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Review

AMPK: An odyssey of a metabolic regulator, a tumor suppressor, and now a contextual oncogene

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A B S T R A C T

Metabolic reprogramming is a unique but complex biochemical adaptation that allows solid tumors to tolerate various stresses that challenge cancer cells for survival. Under conditions of metabolic stress, mammalian cells employ adenosine monophosphate (AMP)-activated protein kinase (AMPK) to regulate energy homeostasis by controlling cellular metabolism. AMPK has been described as a cellular energy sensor that communicates with various metabolic pathways and networks to maintain energy balance. Earlier studies characterized AMPK as a tumor suppressor in the context of cancer. Later, a paradigm shift occurred in support of the oncogenic nature of AMPK, considering it a contextual oncogene. In support of this, various cellular and mouse models of tumorigenesis and clinicopathological studies demonstrated increased AMPK activity in various cancers. This review will describe AMPK's pro-tumorigenic activity in various malignancies and explain the rationale and context for using AMPK inhibitors in combination with anti-metabolite drugs to treat AMPK-driven cancers.

1. Introduction

Energy homeostasis involves balancing energy-producing and consuming processes to ensure a normal state in an organism. Over billions of years through evolution, organisms from prokaryotes to eukaryotes have evolved to produce energy for various functions, including multiplication, division, locomotion, and reproduction. Nutrient sensing in organisms is probably as old as the origin of the animal kingdom goes. Even in prokaryotes like *Escherichia coli (E. coli)*, a process called chemotaxis is conserved throughout the evolution in which the organisms sense the chemical composition of the surroundings and accordingly direct their movement [1]. *E. coli* are known to have five different dimeric transmembrane receptors that help them to sense different nutrients such as Tar (for aspartate, maltose, Co2+, and Ni2+), Trg (for ribose and galactose), Aer (for flavine adenine dinucleotide (FAD), Tsr (for Serine) and Tap (for dipeptides) [2]. Besides that, most prokaryotes and plants contain PII proteins, the primary function of which is to detect nitrogen deficiency [3]. Likewise, numerous nutrient-sensing proteins and mechanisms have been discovered as the evolutionary tree progressed from prokaryotes to yeast, one of the simplest eukaryotes. Yeasts like *Saccharomyces cerevisiae* and *Candida albicans* have been shown to possess an extracellular amino acid sensing pathway viz Ssy1-Ptr3-Ssy5 pathway (SPS pathway) and Snf3 and Rgt2 as extracellular glucose sensors [4]. Apart from the SPS pathway to detect amino acids, a separate pathway evolved in eukaryotes to sense intracellular amino acid levels. The general amino acid control non-derepressible 2 (GCN2) pathway detects amino acid levels by recognizing uncharged transfer RNAs that accumulate when amino acids are unavailable during protein synthesis [5]. A related mechanism known as the stringent response is preserved in response to amino-acid insufficiency, fatty acid deficit, and other stress conditions in bacteria [6]. As part of the stringent response, bacteria increase alarmone synthesis, which controls replication, translation, and transcription to adapt to harsh conditions [7]. Another protein signaling pathway involving the mechanistic target of rapamycin complex 1 (mTORC1), a Serine/Threonine kinase associated with amino acid sensing, is found in eukaryotes. Though mTORC1 is not a direct sensor of amino acid levels, it is activated in deficiency of amino acids, especially particular ones like leucine in mammalian cells [8]. Apart from these, various molecules and proteins are involved in sensing other nutrients and have been extensively reviewed [3]. Glucose levels need to be sensed in organisms as it is the primary energy source. The protein involved in glucose and energy-sensing happens to be the subject of our review, i.e., AMPK. Depending on the cell's glucose or amino acid levels, both AMPK and GCN2 are involved in the mTOR1 pathway [9,10].

The story of energy metabolism in eukaryotes begins with aerobic bacteria that established an endosymbiotic relationship with eukaryotic cells, leading to the development of what we now know as the cell's

Abbreviations: AMPK, Adenosine monophosphate (AMP)-activated protein kinase; HIF1α, Hypoxia-inducible factor 1-alpha; CBS domains, Cystathionine-β-synthase domains; LKB1, Liver kinase B1.

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powerhouse, the mitochondria. Even though glycolysis, a cytosolic process, generates energy in the form of adenosine triphosphate (ATP), the energy generated by mitochondria via the tricarboxylic acid (TCA) cycle and oxidative phosphorylation (OXPHOS) is much higher. In OXPHOS, glucose taken up by cells is completely oxidized into carbon dioxide, electrons are generated and then transferred through the electron transport chain (ETC) from electron acceptors to donors. This process happens on the inner membrane of mitochondria. This energy generated by the ETC is then used to pump protons across the inner mitochondrial membrane, thereby creating a potential gradient across the membrane. The protons then flow down the potential gradient via the complex V of the ETC, an enzyme called ATP synthase, leading to the phosphorylation of adenosine diphosphate (ADP) into ATP [11]. Through evolution, as the number of mitochondria within a eukaryotic cell increased, so did the surface area of the inner mitochondrial membrane accessible for ATP production, increasing the requirement for a molecule or system that detected a cell's energy level to control the powerhouse's functioning. AMPK fits the role of an energy sensor in a cell perfectly. AMPK is activated when ATP is depleted, or adenosine monophosphate (AMP) or ADP levels increase. It may also detect glucose levels in the cell and, being a kinase, phosphorylate proteins in different pathways to turn on or off the ATP generation or breakdown processes, thus maintaining energy homeostasis as needed. AMPK is also engaged in mitochondrial biogenesis and mitophagy if the cell signals stressful conditions [12].

The ancestral functions of AMPK were known by the roles played by its orthologs in lower eukaryotes. In 1977, *cat1* and *cat3* mutants generated in *Saccharomyces cerevisiae* could not grow on glycerol or maltose, *ccr1* mutants did not grow on ethanol, and *snf1*, *snf4* mutants did not grow on alternative carbon sources like sucrose and raffinose. Later, the *cat1, ccr1,* and *snf1* were recognized as alternative alleles of sucrose non-fermenting 1 (SNF1), whereas the *cat3* and *snf4* were alleles of another gene known as sucrose non-fermenting 4 (SNF4). Like the AMPK heterotrimeric subunits, Snf1 (catalytic alpha-subunit) forms a complex with Snf4 (a regulatory gamma-subunit) and three other gene products, Sip1, Sip2, and Gal83 (beta-subunits, all of which are necessary for Snf1/Snf4 activity) [13]. In abundant glucose, yeast cells proliferate rapidly by generating ATP through fermentation, similar to the Warburg effect seen in rapidly proliferating mammalian cells, except that the end product in yeast is ethanol rather than lactic acid as in mammalian cells. As the glucose source diminishes, the cells detect the same and switch back to the more efficient process of OXPHOS for ATP production. The heterotrimeric SNF1 complex comes into play, sensing glucose availability, recognizing starvation, and triggering the transition from fermentation to OXPHOS, indicating a similar ancestral role for AMPK [9,14]. A similar kinase is conserved in structure and functions in plants called SNF1-related protein kinase (SnRK1) [15].

2. Metabolic alterations in cancer

Cancer cells are transformed cells with aberrant metabolic pathways, ensuring their survival and proliferation under the most unfavorable conditions. This makes altered metabolism a necessary feature of cancer, which was essentially derived from Otto Warburg's pioneering work on aerobic glycolysis in the 1920s, or what is now known as the Warburg effect, as described by Efraim Racker [16]. The tumor ecosystem comprises a diverse population of cancer cells and various stromal cell types, such as immune cells, adipocytes, and cancer-associated fibroblasts (CAF), contributing to a unique microenvironment. This, in turn, affects tumor growth and related processes such as proliferation, metastasis, apoptosis, and tumor elimination (Fig. 1A) [17]. Solid tumors often develop a poor vascular system because of the rapid proliferation of tumor cells, limiting essential nutrients such as oxygen and glucose, resulting in metabolic and hypoxic stress in the tumor cells. Low oxygen levels (0.3–2%) in solid tumors induce cells to adopt the hypoxia-inducible factor 1-alpha (HIF1α) pathway, promoting cell survival by transcriptionally upregulating glycolytic enzymes, glutaminolysis enzymes, and glucose transporters [18,19]. Cancer cells also upregulate the essential machinery like a vascular endothelial growth factor for angiogenesis, i.e., blood vessel formation, via HIF1α to survive and proliferate under hypoxic conditions [20]. These enhanced activations of various pathways deplete the cells' glucose stores, resulting in the onset of glucose stress (0.4–0.6 mM) (Fig. 1B). As a result, some cancer cells rearrange their metabolic pathways away from glycolysis and

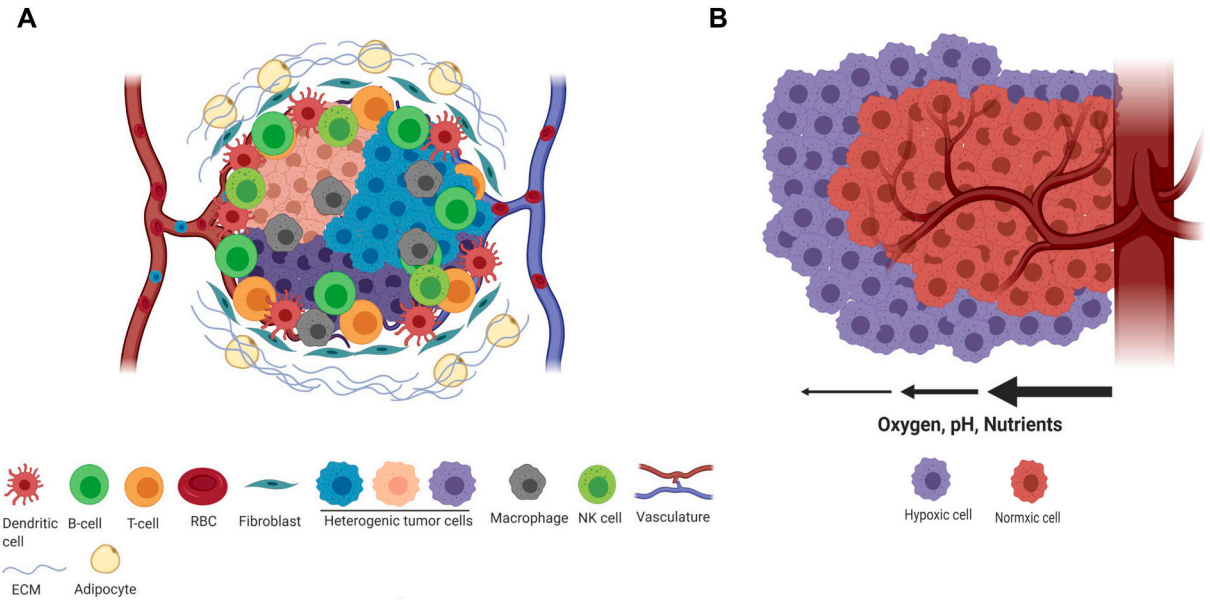

Fig. 1. A) Tumor ecosystem. A tumor is a multifaceted ecosystem encompassing various cell types that shows heterogeneity. The cell types inside a tumor usually comprise a heterogeneous collection of cancer cells, normal cells that have not been transformed, immune cells like lymphocytes, dendritic cells, macrophages, natural killer cells, cancer-associated fibroblast (CAFs), adipocytes, and vascular system along with extracellular matrix (ECM). **B) Tumor heterogeneity.** Besides accommodating the tumor cells, the tumor microenvironment (TME) possesses irregular vasculature, hypoxia, a gradient of nutrients, and differential pH. The regions near blood vessels are rich in oxygen and nutrients (red-colored cells), and the regions away from the blood vessels are devoid of the same (blue-colored cells).

toward glutaminolysis or other lipolytic pathways to survive [21].

Glucose and glutamine are the primary carbon and nitrogen sources for rapidly dividing cells and act as the main building blocks of the macromolecules of the cell [22]. Glucose is utilized systematically through glycolysis and further in the TCA cycle and OXPHOS in normal cells [23]. On the other hand, rapidly proliferating cells use glucose through glycolysis and generate lactate even in the presence of oxygen, a process known as the Warburg effect [24]. Intermediates of glycolysis are utilized to synthesize nucleic acids, lipids, proteins, and other macromolecules in rapidly dividing cells [22]. Glutamine is another essential energy nutrient in these cells, utilized in the TCA cycle by entering as an anaplerotic substance. In the absence of glucose, cancer cells prefer to utilize glutamine as one of the alternative carbon sources, for which there is a need to suppress tumor suppressor genes that act in inactivating this pathway [25]. Tumors also upregulate certain transcription factors, such as the bHLH transcription factor (cMYC), which is a transcription factor that is highly expressed in a variety of malignancies, including breast and lung cancer, and regulates certain genes involved in cell proliferation, apoptosis, and cellular transformation by binding to enhancer box sequences, and kinases such as AMPK, which serve as a metabolic sensor in response to low nutrient availability, modulating metabolic pathways such as glycolysis, glutamine metabolism, TCA cycle, and OXPHOS [116,27]. cMYC, for example, upregulates the transcription of glutamine metabolic enzymes such as glutaminase, an amidohydrolase enzyme responsible for the production of glutamate from glutamine, glutamate dehydrogenase, glutamic-oxaloacetic transaminase, and 2-oxoglutarate dehydrogenase, enzymes involved in glutaminolysis which converts glutamate to α-ketoglutarate [28]. cMYC is also crucial in glutamine metabolism and the upregulation of glutamine transporters such as solute carrier family 1 member 5 (SLC1A5), the essential transporter in glutamine uptake in cancer cells under glucose deprivation conditions [29]. The loss of function of tumor suppressor genes such as p53, Phosphatase, and tensin homolog deleted on chromosome 10 (PTEN), or mutations in p53, among others, has been extensively documented as a cause of altered metabolism [30,31]. Similarly, a gain of function mutation in Ras, Raf, Protein Kinase B (AKT), and other proteins has received significant interest since these proteins are involved in potentially druggable pathways in cancer therapy [32,33]. AMPK is a stress response kinase activated in response to low energy, regardless of the tissue, cell, or origin. In recent years, there has been a surge of interest in AMPK as a metabolic tumor promoter and, therefore, a possible target in cancer therapy. In this review, we have explored AMPK's role as a metabolic sensor, a tumor suppressor, and an oncogene.

3. AMPK: A metabolic sensor

3.1. Structure of AMPK

AMPK is a highly conserved, heterotrimeric protein consisting of three subunits, namely α, β, and γ, each of which has various isoforms produced by distinct genes. The α forms a catalytic monomer, whereas β and γ serve as regulatory subunits. Humans have two isoforms of the catalytic subunit-α, namely subunit α1 encoded by *PRKAA1* and subunit α2 encoded by *PRKAA2*. Similarly, the regulatory subunit-β has two isoforms, β1, and β2, which are encoded by *PRKAB1* and *PRKAB2* genes, respectively, whereas the other regulatory subunit-γ has three isoforms 1, 2, and 3, which are encoded by *PRKAG1, PRKAG2*, and *PRKAG3*, respectively. Twelve functional AMPK complexes can be formed by the amalgamation of any three different isoforms mentioned but comprising one each from α, β, and γ subunits (Fig. 2) [34,35].

We attempted to analyze the expression and mutational spectrum of AMPK isoforms using the data collected from various datasets such as The Cancer Genome Atlas (TCGA), cBioPortal, and Gene Expression

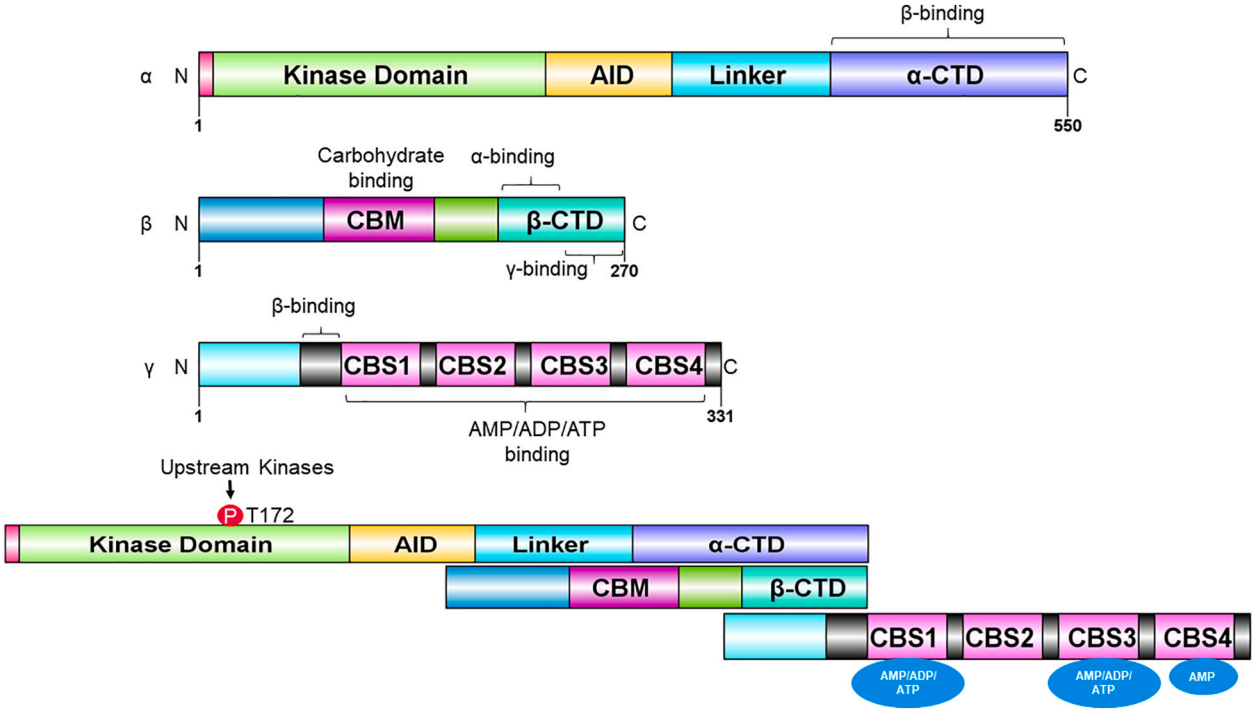

Fig. 2. The physical map of mammalian AMPK.
A) AMPK functional complex is made up of a catalytic protein subunit (α) and two regulatory protein subunits (β and γ). AMPK α consists of a kinase domain, auto-inhibitory domain (AID), α carboxy-terminal domain (α-CTD), whereas AMPK β contains a carbohydrate-binding module (CBM), carboxy-terminal domain (β-CTD). In contrast, AMPK γ contains a β-binding domain, cystathionine β-synthase domains (CBS1, CBS2, CBS3, CBS4), forming two Bateman domains that bind with AMP/ADP/ATP. **B)** Under low energy conditions, AMP/ADP binds to the CBS domains present in the γ subunit, inducing conformational changes in the catalytic domain of the subunit-α, which is then phosphorylated at Threonine 172 (T172) by upstream kinases such as liver kinase B1 (LKB1), Calcium/calmodulin-dependent protein kinase kinase (CaMKK), and TGFβ-activated kinase 1 (TAK1). DOG 1.0 was used to create illustrations of protein domains and phosphorylation sites in AMPK [149].

Profiling Interactive Analysis (GEPIA) [36,37]. The data revealed that isoforms of AMPK are differently expressed in various cancers. These isoforms could behave like tumor suppressors or promoters, depending on the context. AMPKα1 (*PRKAA1*) overexpression is found in stomach and esophageal carcinoma, while AMPKα2 (*PRKAA2*) has higher expression in prostate and liver cancer, among the most aggressive cancer types. On the other hand, AMPKβ1 (*PRKAB1*) is overexpressed in the colon, stomach, liver, and esophageal cancers. The other AMPKβ2 (*PRKAB2*) is overexpressed in the liver and esophageal cancer (Fig. 3A). AMPKγ1 (*PRKAG1*) is highly expressed in most cancer types, but AMPKγ2 (*PRKAG2*) expression is considerably lower in some cancer types stated above, indicating that its expression is essential for tumor suppressor action. AMPKγ3 (*PRKAG3*) expression, on the other hand, is considerably unchanged between the normal and tumor groups, showing that its activity is neutral in cancer growth (Fig. 3A). Previous literature shows that isoforms of AMPK such as α1, β1, or γ1 are higher in glioblastoma (GBM) than in normal tissue or low-grade glioma (LGG), and their expression is required for patient-derived cell survival [38]. Since AMPKγ1 is highly expressed in various malignancies, we further narrowed our search to study the various types of mutants which affect tumor growth. Several types of mutations, such as missense, nonsense, and fusion type of mutants, were observed in various types of cancer harboring the AMPKγ1 encoding gene (Fig. 3B and C). Similarly, other AMPK isoforms harbor diverse mutations in various cancer types. Since missense and nonsense mutations and other types of mutations were not studied much, there is much scope to explore this area to show AMPK's

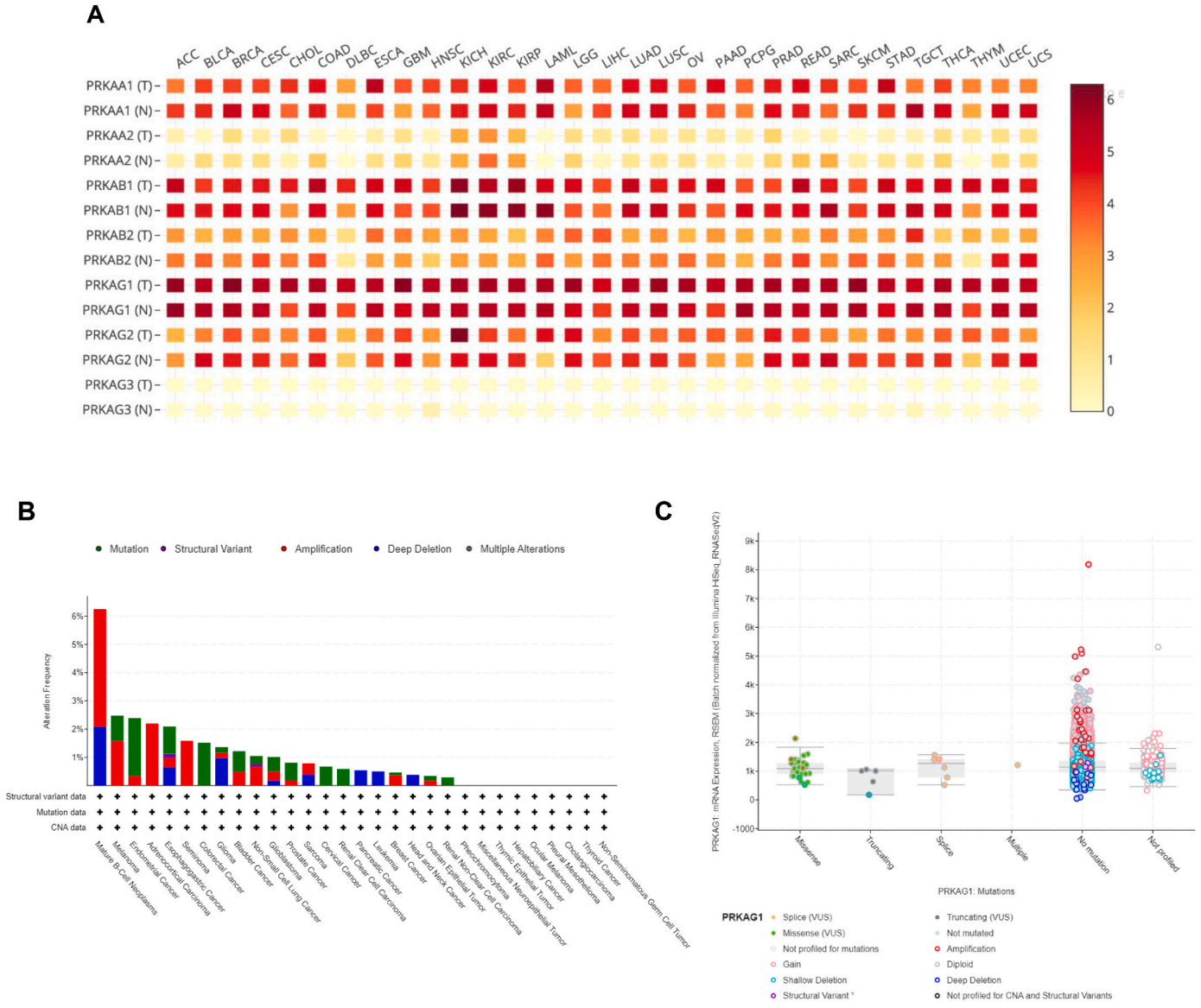

Fig. 3. A) Heat map showing the expression of AMPK isoforms in various cancers compared to normal tissue (T-tumor tissue, N-normal tissue). Abbreviations: ACC: Adrenocortical carcinoma, BLCA: Bladder Urothelial Carcinoma, BRCA: Breast invasive carcinoma; CESC: Cervical squamous cell carcinoma and endocervical adenocarcinoma; CHOL: Cholangio carcinoma; COAD: Colon adenocarcinoma; DLBC: Lymphoid Neoplasm Diffuse Large B-cell Lymphoma; ESCA: Esophageal carcinoma; GBM: Glioblastoma multiforme; HNSC: Head and Neck squamous cell carcinoma; KICH: Kidney Chromophobe; KIRC: Kidney renal clear cell carcinoma; KIRP: Kidney renal papillary cell carcinoma; LAML: Acute Myeloid Leukemia; LGG: Brain Lower Grade Glioma; LIHC: Liver hepatocellular carcinoma; LUAD: Lung adenocarcinoma; LUSC: Lung squamous cell carcinoma; MESO: Mesothelioma; OV: Ovarian serous cystadenocarcinoma; PAAD: Pancreatic adenocarcinoma; PCPG: Pheochromocytoma and Paraganglioma; PRAD: Prostate adenocarcinoma; READ: Rectum adenocarcinoma; SARC: Sarcoma; SKCM: Skin Cutaneous Melanoma; STAD: Stomach adenocarcinoma; TGCT: Testicular Germ Cell Tumors; THCA: Thyroid carcinoma; THYM: Thymoma; UCEC: Uterine Corpus Endometrial Carcinoma; UCS: Uterine Carcinosarcoma; UVM: Uveal Melanoma; **B)** Mutation analysis of AMPK isoform PRKAG1 in pan-cancer data sets of cBioPortal. **C)** Copy number alterations of AMPK isoform PRKAG1 in pan-cancer data sets of cBioPortal.

role in cancer progression. Since AMPK activation depends on all the subunits, its role depends on the entire complex. Hence, targeting any subunit critical for the action can be helpful in therapeutic targeting.

3.2. AMPK activation mechanisms

AMPK is a serine/threonine kinase activated when cellular ATP levels are low. Many metabolic stresses induce AMPK activation, including amino acid insufficiency, low oxygen or low glucose stress, extracellular matrix (ECM) loss, strenuous exercise, and mitochondrial damage [39–43]. When AMP/ADP levels are high, AMP binds with the cystathionine-β-synthase-1 (CBS-1), CBS-3, and CBS-4 domains of the γ-subunit of AMPK, whereas ADP binds more strongly to the CBS1 and CBS3 domains than the CBS4 domain. Since CBS-2 has Aspartic acid (Asp) instead of Alanine (Ala) at the binding site, AMP/ADP cannot bind to this domain compared to the other CBS domains. The binding of the AMP/ADP to the γ-subunit results in a conformational shift in the heterotrimeric protein complex, exposing the catalytic domain in the α-subunit. Kinases present upstream of the AMPK, such as Liver kinase B1 (LKB1) under higher levels of AMP or ADP, also calcium/calmodulin-dependent protein kinase kinase (CaMKK) under high levels of calcium, or transforming growth factor (TGF) activated kinase (TAK1) under the cell survival signals like the Toll-like receptors, interleukins and transforming growth factor-beta [44,45], can phosphorylate AMPK at Threonine 172 (T172), resulting in AMPK activation (Fig. 4) [34,45]. Under high levels of AMP or ADP which binds more strongly to the AMPK γ subunit, protein phosphatase 2C (PP2C), protein phosphatase 2A, and protein phosphatase-Mg2+/Mn2+ dependent 1E cannot dephosphorylate phospho-AMPK (T172), resulting in prolonged AMPK activation [46]. Sirtuin-1, a nicotinamide adenine dinucleotide-dependent deacetylase, deacetylates LKB1, which increases LKB1 activation, suggesting a link between the two different energy-sensing regulators, AMPK and Sirtuin-1 [47,48]. Another study shows that myristoylation of the AMPK β subunit is required for AMPK activation [49].

Numerous pharmacological compounds, including 5-Aminoimidazole-4-carboxamide ribonucleotide (AICAR), metformin, and 2-deoxy-d-glucose (2-DG), have been shown to activate AMPK [50]. An exciting study by Zong *et al.* (2019) unveiled that different levels of nutritional stress activate different pools of AMPK in a hierarchal and spatiotemporal manner in the cells, leading to varied phosphorylation of substrates that could have important physiological implications [51]. Nutrient and non-nutrient components of one's diet, such as α-linoleic acid, monounsaturated fatty acids, berberine, curcumin, and other natural compounds, can also regulate AMPK activation [52]. Various direct and indirect activators of AMPK have potential therapeutical significance. Their mode of action and structures have been previously described [53]. In recent studies, for instance, a pan-AMPK activator, O304, has been shown to suppress the dephosphorylation of AMPK, thereby increasing its activity. O304 has shown promising effects in both animals and phase IIa clinical trials in type II diabetes mellitus (Type II DM) treated with metformin, but its role as an anti-cancer compound remains deciphered [54]. Osteocalcin is a bone-derived hormone that regulates energy metabolism secreted by osteoblasts [55]. Treatment with uncarboxylated Osteocalcin (UnoC) to the mouse bone marrow-derived mesenchymal stem cells (BMSC) leads to osteogenic differentiation and inhibits adipogenesis through the AMPK-mediated pathway [56]. It has been shown that metformin, an AMPK activator, stimulates Osteocalcin expression in osteoblasts, implicating AMPK activation as a prospective osteoporosis treatment, but its role in cancer prevention is not explored much [57]. Similarly, metformin's cardioprotective and its anti-diabetic roles via AMPK activation have also been established, but its role as an anti-cancer compound is still being explored and warrants more studies [58]. Similar to these compounds, various other compounds are known to activate AMPK via various mechanisms described in Table 1, and their anti-cancer properties need to be explored in various types of cancers.

3.3. AMPK as a metabolic sensor

The potential to recognize metabolic stress is crucial for cellular adaptation to be efficient. Being the metabolic sensor, AMPK maintains energy homeostasis in response to multiple stresses by phosphorylating and regulating proteins involved in various physiological processes, including glucose, amino acid, and fatty acid metabolism. AMPK suppresses the energy-consuming processes while promoting the energy-producing pathways to maintain energy homeostasis and cell survival under stress conditions. For example, the rate-limiting enzyme of fatty acid synthesis, Acetyl-CoA carboxylase (ACC), converts acetyl Co-A to Malonyl Co-A, the raw material in fatty acid synthesis. AMPK phosphorylates ACC and inhibits its activity, decreasing the malonyl Co-A product, reducing the fatty acid synthesis, and preserving ATP [78,79]. AMPK also promotes β-oxidation by activating the expression of carnitine acyl-transferase I (CPT-1). CPT-1 converts the acyl-CoA into acetyl-CoA, which is then integrated into the TCA cycle and oxidized to produce ATP [80]. AMPK regulates cholesterol homeostasis by phosphorylating the 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMG-CoA reductase) at Serine 871 (S871). As part of the cholesterol synthesis, HMG-CoA reductase catalyzes the conversion of HMG-CoA

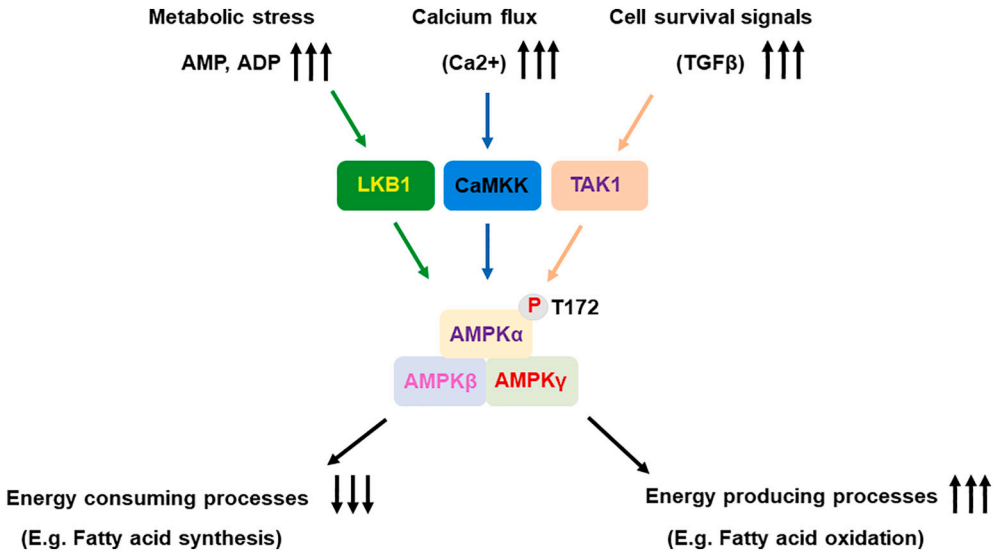

Fig. 4. AMPK activation mechanisms.
AMPK can be activated by metabolic stress (small molecule activators of AMPK include AICAR, 2-DG, which increases the AMP and ADP levels), hypoxia, or loss of ECM, calcium flux, and cell survival signals like transforming growth factor 1-beta (TGF-1β). Upon activation, AMPK suppresses the numerous biochemical processes that deplete energy, such as fatty acid synthesis, and promotes energy-producing pathways such as β-oxidation.

Table 1
List of AMPK activators and their mechanism of action in various cellular functions

Name	Mechanism	Target	Reference
AICAR	Acts as AMP analog	Binds with CBS domain of AMPKγ subunit	[59]
Benzimidazole (991)	Reduces the dephosphorylation of pAMPK (T172)	AMPKβ subunit	[60]
Berberine	Increases AMP	Complex I of ETC	[61]
Compound 13	Increases AMP	AMPKα1 subunit	[62]
Cryptotashinone	Increases AMP	Binds with mTOR	[63]
Curcumin	Increases AMP	Complex V of ETC	[64]
Epigallocatechin 3-gallate	Increases AMP	Complex V of ETC	[65]
Genistein	Increases AMP	Complex V of ETC	[66]
Ginsenoside Rb1	Increases AMP	Inactivates the Acetyl-CoA carboxylase (ACC)	[67]
Metformin	Increases AMP	Complex I of ETC	[57]
MT63-78	Reduces the dephosphorylation of pAMPK (T172)	AMPKβ subunit	[68]
Pioglitazone	Increases AMP	Complex I of ETC	[69]
PT1	Relieving the auto-inhibition	AMPKγ subunit	[70]
Quercetin	Increases AMP	Complex V of ETC	[71]
Resveratrol	Increases AMP	Complex V of ETC	[72]
Rosiglitazone	Increases AMP	Complex I of ETC	[73]
Salicylate	Binds with AMPKβ subunit, where A769662 binds	AMPKβ subunit	[74]
A769662	Reduces the dephosphorylation of pAMPK (T172)	AMPKβ subunit	[75]
Troglitazone	Increases AMP	Complex I of ETC	[76]
α-Lipoic acid	Increases Calcium flux	Targets CaMKK	[77]
Magnolol	Translocate the LKB1 to the cytoplasm	Targets LKB1	[63]
OS304	Reduces the dephosphorylation of pAMPK (T172)	Phosphatase 2C	[54]

into mevalonic acid [81].

Similarly, the metabolic functions of AMPK in glycolysis, TCA cycle, and other carbohydrate metabolism have been extensively reviewed [82]. It has also been revealed that AMPK plays an essential role in glycolysis by regulating enzymes such as phosphofructokinase (PFK), which promotes glycolysis in cancer cells. It has also been found that AMPK enhances glucose uptake in cancer cells via increasing glucose transporters (GLUT) expression.

4. AMPK acts as a tumor suppressor

Due to its ability to inhibit oncogenic mTOR signaling by directly phosphorylating tuberous sclerosis complex and the regulatory-associated protein of mTOR, AMPK was initially ascribed as a tumor suppressor [83,84]. Subsequently, another study by Penfold *et al.* supported this in prostate cancer cells, where AMPK could inhibit tumor growth by repressing de novo fatty acid synthesis [85]. However, another study showed that AMPK could block medulloblastoma tumor growth by mitigating the functions of a glioma-associated oncogene, a transcription factor, by directly phosphorylating it [86]. Mounting evidence further surfaced in the literature about the tumor suppressor functions of AMPK as it could block the cell cycle by controlling cell-cycle promoters. Phosphorylation of serine/threonine-protein kinase B-Raf (BRAF) at Ser729 by AMPK renders its binding partner from kinase suppressor of Ras (KSR1) to 14-3-3 proteins, resulting in blockade of cell cycle progression and thus cell proliferation [87]. Similarly, AMPK also impairs the cell cycle by inducing the expression of p27, p21, p53, and pRb proteins, which play a critical role in controlling cell growth and division [88,89].

Additionally, AMPK could exert its tumor suppressor functions by modulating epigenetic regulators. AMPK could suppress polycomb repressive complex-2 mediated oncogenic functions in breast and ovarian cancers by directly phosphorylating enhancer of zeste homolog 2 [90]. AMPK also activates the tumor suppressor function of Tet methyl cytosine dioxygenase 2, a methyl cysteine dioxygenase, by phosphorylating it at Ser99 [91]. AMPK can be ubiquitinated by oncogenic melanoma antigen gene-tripartite motif-containing protein 28 ubiquitin ligase and subsequently degraded by proteasome pathway, resulting in upregulation of mTOR signaling and autophagy in breast, lung, and colon cancers [92]. In support of numerous in vitro cellular models, research on mouse models has further strengthened the tumor suppressor functions of AMPK in various clinical settings. For instance, p53 null mice could survive longer in the presence of AMPKβ1 as its deletion could induce the early onset of T cell lymphoma [93,94]. Collectively these studies point out that AMPK has certain tumor suppressor functions (Fig. 5).

5. AMPK acts as a contextual oncogene

AMPK can function as either friend or foe in a context-dependent manner. In response to metabolic stress, AMPK activation increases energy-producing pathways while decreasing energy-consuming pathways, thus establishing energy homeostasis. To maintain energy homeostasis under metabolic stress, AMPK promotes various processes, including glycolysis, mitochondrial biogenesis, TCA cycle, and fatty acid oxidation. It promotes mitochondrial biogenesis through the AMPK-p38-peroxisome proliferator-activated receptor-gamma coactivator-1α (PGC1α) axis. It also functions as a tumor promoter in response to various stresses, such as hypoxia or glucose deprivation, and allows cancer cells to adapt metabolically to ensure growth and survival. Data from both *in vitro* and *in vivo* studies have shown a significant connection between AMPK activation and cancer progression. AMPK can phosphorylate various substrates under metabolic stress with varying outcomes as a kinase. For example, AMPK phosphorylates pyruvate dehydrogenase E1 Subunit Alpha at S295 and S314, increasing TCA cycle activity. This enhanced TCA cycle enables cancer cells to adapt to metabolic stress in the metastatic microenvironment [95,96]. AMPK also phosphorylates the mitochondrial fission factor (MFF) at S146 under energy stress, promoting mitochondrial fission. Under normal conditions, Inositol suppresses AMPK activation by binding to the AMPKγ subunit, whereas in energy stress conditions, the AMP: Inositol ratio increases, which relieves AMPK inhibition. AMPK then phosphorylates MFF to promote mitochondrial fission, enabling cancer cells to survive under energy stress [97]. The LKB1-AMPK signaling pathway has been shown to regulate glucose starvation-induced oxidative stress in cancers, inducing matrix metalloproteinase-9 (MMP-9) expression, apart from its roles in tumor invasion and metastasis also aids in angiogenesis [98]. AMPK also helps tumor cells deal with an energy crisis and promotes tumorigenesis by modulating nucleotide synthesis by phosphorylation-dependent conversion of phosphoribosyl pyrophosphate synthetase 1/2 hexamer to monomer, a protein that catalyzes the first reaction in nucleotide synthesis [99]. AMPK has also been shown to be a potential therapeutic target for pre-B acute lymphoblastic leukemia and glioblastoma [38,100]. It was reported in glioblastoma cells that when glucose is depleted, AMPK aids in the transport of acetyl-CoA synthetase 2 into the nucleus, where it is acetylated and promotes autophagy and carcinogenesis [101]. An accumulating body of data supports AMPK's overexpression or activation and carcinogenic actions in different cancers, and as a result, AMPK is considered a possible therapeutic target in cancer [34,102]. Here, we discuss AMPK activation and its possible role in the progression of various cancers (Fig. 6 and Table 2).

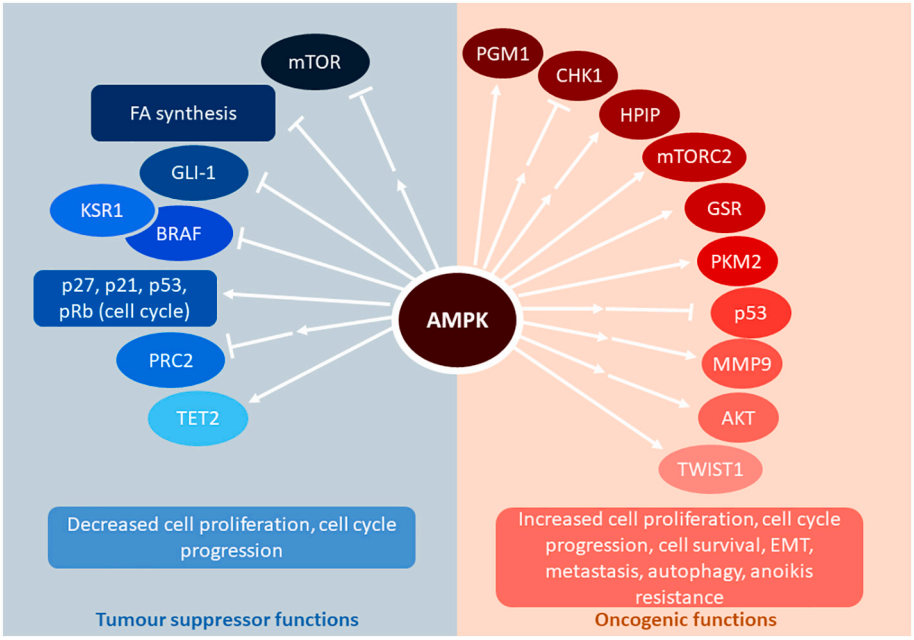

Fig. 5. Oncogenic and tumor suppressor functions of AMPK. AMPK could mediate these functions via either activation or suppression of downstream signaling proteins, as depicted. Arrow indicates activation, -| indicates inhibition or inactivation.

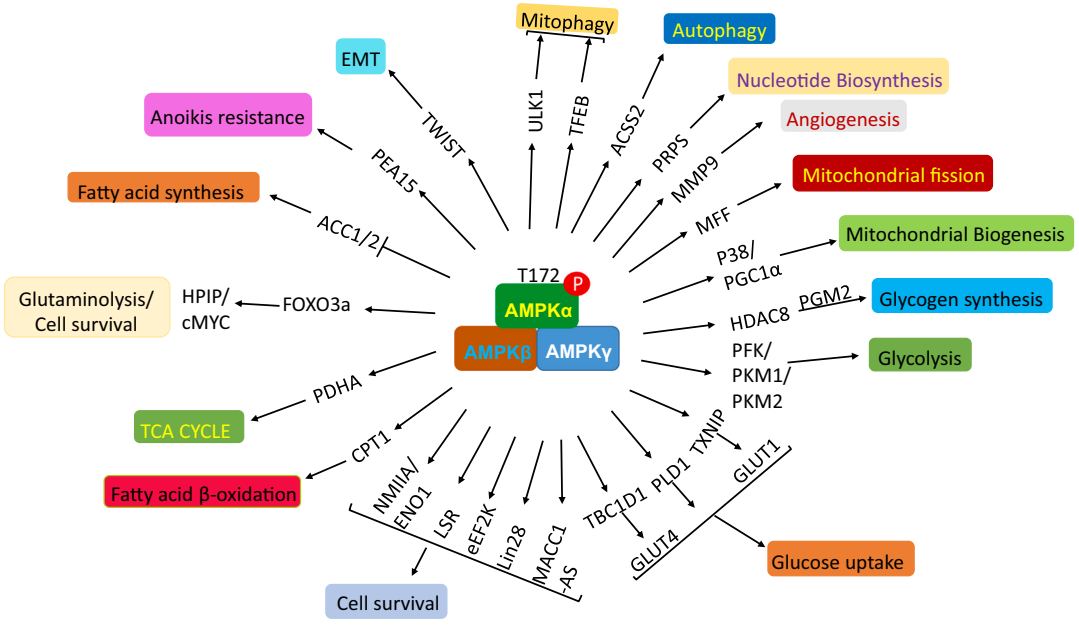

Fig. 6. AMPK signaling under metabolic stress.
AMPK acts as a metabolic sensor and contextual oncogene. Depending on the context and the cell type, AMPK phosphorylates and either activates or inhibits several substrates involved in glucose uptake, glycolysis, TCA cycle, fatty acid oxidation, glycogen synthesis, mitochondrial biogenesis, and autophagy to maintain energy homeostasis, oncogenic activity.

5.1. Lung cancer

Lung cancer is the most diagnosed type of cancer (11.4 percent of all cases) and the leading cause of cancer mortality worldwide (18% of all cancer deaths) (GLOBOCAN, 2020) [130]. The severity of lung cancer is determined by its aggressiveness and the milieu around the tumor. As mentioned earlier, AMPK promotes mitochondrial biogenesis during glucose deprivation in lung cancer cells through the AMPK-p38-PGC1α axis [12]. The pathway involving AMPK and pyruvate kinase M (PKM1) is shown to be essential for cell survival under hypoglycemic conditions. Depletion of PKM1 increases cell death even in the presence of AMPK, suggesting that the AMPK-PKM1 axis is required for cell survival [103]. Under glucose-limited conditions, AMPK is also known to regulate the expression of Phosphofructokinase-2 (PFK2), another glycolytic enzyme that converts the fructose 6-phosphate to fructose-2,6-bisphosphate (F-2,6BP) [104]. It is essential to maintain the reduced nicotinamide adenine dinucleotide phosphate levels during glucose deprivation, matrix detachment growth, and anchorage-independent growth by inhibiting the fatty acid synthesis and increasing fatty acid oxidation [105]. While LKB1-AMPK signaling maintains energy and oxidative stress

Table 2
List of AMPK-mediated pathways in the progression of various cancers under metabolic stress

Cancer type	Pathway	Phenomenon regulated by AMPK	References
Lung	AMPK-p38-PGC1α	Mitochondrial biogenesis	[12]
	AMPK-PKM1	Glycolysis	[103]
	AMPK-PFK2	Glycolysis	[104]
	AMPK-ACC1 and 2	Inhibiting the fatty acid synthesis and promoting β-oxidation	[105]
	MMP-9 induction	Increases the metastasis	[98]
	AMPK-PGM1	Increases the glycogenolysis	[106]
Breast	CREB/PGC1α/ERR	Glycolysis	[107]
	GLUT1, GLUT4, SLC1A5	Glucose and glutamine uptake	[108]
	CPT1C	Fatty acid oxidation	[109]
	AMPK-CHK1-ubiquitin	Reduced cell cycle arrest	[110]
	AMPK-SKP2-AKT	Cell survival	[111]
	AMPK-PEA15	Anoikis resistance	[112]
	AMPK-PHLPP2-AKT	Autophagy and anoikis resistance	[113]
	AKT-PP2C-AMPK	Matrix reattachment	[113]
	AMPK-AKT feedback loop	Driver for heterogeneity and phenotypic switching	[114]
	AMPK-TWIST	EMT and metastasis	[115]
	AMPK-FOXO3a-HPIP	Glutamine import and glutaminolysis	[116]
Prostate	AMPK-GLUT1	Androgen synthesis and glucose stress resistance	[117]
	AMPK-RAC-PI3K	Macropinocytosis and cell survival	[118]
Hepatocellular carcinoma	HBx-CaMKK-AMPK-ACC	Activation of β-oxidation	[119]
	AMPK-mTORC2-AKT	Cell survival	[120]
Renal	AMPK-PKM2	Glycolysis and pro-tumor activity	[121]
	CaMKK-AMPK-p53	Increase in autophagy	[122]
	HSP60-AMPK	Warburg effect	[123]
Colorectal	Increased AMPK activity	Cell survival	[124]
	NMIIA/ENO1-AMPK-mTOR	Cell survival	[125,126]
Gastric	MACC1-AS1-AMPK/Lin28	Cell survival	[127]
medulloblastoma and glioblastoma multiforme	AMPK-eEF2K	Cell survival	[128]
Ovarian	LSR/LKB1/AMPK	Cell survival	[129]

homeostasis, it also has the ability to promote cancer progression and metastasis under metabolic stress by inducing MMP-9 [98]. As a serine/threonine kinase, AMPK also contributes to cell survival by phosphorylating specific proteins involved in glycolysis and glycogen synthesis. For example, AMPK promotes the expression of phosphoglucomutase 1 (PGM1), a glycogen metabolizing enzyme catalyzing the bi-directional interconversion of glucose 1-phosphate and glucose 6-phosphate via phosphorylating histone deacetylase 8 in lung cancer cells subjected to glucose stress [106]. These findings indicate that AMPK acts as a tumor promoter in lung cancer under metabolic stress.

5.2. Breast cancer (BC)

BC is one of the most prevalent gynecological cancers worldwide. Because of its heterogeneous nature, due to the expression of various types of receptors, more sophisticated strategies for overcoming nutritional stress were found in cancer cells. Typically, tumor cells reap the benefits of metabolic transformation by initiating the Warburg effect, which is a process in which cancer cells prefer glucose over oxygen, as previously explained. Because cancer cells have increased glycolysis, targeting glycolysis with inhibitors such as 2-DG has a beneficial effect; however, AMPK, a contextual oncogene that rescues cancer cells via various pathways such as cAMP-responsive element binding protein 1-PGC1α estrogen-related receptor alpha (CREB/PGC-1/ERRα), has a different effect. As a result, glycolysis and AMPK inhibitors have a synergistic impact on killing cancer cells [107]. Cancer cells require more glucose under normal and metabolic stress conditions due to their higher glycolytic rate. Consequently, cancer cells rewire their pathways, resulting in increased expression of glucose transporters such as glucose transporter 1 (GLUT1) and glucose transporter 4 (GLUT4) and glutamine transporters such as SLC1A5 [108]. Cancer cells also respond to stress by increasing the activity of carnitine palmitoyltransferase 1C (CPT1C), an enzyme required for fatty acid oxidation and ATP generation [109]. Aside from metabolic roles, AMPK is vital in post-translational modifications like phosphorylation and ubiquitination. When cells are subjected to glucose stress, checkpoint kinase 1 (CHK1) is ubiquitinated following phosphorylation by AMPK as part of an adaptive process to ensure cell survival [110]. In response to metabolic stress, AMPK activates AKT by phosphorylating S-phase kinase-associated protein 2 (SKP2) at S256, activating its ubiquitination activity, and subsequently, this ubiquitin ligase activates AKT, driving carcinogenesis under metabolic stress [111].

Apart from metabolic stress, cancer cells often experience anoikis (in Greek, homelessness), an apoptotic process that occurs when cells lose interaction with the extracellular matrix. Anoikis resistance drives tumor progression and also metastasis [131]. Cancer cells adopt specific pathways to prevent anoikis, such as AMPK activation by upstream kinases. AMPK promotes anchorage-independent growth or anoikis resistance in breast cancer cells by phosphorylating a novel substrate, proliferation, and apoptosis adaptor protein 15 (PEA15) at S116 [112]. Under suspension conditions in breast cancer cells, researchers discovered that increased AMPK levels triggered the AKT phosphatase, PH domain, and leucine-rich repeat protein phosphatase (PHLPP2), which resulted in a reduction of active AKT levels, ensuring AMPK-mediated autophagy and anoikis resistance. On the contrary, upon attachment to the substratum, AKT activation was triggered, which then activated PP2C, an AMPK phosphatase that decreased the phosphorylated AMPK, establishing a double-negative feedback loop between the two proteins, AKT and AMPK [113]. In 2021, the same group expanded on their findings, demonstrating that the two phenotypic states created by the AMPK-AKT feedback loop, $pAKT^{high}/pAMPK^{low,}$ and $pAMPK^{high}/pAKT^{low}$, could switch between the two states, acting as a driver for heterogeneity and phenotypic switching in a population of adherent breast cancer cells [114]. Besides its role in cell survival and proliferation, AMPK is also implicated in breast cancer cell invasion and migration. When AMPK is activated, the expression and nuclear localization of twist family bHLH transcription factor 1 (TWIST-1), a transcription factor involved in epithelial-to-mesenchymal transition (EMT), is enhanced. As a result, the EMT and metastasis activity of breast cancer cells is increased [115]. Recent work from our group revealed that AMPK promotes hematopoietic PBX1-interacting protein (HPIP)

induction under metabolic stress through Forkhead Box O3 (FOXO3a)-mediated transcriptional upregulation. This induced HPIP enhances cell survival under metabolic stress conditions. This study demonstrated that HPIP forms a transcription complex with cMYC and promotes the transcription of glutamine importer and glutamine metabolic enzymes, hence promoting glutamine import and glutaminolysis. Interestingly, this study also provided clues on how cancer cells undergo apoptosis in response to chronic glucose stress. When cancer cells are subjected to chronic glucose stress, HPIP is degraded via ring finger protein 2 (RNF2) dependent ubiquitination and proteolysis, culminating in cell death via apoptosis [116]. Whether AMPK activates RNF2 under chronic glucose stress is one of the caveats of this study, and thus further investigation is warranted. This study highlights the importance of AMPK in cell survival under metabolic stress and implies that AMPK has a protumorigenic role in breast cancer. Based on these, when breast cancer tumors are exposed to metabolic stress, AMPK seems to function as a tumor promoter.

5.3. Prostate cancer

According to research conducted by H.U. Park *et al.*, AMPK was active in 40% of prostate cancer tissues. The role of AMPK in cell survival under energy-depleted circumstances was found in the same research utilizing AMPK inhibition (Compound C) or AMPK depletion (using gene-specific siRNA). This resulted in the cells being more susceptible to apoptosis in energy-depleted conditions, indicating that it functions in cell survival [117]. Glucose deprivation enhances AMPK-mediated androgen synthesis in PCa cells. Because of an increase in GLUT1 expression, followed by an increase in glutathione levels, androgen-sensitive PCa cells become even more resistant to glucose depletion-induced cell death [118]. When cells are starved for glucose, they rearrange their metabolic pathways and adopt specific additional survival strategies. PTEN-deficient prostate cancer cells, for example, activate the AMPK pathway to grow in low-nutrient conditions by scavenging necrotic debris and extracellular protein through macropinocytosis [132]. Based on the evidence presented above, AMPK seems to function as a tumor promoter in prostate cancers when the tumor is exposed to metabolic stress.

5.4. Hepatocellular carcinoma (HCC)

HCC is the fifth most common kind of cancer, with a high recurrence rate and a poor prognosis. The disease's development is influenced by many mechanisms, including the AMPK pathway. It has been shown that the Hepatitis B virus (HBV) X protein (HBx) activates AMPK and ACC through a calcium-dependent CaMKK pathway, which is needed for the activation of fatty acid oxidation in HCC and is known to enhance cell survival under metabolic stress [119]. AMPK phosphorylates one of the components of the mTORC2 complex, causing the mTORC2-AKT axis to be activated and, as a result, increasing the survival of liver cancer cells under metabolic stress [120]. Interestingly, it has been shown that when glucose is restricted in HCC, AMPK arrests cells in the G0/G1 phase, eventually leading to apoptosis. PKC initially favors this but subsequently inhibits AMPK activation, alleviating apoptosis [133].

5.5. Renal carcinoma

Metformin, which is extensively used to treat Type 2 diabetes, has anti-cancer properties, but its function in cell proliferation is controversial. Recently, it was reported that metformin-mediated AMPK activation increases renal cancer cell proliferation during glucose deprivation through its interaction with pyruvate kinase M2 (PKM2), suggesting that metformin-mediated AMPK activation has pro-tumor activity [121]. In another research, AMPK is activated in response to increased calcium levels in cells owing to increased autophagy, which destroys p53 and eventually increases clear cell renal carcinoma proliferation (ccRCC) [122]. Another study found that down-regulation of heat shock protein 60 impairs the function of the respiratory complex I, resulting in excessive reactive oxygen species (ROS) production and AMPK activation, which increases the Warburg effect in ccRCC cells and promotes cell proliferation and metastasis [123].

5.6. Various other cancers

Elevated levels of AMPKα were also observed in colorectal cancer (CRC) patients with poor prognoses [124]. Activating the AMPK/mTOR pathway by non-muscle myosin IIA (NMIIA) or enolase-1 (ENO1) was reported in CRC [125,126]. In another study AMPKα1 regulates glutathione reductase (GSR) phosphorylation, perhaps via residue Thr507, which increases its activity. This increased GSR leads to the redox homeostasis in CRC, leads to its progression under metabolic stress [124]. In gastric cancer, MET Transcriptional Regulator-antisense RNA-1 (MACC1-AS1) is reported to activate the AMPK/Lin28 pathway to confer cell survival in response to metabolic stress [127]. AMPK also supports the survival of cMYC-positive melanoma cells, but it does so via suppressing oxidative stress [128]. In human medulloblastoma and glioblastoma multiforme, AMPK increases cell survival in response to acute stress by activating eukaryotic elongation factor 2 kinase (eEF2K), limiting translation elongation and eEF2K expression, which correlates with increased overall survival [134]. The LSR/LKB1/AMPK pathway is essential in ovarian cancer cell survival and tumor formation [129]. According to these lines of evidence, AMPK activation or expression is increased in various cancers, and its expression regulates cancer growth in both normal and metabolic stress conditions.

5.7. Targeting AMPK in cancers

Because AMPK is essential for cell survival under metabolic stress, combining anti-metabolic drugs with AMPK inhibitors or genetically depleting AMPK is often considered an effective therapy. Despite compound C (CC) /Dorshomorphin being known to inhibit AMPK effectively, they also have the possibility of inhibiting other kinases. For example, CC can also inhibit bone morphogenetic protein receptor type I [135] and activin-like kinase receptors 2, 3, and 6 [136]. Owing to the lack of AMPK inhibitors, researchers are looking into developing novel therapeutic compounds that specifically target AMPK. In addition to small molecule inhibitors, AMPK can be targeted by small interfering RNA (siRNA), short hairpin RNA (shRNA), or guided RNA (gRNA), which selectively deplete AMPK. According to recent research, gRNA may target AMPK activation and cancer. Saito *et al.* reported a combination of AMPK depletion utilizing gene-specific gRNA and metabolic stress inhibitors that substantially suppress acute myeloid leukemia growth by inducing oxidative stress and DNA damage [137]. Several studies have shown that AMPK acts as a context-dependent oncogene and can be targeted using small molecular inhibitors. Recent research suggests that inositol acts as an endogenous inhibitor of AMPK. Under normal conditions, inositol binds to the AMPKγ subunit, competing with AMP, inhibiting AMPK activation. However, under energy stress, decreased enzymatic activity of Inositol monophosphatase 1/2 leads to reduced levels of inositol, which consequently increases the AMPK activation. Hence, a combination of inositol and metabolic drugs may have potential therapeutic effects in treating cancers showing elevated AMPK activation. Osimertinib, an epidermal growth factor receptor and a tyrosine kinase inhibitor, is used to treat colorectal cancer (CRC); however, it has several side effects. It stimulates various pathways such as activation of the RAS–mitogen-activated protein kinase or RAS–-phosphatidylinositol 3-kinase (PI3K) pathways or LKB1-AMPK pathway, or amplification of *MET/HER2* genes which are responsible for CRC drug resistance. As a result, treating CRC with Osimertinib in combination with LKB1-AMPK inhibitors or the described pathway inhibitors has a potential therapeutic effect [138]. By phosphorylating various substrates, including PFK2 and 6-Phosphofructo-2-Kinase/Fructose-2, 6-

Bisphosphatase 3 (PFKFB3), AMPK promotes glycolysis. Because phosphorylation of PFKFB3 by AMPK leads to increased expression of PFKFB3, which promotes F-2,6BP, an allosteric activator of glycolysis, therefore a combinatorial therapy of AMPK and glycolysis inhibitors may be beneficial in cancer therapy [139]. Autophagy is also necessary for tumor cell survival in the face of metabolic stress. Consequently, targeting autophagy is another approach in cancer treatment, although chemoresistance is a significant obstacle. AMPK and several other pathways are known to mediate chemoresistance. Increased glycolysis, seen in several cancers, requires AMPK activation. Telmisartan, a novel AMPK phosphorylation inhibitor, suppresses autophagy flux, ultimately generating reactive oxygen species and stimulating TNF-related apoptosis-inducing ligand expression in lung cancer [140]. All these lines of evidence suggest that targeting AMPK using a single agent or in a combination of drugs that induce resistance through an AMPK-mediated pathway has a potential benefit in cancer treatment.

6. Pitfalls in cancer therapy while using AMPK activators or inhibitors

AMPK is an ingenuous double-edged sword as it carries tumor suppressor function on the one hand and oncogenic activity in specific contexts. AMPK acts as a tumor suppressor before oncogenic insult occurs. However, AMPK can exert either tumor-suppressive or promoting functions after the onset of cancer, depending on the cell type or state [141]. This notion is supported by a wide range of studies, including cellular and in vivo mouse models accompanied by various clinical settings. This implies that AMPK should be considered a potential therapeutic target cautiously and judiciously. The way forward for AMPK to be perceived as a potential therapeutic candidate in oncology includes considering the mutational spectrum of cancer, as p53 mutant tumor growth could be suppressed by deletion of AMPKβ1 [93]. Other factors that influence the potential therapeutic candidature of AMPK include the nature of cancer, its metabolic status, for instance, if it's glycemic or nonglycemic, and the associated stresses such as glucose stress or hypoxic driven cancer progression as HIFα1 is known to activate AMPK signaling. It also includes the nature of the chemical agents that could modulate AMPK activity in treating various cancers. Metformin, which is being used to treat type II Diabetes Mellitus (DM), synergistically works with specific miRNAs such as miR-365 to impede tumor growth via the AMPK pathway [142]. Metformin can also exert anticancer effects by inhibiting the sonic hedgehog signaling pathway in breast cancer, dependent on AMPK [143]. Similar observations were also found in gastric cancer cells [144]. These studies imply that Metformin, an anti-diabetic agent, has an advantage over other anti-diabetics due to its anticancer activity. Besides Metformin, several small molecular chemical agents are known to showcase their anti-tumor activities in various cancers. For example, N-cystaminylbiguanide (MC001), a novel biguanide small molecule derivative, also exhibits anti-tumor effects by activating AMPK [145]. Similarly, Eupatilin shows an anti-cancer effect against pancreatic cancer cells via glucose uptake inhibition, AMPK activation, and cell cycle arrest [146]. Yet another agent, ASP4132, also suppresses tumour growth in non-small lung cancer by activating AMPK [147]. Together these reports imply that AMPK has mixed favour in cancer therapy.

7. Conclusions and future directions

Evidence supporting metabolic rewiring for cancer progression is mounting. It is well documented that AMPK signaling is intertwined in altered metabolism-driven cancers. Also, there is abundant evidence regarding the oncogenic role of AMPK in various cancers. Therefore, combining anti-metabolic drugs with AMPK inhibitors is often considered an effective therapy in the arsenal of therapeutic treatments for cancer. Though phosphorylation at Threonine 172 (T172) has been an important regulatory mechanism for activating AMPK, other potential mechanisms controlling AMPK activity or protein levels such as micro RNAs (miRNAs), long non-coding RNAs (lncRNAs), circular RNAs (circRNAs) are to be focused on and explored as alternative therapeutic purposes. The availability of the crystal structure of AMPK has opened several new avenues for bioinformaticians and synthetic chemists to investigate and test for potential AMPK inhibitors. This calls for exploring novel small molecule inhibitors of AMPK. The future holds promising scope in expanding our horizons with respect to AMPK as a potential therapeutic target to treat various cancers.

8. Methodology

Breast, Lung, Colorectal, Prostate, Stomach, Liver, Cervix, Oesophagus, Thyroid, and bladder cancers are among the top ten malignancies in terms of incidence, according to GLOBOCAN (2020) [130]. We choose various cancers along with the most aggressive cancers mentioned above for our study to check the expression of AMPK isoforms using GEPIA data sets [36]. We used Log2FC-cutoff as 1, p-value cut-off as 0.05, and then used TCGA normal and GTEx data sets to compare with cancer data sets. We used cBioPortal [37,148] for the mutations and other analyses and then represented images directly or generated using the GraphPad Prism version 8.0.0 for Windows.

Author contributions

VP and BM – Conceptualization; VP – Data curation; Formal analysis; Validation; BM – Funding acquisition; Supervision; Project administration; VP, YGM – Investigation, Methodology; VP, YGM, and BM – Writing an original draft, review, editing, revision and approved the final version of the manuscript.

Declaration of Competing Interest

The authors declared there is no conflict of interest

Data availability

Data will be made available on request.

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