatly suppresses tumor burden and progression [149]. Moreover, the TNF-α-AMPK-ACC1 axis is aberrantly activated among pancreatic cancer models, implying the ACC1 involvement in inflammation-induced tumorigenesis [150]. On the contrary, inhibition of ACC1 by TOFA induces cell apoptosis amid colon cancer and lung cancer cells, which reflects its role on maintaining cell longevity [151]. Clinically, higher expression of ACC1 predicts poorer outcome of patients with certain types of tumors, such as head and neck, gastric cancer and colorectal cancer [152]. Thus, more evidences are still needed to clarify the in-depth mechanisms of ACC1 signaling in tumorigenesis in order to promote its clinical utilization.

2.3.2.2. HMGCR: HMG-CoA reductase (HMGCR), serving as the central enzyme to accelerate the *de novo* synthesis of cholesterol in liver, is governing the rate-limiting step of the transformation from HMG-CoA to mevalonate. It has been already clarified that AMPK is the major inhibitor of HMGCR in rat models by phosphorylating its Ser871 residue as protein kinase C (PKC) and calmodulin-activated protein kinase (CAMK) do [153][154]. Thus, activation of the AMPK-HMGCR axis is a direct respondence to cellular stresses via an acute adaptive pattern, restricting the cholesterol metabolism and promoting catabolic activity in liver (Table 3).

HMGCR has been widely regarded as a candidate that potentially participates in cancer metabolism due to its core role on stimulating the production of cholesterol. Specifically, Statins, well-known inhibitors of HMGCR, have been clinically correlated to prolonged survival expectancy among cancer sufferers, such as endometrial cancer [155] and

esophageal adenocarcinoma [156]. Moreover, lower risk of tumor initiation or dissemination have been observed in a variety of cancer types following the administration of Statins, revealing a great possibility to expand its therapeutic indications towards tumorous field. Unexpectedly, the majority of tumors bearing over-expression of HMG-CoA reductase demonstrate modest phenotype and favorable prognosis, especially in breast [157] and colorectal malignancies [158]. However, there is in scarcity of statements that compare the expression disparity between active and inactive form of HMGCR. This indicates that the elevation of inactive form might contaminate the tumor-promoting role of HMGCR activation, since the excessively biological assembly of lipid and cholesterol is one of the major metabolic hallmarks of cancer cells. Therefore, those puzzles are waiting for more solid experimental evidence for further mechanistic interpretations.

2.3.2.3. Glycogen synthase: Glycogen synthase (GS) is a key promoter of glycogen biosynthesis in liver and skeletal muscles. Actually, there is a complex network governing the activity of glycogen synthase, including allosteric stimulation, inhibitory phosphorylation and negative feedback regulation. Glycogen synthase becomes activated under circumstances of glycogen deprivation, which typically occurs during endurance trainings via an insulin/GSK-3-independent manner [159].

Multiple kinases are capable of phosphorylating glycogen synthase, in which GSK-3-mediated continuous phosphorylation of glycogen synthase slightly restricts its activity under physiological baseline conditions. More interestingly, AMPK also directly phosphorylates glycogen synthase at the Ser7 residue to antagonize the producing of glycogen both *in vivo* and *in vitro* [159, 160]. As a result, aberrant regulation of the AMPK-GS axis modulates glycogen accumulation in cardiac and skeletal muscles as well as liver cells [161]. Conversely, despite of unclear upstream mechanisms, the aberrant glycogenesis in leukemic cells is concomitant with AMPK suppression and GS activation [162].

Abnormal glycogen storage is characterized as a feature of most malignancies, for example, ovarian clear cell carcinoma. In keeping with this notion, cellular glycogen accumulation is observed with highly expressed active glycogen synthase induced by hypoxia-HIF1α signals [163]. Notably, silencing of glycogen synthase leads to reduced glycogen production as well as invasiveness in xenograft glioma mice model, partially due to the abnormal PTEN-PI3K pathway [164]. Furthermore, over-activity of glycogen synthase is a strong catalyst of uncontrollable growth in prostate cancer [165] and renal clear cell carcinoma [166]. More importantly, the activation of glycogen synthase is an essential step for the initiation and development of hepatoma evidenced *in vitro*, *in vivo* or in clinical due to the fact that liver is the most important glycogenesis organ (Table 3) [167, 168]. However, its possibly oncogenic role in hepatocellular carcinoma has not yet been proven, anticipating for further investigation.

2.3.3. AMPK downstream substrates in cell cycle regulation and proliferation

2.3.3.1. Raptor: Raptor is a specific subunit of the mammalian target of rapamycin complex 1 (mTORC1), and functions to scaffold mTORC1 with its downstream substrates, including $p70^{S6K1}$ and 4EBP1. The mTORC1 kinase complex is a well-conserved regulator of growth

pathway following the upstream signals of metabolic alterations, specifically sensing the nutrient administration [169]. Nevertheless, Raptor could solely decrease the liver steatosis in rodent models by interacting with PHLPP2 in an mTORC1-independent manner [170]. This implicates that the actual scope of Raptor activity may be far beyond current knowledge.

At present, there are multiple recognized upstream kinases mediating the phosphorylation of Raptor to generate contrary efficacy. For example, GSK-3 could activate mTORC1 functionality via phosphorylating Raptor on Ser859 residue [171]; NLK, however, inhibits the mTORC1 activity by directly phosphorylating Raptor on the Ser863 residue under stressful conditions [169]. Besides, AMPK could largely depress the activity of mTORC1 by phosphorylation Raptor on Ser722 and Ser729, leading to cell cycle arrest and suppressed mitotic proliferation [172].

Clinically, higher expression of both Raptor and mTORC1 has been detected in colorectal cancer and linked to unfavorable prognosis [173]. Knockdown of *Raptor* significantly reverses the malignant properties of ovarian cancer, accompanied with the less recruitment of mTORC1 downstream substrates such as 4EBP1 exanimated in rodent models [174]. Silencing *Raptor* in xenograft mice results in elevated apoptosis and reduced growth potential in hepatocellular carcinoma, which is attributed to the inhibition on mTORC1 and its target effectors [175]. Raptor phosphorylation by the PI3K-PTEN axis in head and neck cancer leads to the connection between mTORC1 and its downstream substrate BMAL1, which is a pivotal clock gene inducing tumor multiplicity in mouse models [176]. Meanwhile, mTORC1-Raptor plays essential roles on maintaining the oncogenic characteristics of T-cell lymphoma, and its depletion obviously shortens cell longevity and triggers premature death [177]. On the other hand, since mTORC1 involves in liver steatosis, whether something similar happens in tumorigenesis remains undetermined, therefore in demand of further mechanistical discoveries.

2.3.3.2. TSC2: Tuberous sclerosis complex (TSC) clinically features systemic occurrence of hamartomas, which is caused by *Tsc1* or *Tsc2* genetic mutations among human patients. TSC2 has been identified as the central connector of adaptive and growth pathways, usually linking upstream kinase Akt and downstream target mTORC1. Mechanistically, inactivated phosphorylation of TSC2 by Akt could significantly suppress mTORC1 activity, leading to inactivation of 4EBP1 and $p70^{S6K1}$, which serve as major regulators of cell growth and organ size. Conversely, AMPK could promote TSC2 functions to inhibit mTOCR1 in response to energy exhaustion, by direct phosphorylating TSC2 on Thr1227 and Ser1345 residues, hence protectively limiting cell expansion and reducing stress-induced apoptosis [178].

Conditional knockout of *Tsc2* significantly elevates the possibility of tumor formation *in vivo* [179]. Specifically, silenced expression of TSC2 is observed in human hepatocellular carcinoma, and indicates well responsiveness to mTORC1-targeted therapy of Everolimus [180]. Furthermore, renal malignancies have been recognized as *TSC2*-associated, thus rapamycin is effective in restricting tumor development among conditional *Tsc2* knockout mice [181]. Meanwhile, through an inhibitory nitrosylation on TSC2, nitric oxide synthase

could inhibit TSC2 by nitrosylation modification, leading to activation of the mTORC1 pathway, resulting in enhanced cell invasiveness in xenograft melanoma models [182]. Notably, further evidence has implicated that *TSC2* insufficiency is able to induce mesenchymal tumorigenesis by recruiting a transcriptional factor HMGA2, which is totally independent of mTOR activation [183]. Thus it gives us a hint that the anti-neoplastic role of TSC2 may be correlated to multiple underlying mechanisms other than the classical mTORC1 involvement.

2.3.3.3. p53: p53, an extensively studied transcriptional factor, plays pivotal role in monitoring and governing cell fate and mitotic cycle, especially notable as a tumor suppressor in a variety of cancers. Mechanically, p53 is activated and translocated into nucleus for transcription of target genes to maintain genomic stability and energy homeostasis under destructive conditions such as DNA breaking or metabolic imbalance. Pathologically, p53-deficiency demonstrates a remarkable decrease on cell viability in the setting of energy deprivation, despite of an increase on cell multiplicity [184].

Currently, the interaction of p53 and AMPK has been molecularly elucidated, in turn, AMPK-mediated phosphorylation of p53 at the Ser15 residue could trigger its transcriptional activity in the case of glucose exhaustion [185]. More interestingly, Sestrins 1/2, members of stress-sensitive gene governed by p53, could promote AMPK activated phosphorylation to comprise an AMPK-p53 feedback loop, which serves as the central mediator of adaptive regulation on cell growth and apoptosis. Besides, DAPK and CK1 also can phosphorylate p53 on the Ser20 residue to exert similar tumor suppressive functions [186].

Since gain-of-function mutations of *P53* occurring nearly 50% of human tumors, including colorectal liver, breast and lung cancer, the anti-tumor activity has become the most investigative aspect of p53 function during the past decade. Generally, activated p53 interacts with its tumor-inhibitory partners to initiate the growth-restricting pathways and repair DNA mismatches [187]. Specifically, as the downstream target of RP-MDM2 axis, p53 directly antagonizes RAS-involved tumorigenesis in rodent melanoma models [188]. Moreover, restoration of p53 could enhance the chemosensitivity of skin cancer cells by inducing the production of NEAT1 paraspeckles [189]. p53 also exerts its tumor suppressive role via upregulating miR-139-5p, subsequently to inactivate oncoprotein PDE4D in xenograft colorectal carcinoma models [190]. Recently, nerve growth factor receptor (NGFR), the novel inactivator and downstream target of p53, has been characterized to inhibit tumor suppressor function of p53 in glioblastoma, lead to reduced apoptosis and enhanced migratory capability [191]. Hence, targeted p53 strategy seems to be a promising therapeutic option among patients refractory to routine treatments, either by p53 activator such as APR-246 or exogenous p53 supplements.

2.3.3.4. p27: p27 (also termed as Kip1), a member of the Cip/Kip family along with p21 and p57, functions as a vital inhibitor of cyclin dependent kinase (CDKs) in mammalian cells. To this end, p27 arrests cell cycle in G1 phase by targeting cyclin E-Cdk2 and cyclin D-Cdk4, and also manipulates cell migration and longevity independent its role on cell cycle [192].

p27 is manipulating both in transcriptional and post-transcriptional levels, including transcriptional adjustment, phosphorylation and ubiquitin-involved proteolysis. Thus, AMPK directly phosphorylates p27 on the Thr198 residue under certain stressful conditions, resulting in p27 cytoplasmic sequestration and stabilization [193], which facilitates cells to survive in energy-deprived environments, mainly via mediating autophagy and apoptosis [192].

p27 is considered to perform an anti-oncogenic effector within human malignancies due to its suppressive role on cell cycle regulation. Evidences from two meta-analyses reveal that the activity of p27 is largely depressed in oral squamous cell carcinoma [194] as well as non-small cell lung cancer [195]. In keeping with this notion, p27 expression is positively correlated with survival expectancy and inversely with tumor progression. p27 is also a downstream target of the Hippo signaling, which promotes breast cancer progression in murine models by inhibiting the transcriptional activity of p27 [196].

Multiple oncogenic factors including Skp2 [197] and Mdig [198] inhibiting p27 activation by accelerating its degradation, leading to higher cytoplasmic p27 expression, indicating poorer chemosensitivity and long-term survival among patients of non-small cell lung cancer [199]. Similarly, repressed p27 viability is likewisely identified as an inevitable pusher of neoplastic transformation in prostate. Both miR-150 [200] and miR-24 [201] suppresses the expression of p27 among xenograft mice, playing a contributing role on prostate oncogenesis and progression. Besides, administration of a novel compound CAPE displays beneficial anti-tumor effects in prostate cancer cells, primarily via reactivation and nuclear translocation of p27 [202]. Thus, all these evidences suggest that p27-targeted therapy is of great clinical potential as an anti-neoplastic strategy.

2.3.3.5. ULK1: Lysosomes act as intracellular scavengers by fusing with and then degrading the vesicles containing aberrant proteins and organelles, a process termed as autophagy. This catabolic process participates in a variety of biological situations, such as energy exhaustion, carcinogenesis and neurodegeneration. Degradation of defective components not only protects cells from secondary detriments, but also offers essential nutrients and elements under stressful circumstances [203]. Currently, over 30 autophagy-related genes (ATG) have been identified across species. The Unc-51-like kinase 1 (ULK1) is a mammalian ortholog of yeast ATG1, mechanistically serving as a core initiator of cellular autophagy along with its chaperones ATG13 and FIP200 to form a trimeric complex [204]. Four available residues within ULK1 are identified as the activating phosphorylation sites by AMPK, including Ser467, Ser555, Ser637 and Thr574 [205]. More interestingly, all three constitutive subunits of AMPK could be phosphorylated and inhibited by ULK1, indicating a feedback loop between both effectors [206]. Besides, ULK1 is also phosphorylated by mTOR on Ser757 to inhibit its functions in autophagy [207]. These results potently provide the central role of ULK1 in terms of linking metabolism with autophagy.

During the past decade, the relationship between autophagy and tumorigenesis has become a hot issue among scientific communities. Clinically, overexpression of ULK1 plays an oncogenic role in most of tumor types, including hepatocellular carcinoma [208], esophageal squamous cell carcinoma [209], nasopharygeal carcinoma [210] as well as colorectal cancer

[211], which predicts poorer prognosis and severer progression. In addition, the protective autophagy induced by ULK1 is observed among mice with xenograft prostate cancer, thus preventing apoptosis and triggering neoplastic advancement [212].

Specially, the mTOR/ULK1 signaling also generates autophagic protection in chronic myeloid leukemia cells, antagonizing the chemotherapeutic benefits of regular regimen [213]. However, contrary outcome has been obtained in breast cancer specimens, among which lower ULK1 expression indicates unfavorable prognosis and local development [214]. Based on current perspectives, the exact interplay between autophagy and tumorigenesis mechanistically depends on different tumoral phases and types. Roughly, autophagic activity exerts inhibitory impact on tumor initiation by degrading misfold proteins while stimulatory effect during tumor development via decreasing lethal accumulations [215]. This may help us to comprehend the inconsistent role of ULK1 in various cancers, although the more specific explanations are still in deficiency.

3. Discussion and perspective

As we summarized above, accumulating investigations have outlined the hub-like role of AMPK in regulation of cell metabolism, autophagy, inflammation, proliferative cycle and tumorigenesis. Knockout and clinical evidences of AMPK subunits as well as its upstream and downstream molecules, listed in Table 1, Table 2 and Table 3, respectively, offer a more comprehensive perspective of the functional characteristics of AMPK signaling under both physiological and neoplastic circumstances. The translational medicine emphasizes the connection and transformation between basic research and clinical applications, trying to rectify the current dilemma that the published studies actually display little clinical significance despite of the absolute amount of literatures increase in a rapid rate annually [216]. On basis of our comprehensive review theming AMPK functionality, both *in vivo* and *in vitro* experiments have particularly declared its potential role as a tumor suppressor, implicating the underlying therapeutic worthiness of AMPK targeted strategy as an alternative option against routinely refractory malignancies.

To this end, metformin is the most widely prescribed anti-diabetic drug, and it’s function mainly through pharmaceutically targeting and stimulating the activity of AMPK heterotrimer (Table 4 and Figure 2). Besides its classical indications, several clinical trials have reported the comparative results of metformin usage within different cancers. In detail, neoadjuvant of metformin exhibits significantly anti-proliferative effects against ER-positive [217] and luminal B breast cancer [218]. However, the therapeutic benefits of metformin remain in controversies in digestive tumors, and the combination of metformin with gemcitabine or erlotinib does not improve the clinical prognosis of pancreatic cancer patients [219]. Nevertheless, employment of metformin patients could remarkably decrease the risk of malignant transformation for colon polyps [220] [221]. Taken together, the plausible interpretations of all these inconsistencies in metformin efficacy may mainly due to the distinctive activation status of the AMPK signaling. Moreover, the clinical trials towards neuroendocrine tumors as well as prostate cancer are still undergoing, which we believe will become vital additions to future analysis.

5-Aminoimidazole-4-carboxamide riboside (AICAR or acadesine) is another well-investigated compound to structurally mimic AMP and functionally activate AMPK [222]. Accumulating evidences have demonstrated the therapeutic efficacy of AICAR administration in diverse malignancies. Clinically, AICAR intervention-mediated AMPK activation could significantly reverse the overexpression of HER2 and EGFR *in vitro*, hence triggering cell cycle arrest as well as shortening cell longevity in breast cancers [223, 224]. Meanwhile, AICAR synergizes with 5-fluorouracil (5-FU), a suicide inhibitor, to enhance apoptosis in colorectal [225] and gastric cancer cells [226]. Moreover, similar anti-neoplastic impact of AICAR is obtained within hepatocellular carcinoma [227], ovarian cancer [54] as well as hematological malignancy [225].

On the other hand, AMPK-independent mechanism of AICAR in regulation of tumorigenesis has been discovered. Specifically, AICAR generates programmed necrosis in prostate cancer cells via an N-acetylcysteine and cyclophilin-D dependent signals, instead of AMPK pathway [228]. Furthermore, AICAR is also able to inhibit the activation of the JNK/NANOG pathway to suppress its malignant properties in hepatocellular carcinoma [[229]. Overall, these results indicate the huge clinical potential of AICAR in the field of cancer treatment, although more clinical trials should be implemented for further safety and efficacy assessment.

Moreover, in addition to the above-mentioned activators, there are still various compounds serving as direct agonists or antagonists of AMPK, which exhibit great potentials for clinical applications (Table 4 and Figure 2). Taken together, AMPK and its signaling pathway has become a promising therapeutic target in terms of diverse human disorders, especially in metabolic syndrome and cancers.

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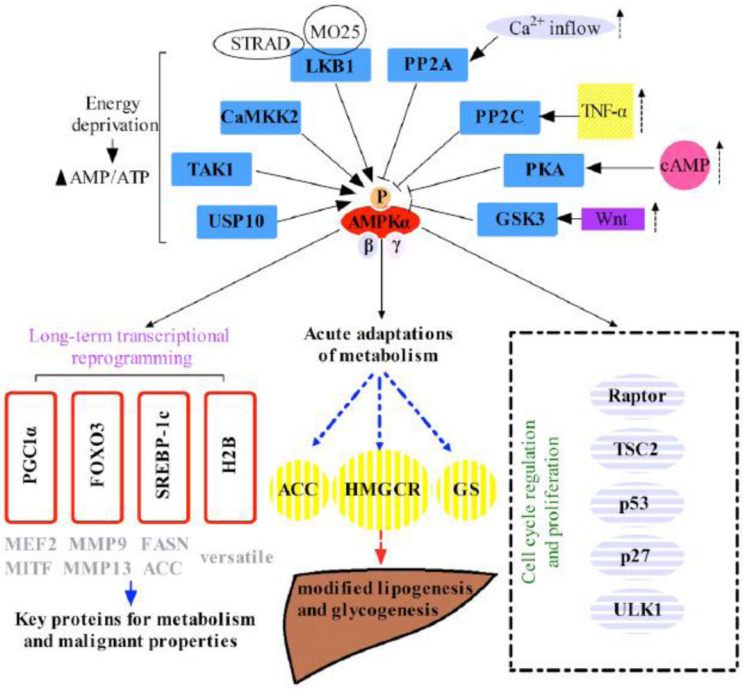

Figure 1.

The graphical demonstration of the AMPK complex and its signaling components including both upstream regulators and downstream effectors.

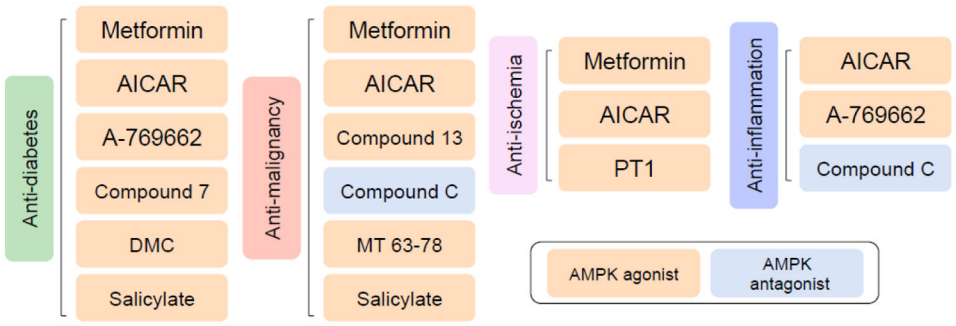

Figure 2.

The clinical relevance of AMPK-targeted therapies in combating human disorders including diabetes, neoplasms, ischemia and inflammation.

Table 1

A summary of knockout phenotypes of major AMPK complex subunits in mice.

AMPK subunits	Knockout mode	Phenotypic characteristics	Neoplastic implications	References
Ampka1	*Ampka1*$^{-/-}$	Splenomegaly and anemia	Context-dependent role in tumorigenesis	[230]
	Ampka1$^{-/-}$	Shorter circadian period		[231]
	Ampka1$^{-/-}$	Endothelial dysfunction and vascular inflammation		[232]
	Ampka1$^{-/-}$	Spermatozoa abnormality and defective androgen production		[233]
	Ampka1$^{-/-}$	Delayed liver regeneration		[234]
	Ampka1$^{-/-}$	Decreased scar maturation and contractility following heart infarction		[235]
	Conditional *Ampka1*$^{-/-}$ (pancreatic beta cell)	Normal insulin secretion		[236]
	Conditional *Ampka1*$^{-/-}$ (myoblast)	Reduced myogenesis		[237]
	Conditional *Ampka1*$^{-/-}$ (spinal cord)	Thermal hyperalgesia and mechanical allodynia		[238]
	Conditional *Ampka1*$^{-/-}$ (satellite cell)	Dysfunctional myogenic differentiation		[239]
	Conditional *Ampka1*$^{-/-}$(chondrocyte)	Normal bone growth		[240]
	Conditional *Ampka1*$^{-/-}$ (vascular smooth muscle)	Production of atherosclerotic calcification		[241]
	Conditional *Ampka1*$^{-/-}$ (macrophage)	Failed collateral remodeling and arteriogenesis		[242]
	Conditional *Ampka1*$^{-/-}$ (catecholaminergic cell)	Severer hypoventilation and apnea in the setting of hypoxia		[243]
Ampka2	*Ampka2*$^{-/-}$	Lowered insulin secretion and sensitivity	Context-dependent role in tumorigenesis	[244]
	Ampka2$^{-/-}$	Longer circadian period		[231]
	Ampka2$^{-/-}$	Increased microtubule proliferation in cardiac hypertrophy		[245]
	Ampka2$^{-/-}$	Enhanced bone resorption and reduced bone mass		[246]
	Ampka2$^{-/-}$	Impaired glycolysis in postmortem skeletal muscle		[247]
	Ampka2$^{-/-}$	Attenuation of hepatic injury caused by metastasized tumor		[248]
	Ampka2$^{-/-}$	Upregulation of mesenchymal transition of renal tubular epithelial cells		[249]
	Ampka2$^{-/-}$	Aggravated left ventricular hypertrophy and dysfunction induced by hypertension		[250]
	Ampka2$^{-/-}$	Atherosclerosis and endothelial dysfunction		[251, 252]
	Ampka2$^{+/-}$	Reduced glucose uptake and normal fatty acid uptake		[253]
	Conditional *Ampka2*$^{-/-}$ (liver)	Decreased hepatic glucose production		[254]

AMPK subunits	Knockout mode	Phenotypic characteristics	Neoplastic implications	References
	Conditional *Ampkα2*$^{-/-}$ (pancreatic beta cell)	Impaired insulin secretion		[255]
	Conditional *Ampkα2*$^{-/-}$ (vascular smooth muscle)	Elevated neointima formation and vascular smooth muscle cell migration		[256, 257]
	Conditional *Ampkα2*$^{-/-}$ (skeletal muscle)	Normal insulin sensitivity and diminished adipose storage in skeletal muscle		[258]
Ampkβ	*Ampkβ1*$^{-/-}$	Reduced bone density and normal osteoclast differentiation	Context-dependent role in tumorigenesis	[259]
	Ampkβ2$^{-/-}$	Reduced bone density and normal osteoclast differentiation		[259]
	Ampkβ2$^{-/-}$	Deficient exercise endurance and deteriorative glucose intolerance		[24]
	Conditional *Ampkβ1*$^{-/-}$*β2*$^{-/-}$ (skeletal muscle)	Decreased amount of capillary and resultant myopathy in nonpostural muscle		[260]
	Conditional *Ampkβ1*$^{-/-}$*β2*$^{-/-}$ (pancreatic beta cell)	Restricted insulin secretion		[261]
Ampkγ	*Ampkγ1*$^{-/-}$	Hemolytic anemia and splenomegaly	Emerging tumor suppressive roles	[33]
	Ampkγ3$^{-/-}$	Attenuated adaptive ability of glucose metabolism in response to fasting		[262]
	Ampkγ3$^{-/-}$	Decreased post-workout glycogen restoration		[263]
	Ampkγ3$^{-/-}$	Damaged homeostasis of circadian oscillators		[264]

Table 2

A summary of knockout phenotypes of major AMPK upstream regulators in mice.

Upstream regulators	Knockout mode	Phenotypic characteristics	Neoplastic implications	References
Lkb1	*Lkb1*$^{-/-}$	Early embryonic death and growth retardation	Versatile roles (mainly tumor suppressive)	[265]
	Lkb1$^{-/-}$	Pancytopenia and quiescence of hematopoietic stem cell		[266]
	Lkb1$^{+/-}$	Development of gastrointestinal hamartomas		[43, 267]
	Lkb1$^{+/-}$	Initiation of hepatocellular carcinoma		[268]
	Lkb1$^{+/-}$	Emergence of pancreatic adenocarcinoma		[269]
	Lkb1$^{+/-}$	Disabled exercise capacity and changed fibre types in diaphragm		[270]
	Conditional *Lkb1*$^{-/-}$ (striated muscle)	Defective voluntary exercise and mitochondrial activity		[271]
	Conditional *Lkb1*$^{-/-}$ (skeletal muscle)	Enhanced insulin sensitivity and ameliorated glucose metabolism		[272]
	Conditional *Lkb1*$^{-/-}$ (pancreatic epithelium)	Impaired acinar polarity and initiation of cystic tumors		[273]
	Conditional *Lkb1*$^{-/-}$ (endothelium)	Early embryonic death and vascular dysfunction		[274]
	Conditional *Lkb1*$^{-/-}$ (pancreatic alpha cell)	Reduced glucagon secretion following hypoglycemia		[275]
	Conditional *Lkb1*$^{-/-}$ (pancreatic beta cell)	Increased amount of beta cells and insulin secretion		[276]
	Conditional *Lkb1*$^{-/-}$ (heart)	Cardiac hypertrophy and malfunction		[277]
	Conditional *Lkb1*$^{-/-}$ (heart)	Spontaneous atrial fibrillation		[278]
	Conditional *Lkb1*$^{-/-}$ (liver)	Damaged bile acid transport and abnormal accumulation		[279]
	Conditional *Lkb1*$^{-/-}$ (spinal cord)	Disabled hind-limb and degenerative axon		[280]
	Conditional *Lkb1*$^{-/-}$ (T cell)	Lowered level of peripheral T cells		[281]
	Conditional *Lkb1*$^{-/-}$ (adipose tissue)	Improved thermogenesis and increased brown adipose tissue mass		[282]
	Conditional *Lkb1*$^{-/-}$ (osteoblast)	Elevated density and porosity in trabecular and cortical bone respectively		[283]
	Conditional *Lkb1*$^{-/-}$ (Schwann cell)	Developmental retardation in myelination and myelin maturity		[284]
	Conditional *Lkb1*$^{-/-}$ (inner ear)	Malformed and dysfunctional stereocilia		[285]
	Conditional *Lkb1*$^{-/-}$ (cerebellum)	Enhanced granule cell precursors proliferation, abnormal granule cell migration and impaired motor function		[286]
	Conditional *Lkb1*$^{-/-}$ (oocyte)	Swollen ovaries and infertility		[287]

Upstream regulators	Knockout mode	Phenotypic characteristics	Neoplastic implications	References
Camkk2	*Camkk2*$^{-/-}$	Impaired long-term and spatial memory in male mice but normal in female mice	Largely oncogenic roles	[288]
	Camkk2$^{-/-}$	Ameliorated glucose level and tolerance		[289]
	Camkk2$^{-/-}$	Damaged development of cerebellar granule cells		[290]
	Camkk2$^{-/-}$	Restricted inflammatory responses by macrophage		[291]
	Camkk2$^{-/-}$	Higher density in trabecular bone and activated osteoblast formation		[292]
	Camkk2$^{-/-}$	Dysfunctional blood-brain barrier		[293]
	Conditional *Camkk2*$^{-/-}$ (hypothalamus)	Inhibited secretion of neuropeptide Y and food ingestion		[294]

Table 3

A summary of knockout phenotypes of major AMPK downstream effectors in mice.

Downstream regulators	Knockout mode	Phenotypic characteristics	Neoplastic implications	References
Pgc-1α	*Pgc-1α*$^{-/-}$	Development of Huntington's disease	Oncogenic roles	[295]
	Pgc-1α$^{-/-}$	Impaired early vasculogenesis in retina		[296]
	Pgc-1α$^{-/-}$	Striatal neurodegeneration and locomotive discordance		[297]
	Pgc-1α$^{-/-}$	Cortical hypereactivity		[298]
	Conditional *Pgc-1α*$^{-/-}$ (endothelium)	Retarded wound healing and vascular dysfunction		[299]
	Conditional *Pgc-1α*$^{-/-}$ (adipose tissue)	Insulin insensitivity		[300]
	Conditional *Pgc-1α*$^{-/-}$ (skeletal muscle)	Development of glucose intolerance and whole-body inflammation		[301]
	Conditional *Pgc-1α*$^{-/-}$ (renal tubule)	Normal function of kidney but elevated inflammatory levels		[302]
Srebp-1c	*Srebp-1c*$^{-/-}$	Peripheral neuropathy	Oncogenic roles	[303]
	Conditional *Srebp-1c*$^{-/-}$ (mammary epithelium)	Deficient lactation and lipid synthesis		[304]
	Conditional *Srebp-1c*$^{-/-}$ (pancreatic beta cell)	Increased insulin responsiveness		[305]
Acc	*Acc1*$^{-/-}$	Early embryonic death	Oncogenic roles	[306]
	Conditional *Acc1*$^{-/-}$ (liver)	Decreased triglyceride storage in liver		[307]
	Conditional *Acc1*$^{-/-}$ (adipose tissue)	Delayed growth and reduced level of adipose accumulation		[308]
	Conditional *Acc1*$^{-/-}$ (T-cell)	Impaired peripheral distribution and proliferation of $CD8^+$ T-cell		[309]
	Acc2$^{-/-}$	Elevated insulin sensitivity and ameliorated metabolic syndrome		[310]
	Conditional *Acc2*$^{-/-}$ (heart)	Improvement on overloaded hypertrophy		[311]
	Conditional *Acc2*$^{-/-}$ (skeletal muscle)	Unchanged glucose homeostasis and body weight		[312]
	Conditional *Acc1*$^{-/-}$*Acc2*$^{-/-}$ (liver)	Enhanced fat storage in liver		[313]
Hmgcr	*Hmgcr*$^{-/-}$	Early embryonic death	Versatile roles (mainly oncogenic)	[314]
	Conditional *Hmgcr*$^{-/-}$ (skeletal muscle)	Development of rhabdomyolysis		[315]
	Conditional *Hmgcr*$^{-/-}$ (liver)	Hepatic steatosis and premature lethality		[316]
Gs	Conditional *Gs*$^{-/-}$ (brain)	Disruptive long-term memory and learning ability	Oncogenic roles	[317]
	Conditional *Gs*$^{-/-}$ (skeletal muscle)	Normal exercise endurance and better glucose tolerance		[318]
	Conditional *Gs*$^{-/-}$ (liver)	Elevated glucose intolerance		[319]

Table 4

A list of major agonists and antagonists of AMPK and their potential clinical usage in human diseases

Compounds	Function to AMPK	Clinical relevance	References
Metformin	AMPK agonist	Amelioration of diabetes and other relevant metabolic comorbidities	[320]
		Anti-neoplastic efficacy in various cancers	[321–323]
		Reduction of pulmonary fibrosis induced by Bleomycin	[324]
		Protection against testicular ischemia	[325]
		Neuroprotective impact after brain stroke	[326]
		Survival benefit among patients with acute heart failure	[327]
		Against several aging related and degenerative disorders	[328]
		Improvement on multiple sclerosis	[329]
AICAR	AMPK agonist	Anti-diabetic effect	[330]
		Reversal of alcohol-induced fatty liver	[331]
		Pathological remission of severe spinal muscular atrophy	[332]
		Suppression of multiple malignancies	[226, 333]
		Improvement of dry eye	[334]
		Alleviation of chemical hepatitis	[335]
		Prevention from ischemia and reperfusion injury in diverse organs	[336, 337]
		Enhanced cognition and motor coordination	[338]
A-769662	AMPK agonist	Anti-obesity and diabetes	[339]
		Amelioration of osteonecrosis	[340]
		Reversal of inflammatory arthritis	[341]
Compound 13	AMPK agonist	Anti-tumoral effect in melanoma	[342]
		Protection efficacy in Helicobacter pylori infected gastric epithelium	[343]
Compound 7	AMPK agonist	Improvement on diabetic nephropathy	[344]
DMC	AMPK agonist	Anti-diabetes	[345]
PT1	AMPK agonist	Prevention from ischemic injury on cardiomyocytes	[346]
MT 63–78	AMPK agonist	Inhibition on prostate cancer growth	[347]
Salicylate	AMPK agonist	Against diabetes	[348]
		Decreasing the malignant properties of colorectal cancer, prostate cancer and lung cancer	[349, 350]
Compound C	AMPK antagonist	Inhibitory impact on several cancers including glioma, skin cancer, pancreatic cancer and colorectal cancer	[351–354]
		Alleviation of obesity induced inflammatory reactions	[355]
		Repression on circadian dysrhythmia	[356]