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AMPK Alchemy: Therapeutic Potentials in Allergy, Aging, and Cancer

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Abstract

All cells are equipped with intricate signaling networks to meet the energy demands and respond to the nutrient availability in the body. AMP-activated protein kinase (AMPK) is among the most potent regulators of cellular energy balance. Under ATP -deprived conditions, AMPK phosphorylates substrates and affects various biological processes, such as lipid/glucose metabolism and protein synthesis. These actions further affect the cell growth, death, and functions, altering the cellular outcomes in energy-restricted environments. AMPK plays vital roles in maintaining good health. AMPK dysfunction is observed in various chronic diseases, making it a promising target for preventing and alleviating such diseases. Herein, we highlight the different AMPK functions, especially in allergy, aging, and cancer, to facilitate the development of new therapeutic approaches in the future.

Key Words: AMPK, Allergy, Aging, Cancer

INTRODUCTION

Cellular responses to various metabolic challenges are governed by molecular signaling pathways involved in energy homeostasis maintenance. AMP-activated protein kinase (AMPK) is an evolutionarily conserved serine/threonine kinase that is a critical regulator of cellular energy homeostasis and nutrient metabolism (Hardie, 2011). Moreover, AMPK is an indispensable enzyme under stressful conditions, such as energy imbalance conditions. Three kinases initiate AMPK activation. i. At high AMP:ATP and ADP:ATP ratios, AMP and ADP bind to AMPK, inducing liver kinase B1 (LKB1)-driven phosphorylation (Woods *et al*., 2003; Shaw *et al*., 2004; Carling *et al*., 2011). ii. In energy-deficient conditions, intracellular calcium levels are increased, activating the calcium/calmodulin-dependent protein kinases to phosphorylate AMPK (Shaw *et al*., 2004). iii. Transforming growth factor-β-activated kinase also activates AMPK (Shaw *et al*., 2004). Initially, AMPK was identified as an enzyme catalyzing the phosphorylation-mediated inactivation of major lipogenic enzymes, such as acetyl-CoA carboxylase (ACC) (Carlson and Kim, 1973) and 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase (HMGCR) (Beg *et al*., 1973), to inhibit *de novo* fat synthesis. AMPK elevates the expression levels of glucose transporters on the plasma membrane to enhance glucose uptake, supporting glucose-6-phosphate generation, and facilitating multiple biochemical reactions. Moreover, AMPK regulates protein synthesis, mitochondrial biogenesis, and autophagy by inhibiting the mammalian target of rapamycin (mTOR), peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1α), and unc-51-like autophagy-activating kinases 1, respectively (Hardie *et al*., 2012). Owing to its multifaceted physiological roles, AMPK has emerged as a compelling therapeutic target for AMPK dysfunction-related diseases. Notably, reduced AMPK activity is associated with the development of cardiovascular diseases (Daskalopoulos *et al*., 2016), neurodegenerative disorders (Domise and Vingtdeux, 2016; Marinangeli *et al*., 2016), allergies (Pandit *et al*., 2022), and cancer (Hardie, 2013; Luo *et al*., 2013; Li *et al*., 2015; Pokhrel *et al*., 2021; Pandit *et al*., 2023), suggesting the therapeutic potential of modulating AMPK activity. Many attempts have been made to activate AMPK using various chemicals, such as A769662,

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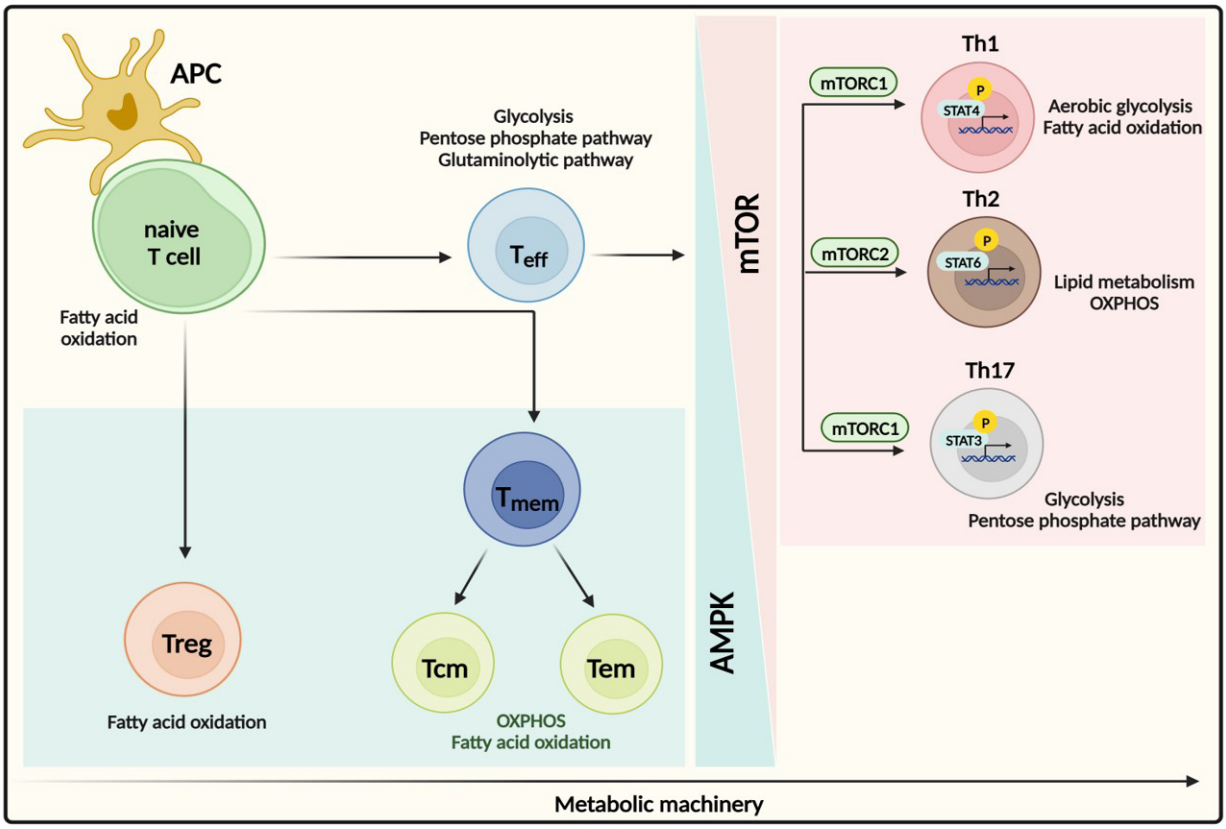

Fig. 1. AMPK regulates metabolic fitness of T cells in resting state. Naive T cells exert elevated AMPK activity to utilized fatty acid oxidation (FAO) for their survival. Upon antigen stimulation through interacting with antigen-presenting cells (APC), naive T cells undergo metabolic reprogramming to support the generation of effector T cells, transforming their energy metabolism to glycolysis (mTOR), the pentose phosphate pathway (PPP), and the glutaminolytic pathway. When they enter memory status, AMPK activity re-emerges to reduce mTOR, followed by a metabolic shift towards oxidative phosphorylation (OXPHOS) and FAO. Moreover, the impacts of mTOR and AMPK vary among the subsets of CD4+ T cells. mTORC1 and mTORC2 enhances the differentiation and function of Th1/Th17 and Th2, respectively, whereas AMPK facilitate the differentiation, stability, and function of Treg cells. The figure is created with BioRender.com.

compound 991, metformin, 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR), and other non-steroidal anti-inflammatory drugs; however, their efficacy needs to be validated further in human patients (Rattan *et al*., 2005; Yao *et al*., 2012; Yue *et al*., 2014). In this review, we discuss the mechanism by which AMPK-mediated signaling/metabolism affects disease progression and suggest AMPK exploitation as a potential therapeutic intervention for various conditions, especially allergies, aging, and cancer.

AMPK AND T CELL-MEDIATED DISEASES

AMPK and T cells

Upon exposure to environmental or immunological cues, AMPK is activated to regulate the metabolic pathways promoting the growth and functions of T cells (Blagih *et al*., 2015). Originally, T cell receptor (TCR)/CD3 stimulation and Ca^{2+} signaling were only identified as AMPK activators (Tamas *et al*., 2006). However, subsequent studies revealed that TCR/CD28 stimulation further potentiates AMPK activity (Zheng *et al*., 2009; MacIver *et al*., 2011). Unlike their elevated levels in the priming stage, AMPK levels gradually declines as T cells enter the effector phase (Tamas *et al*., 2006; Kishton *et al*., 2016).

As an essential component of adaptive immunity, T cells are integral for host defense against various threats via phenotype conversion in response to environmental stimuli (Pennock *et al*., 2013). This phenotypic complexity is linked to the metabolic diversity of T cells (Wang and Green, 2012). In the steady state, naïve T cells require tonic stimuli for their survival, which increases AMPK activity for fatty acid oxidation. However, after complete activation, mTOR is boosted to induce the differentiation of effector T cells, which metabolically rely on the glycolysis, pentose phosphate, and glutaminolysis pathways (Wang *et al*., 2011; Gerriets and Rathmell, 2012). In terms of memory, AMPK significantly increases the mTORC1 activity in T-cells, modulating mitochondrial metabolism for long-term survival (Fig. 1) (Merrill *et al*., 1997). AMPK also modulates the metabolic needs of quiescent T cells by inhibiting fatty acid synthesis and stimulating fatty acid oxidation via phosphorylation and inactivation of ACC1 and ACC2, respectively (Merrill *et al*., 1997). Regardless of the T cell status, glucose deprivation actively triggers AMPK induction to switch glycolytic metabolism to glutamine-dependent oxidative phosphorylation (Blagih *et al*., 2015). Loss of AMPKα1 in T cells reflects suboptimal metabolic fitness characterized by the reduction of glucose uptake and mitochondrial function, causing unresponsiveness of T cells against viral and bacte-

rial infections (Blagih *et al*., 2015). Under glucose-sufficient conditions, effector $CD4^+$ T cells have low levels of AMPK, and mTOR is relieved from negative regulation (Merrill *et al*., 1997) (Fig. 1). The two components of mTOR, mTOR complexes 1 (mTORC1) and 2 (mTORC2), activate the signal transducers and activators of transcription (STATs), further promoting type 1 T helper (Th1), type 2 T helper (Th2), and type 17 T helper (Th17) differentiation (Fig. 1) (Gao *et al*., 2009). In contrast to effector T cells, regulatory T cells (Tregs) intrinsically express high levels of AMPK, promoting mitochondrial metabolism, such as fatty acid oxidation, rather than glycolysis (Fig. 1) (Michalek *et al*., 2011; Kempkes *et al*., 2019). Extrinsic AMPK activation by metformin preferentially induces Tregs (Michalek *et al*., 2011), and LKB1, an AMPK activator, maintains the mitochondrial fitness of Tregs (He *et al*., 2017). AMPK also contributes to Tregs stability (Pokhrel *et al*., 2022). Collectively, the balance between AMPK and mTOR orchestrates T cell transition into distinct subsets Th1, Th2, Th17, and Tregs and status (naïve, effector, and memory cells) by satisfying the metabolic requirements for each setting, implying that AMPK targeting may induce specific T cells to combat specific diseases.

AMPK and allergy

Allergies are hypersensitive immune responses to innocuous substances inducing Th2 responses and mast cell degranulation, leading to symptoms, such as itchy skin, rash, cough, and diarrhea (Kay, 2001). Although there is a paucity of research on the association between AMPK and allergies, metabolic sensors may play essential roles in vigorously growing cells. In the following section, we discuss the recent reports on the effects of AMPK on allergies.

mTORC2, an mTOR complex, is a tyrosine kinase that phosphorylates AKT, serum glucocorticoid-regulated kinase 1, and protein kinase C to modulate cell survival and metabolism; however, it is less elucidated than mTORC1 (Szwed *et al*., 2021). Interestingly, AMPK plays conflicting roles in mTORC2 regulation. AMPK may directly activate mTORC2 to support cell survival under energy- or growth factor-restricted conditions (Kazyken *et al*., 2019, 2021). This may be due to the AMPK-dependent phosphorylation of mTORC2, as observed in mouse embryonic fibroblasts and cancer cell lines (Gao *et al*., 2016). Conversely, activated AMPK may repress both the mTORC1 and mTORC2 signaling pathways in myeloma cells (Wang *et al*., 2018) and non-small cell lung cancer cells (Kang *et al*., 2015). Notably, in CD4 T cells, AMPK represses mTORC2, which negatively regulates the suppressor of cytokine signaling 5 (SOCS5). Enhanced SOCS5 expression by AMPK activation suppresses STAT6, which in turn, hampers GATA-binding protein 3-induced Th2 differentiation and allergic inflammation (Pandit *et al*., 2022) (Fig. 2). Consis-

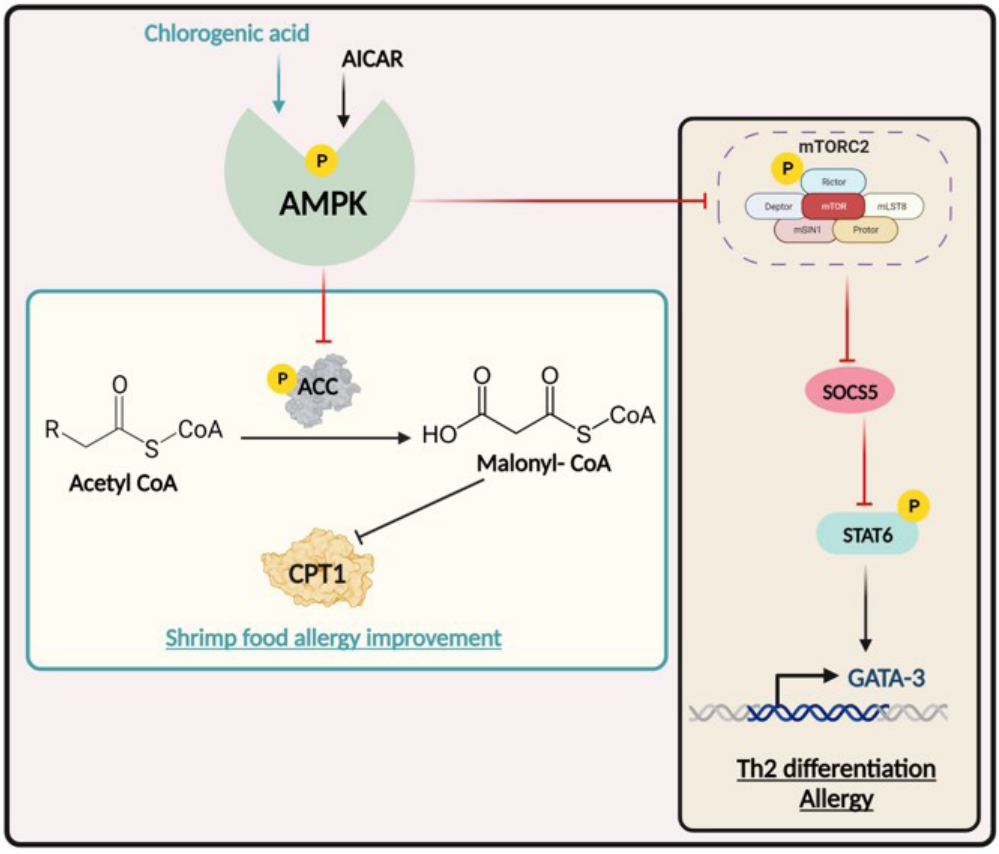

Fig. 2. AMPK ameliorates allergy severity. AMPK-mediated inhibition of mTORC2 leads to increased SOCS5 expression, which represses STAT6 to hamper GATA3-induced Th2 differentiation and allergy exacerbation. In this context, AMPK activators, chlorogenic acid and AICAR, phosphorylate Acetyl-CoA carboxylase (ACC), altering the equilibrium between Acetyl-CoA and Malonyl-CoA, which subsequently impacts the activity of CPT-1. These treatments alleviate shrimp allergy in mouse model. The figure is created with BioRender.com.

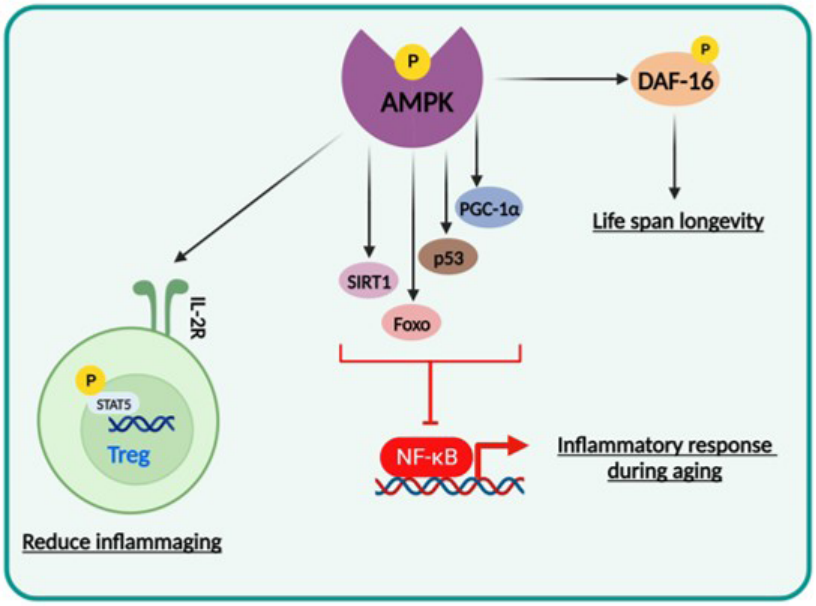

Fig. 3. AMPK mediates anti-aging effects upon AMPK activation. Treg cells show elevated IL-2Rα signaling, which fortifies the function of STAT5. This leads to amplification of IL-2 signaling to enhance the stability and function of Treg cells. Additionally, AMPK inhibits a critical regulator of inflammation, NF-κB, by inducing the activity of SIRT-1, p53, FOXO, and PGC-1α. Moreover, AMPK targets FOXO and DAF-16 to increase lifespan in C. elegans and mammals. The figure is created with BioRender.com.

tently, chlorogenic acid, a polyphenol in plants, alleviates the disease severity of shrimp allergy in a mouse model in which chlorogenic acid activates AMPK, subsequently modulating its targets, ACC and carnitine palmitoyl transferase 1 (Yun *et al*., 2022) (Fig. 2).

AMPK and aging

Aging is a multifactorial process in which the metabolic pathways are drastically altered. As a metabolic sensor, AMPK exerts antiaging effects (Stancu, 2015; Ge *et al*., 2022; Pokhrel *et al*., 2022). Inflammation is a hallmark of aging that increases the levels of pro-inflammatory markers in the body. Typically, Tregs maintain immune homeostasis by restricting excessive immune responses; however, in the elderly, Tregs lose their inhibitory functions, leading to an increased aging-related autoimmune risk (Jagger *et al*., 2014). However, AMPK activation in Tregs induces interleukin-2 (IL-2) signaling to amplify STAT5 phosphorylation (Fig. 3). This enhances the expression of IL-2 receptor α chain to amplify the stability and functions of Tregs, consequently repressing inflammaging (Pokhrel *et al*., 2022). Aging also elevates nuclear factor-kappa B (NF-κB) signaling, a key pathway in inflammation (Salminen and Kaarniranta, 2009; Tilstra *et al*., 2011). AMPK induces several anti-inflammatory mediators, such as sirtuin 1, p53, forkhead box protein O (FoxO), and PGC-1α, to hamper NF-κB activity to resist inflammation-induced stress for enhanced longevity (Salminen *et al*., 2011) (Fig. 3). Furthermore, AMPK extends the lifespan of Caenorhabditis elegans and mammals in a FoxO-dependent manner (Greer *et al*., 2007a). AMPK directly phosphorylates FoxO/daf-16 to induce the expression of long-lived genes that retard aging-related diseases in *C. elegans* (Greer *et al*., 2007a). In mammals, AMPK triggers FoxO3 transcriptional activity, regardless of its localization, which also enhances longevity (Greer *et al*., 2007b).

AMPK and tumor-infiltrating T cells

TME is comprised of various immune, endothelial, and tumor cells. Tumor cells outcompete other cells for nutrients to create an energy-depleted environment; however, unlike in normal tissues, AMPK is repressed in most tumor tissues (Konieczny *et al*., 2023). This abnormal regulation of AMPK in tumors may indicate that tumor cells forcefully diminish AMPK activity for survival. Deletion of AMPKα1 in mouse leads to cytotoxicity in $CD8^+$ T cells by restraining interferon- γ/granzyme B secretion and tumor infiltration, further exacerbating tumorigenesis (Fig. 4) (Rao *et al*., 2015). AMPK exerts its anti-tumor effects by modulating the expression of the immune checkpoint programmed cell death protein 1 (PD-1). Tregs express high levels of PD-1 to inhibit programmed death ligand 1 (PD-L1)-expressing effector T-cells. Loss of AMPK in Tregs promotes PD-1 expression via the HMGCR/ mitogen-activated protein kinase (MAPK)/glycogen synthase kinase-3 beta axis, thereby accelerating tumor growth (Pokhrel *et al*., 2021) (Fig. 4). Ligation of PD-1 prevents the activation of $CD4^+$ T cells. Methionine deprivation in the tumor environment down-regulates AMPK, elevating the expression of PD-1 in $CD4^+$ T cells by increasing the endoplasmic reticulum (ER) stress and spliced form of the X-box binding protein 1 transcript levels (Fig. 4) (Pandit *et al*., 2023). Genetic deletion of *AMPK* exacerbates tumor progression, with more $PD\text{-}1^{high}$ $CD4^+$ T cells in tumor tissues than in wild-type tissues in mice (Pandit *et al*., 2023). Notably, enforcing AMPK activity in combination with PD-1 blockade has shown potent efficacy against ovarian cancer (Yung *et al*., 2022) and melanoma (Pokhrel *et al*., 2021), indicating that AMPK eradicates tumor development in a T cell-dependent manner.

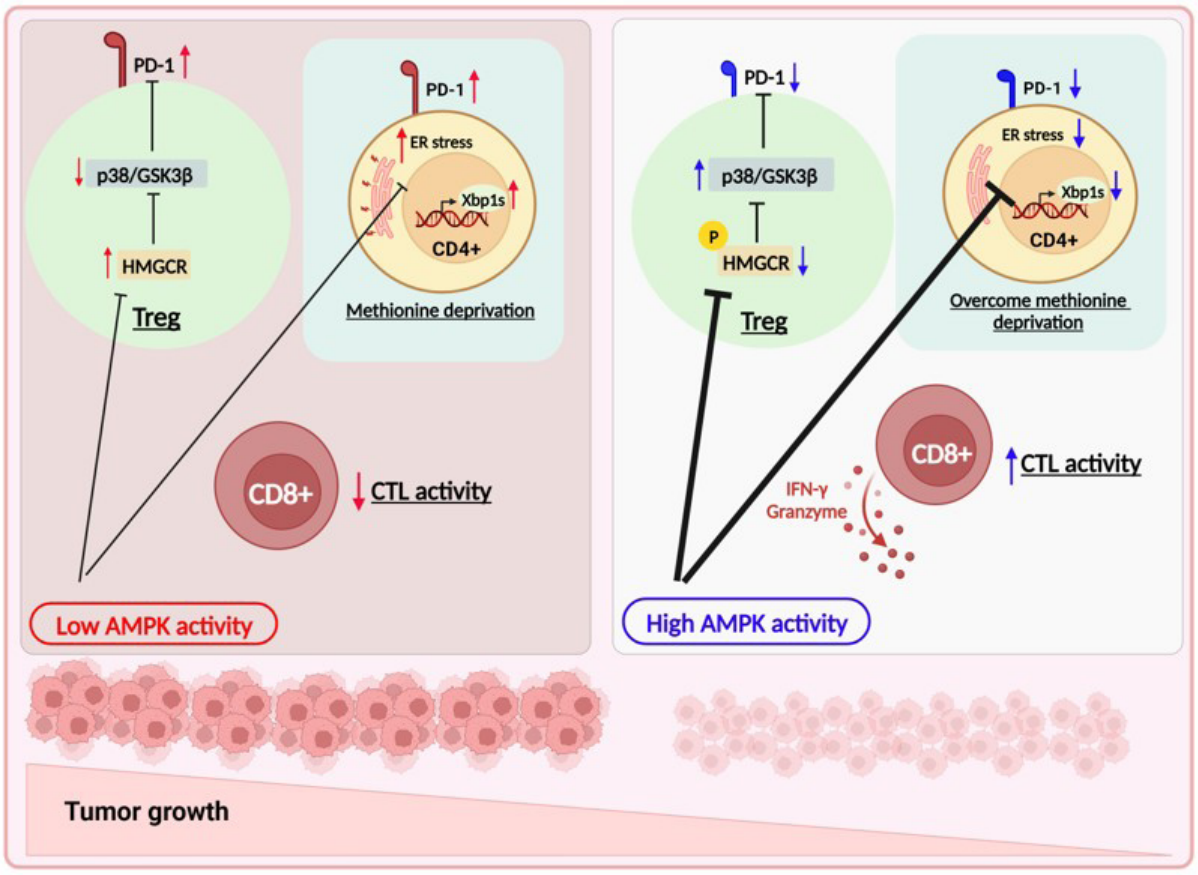

Fig. 4. AMPK modulates tumor-infiltrating T cells. AMPK activates CD8+ T cells to secrete IFN-γ/granzyme b and to infiltrate tumor tissues infiltration, which potentiates CTL activity to retard tumor growth. In tumor-infiltrating Treg cells, HMGCR inhibits p38 and GSK3β to elevated PD-1 on Treg cells. Through activating AMPK, HMGCR is repressed, reversing P38/GSK3β function to downregulate PD-1. In methionine-deficient TME, PD-1 expression on CD4+ T cells is increased through elevated ER stress and Xbp1s transcript, but AMPK activation relieves CD4+ T cells from PD1 expression by limiting ER stress-induced Xbp1s transcription. Solid red and blue arrowed lines depict intact and AMPK mediated expressions within tumor infiltrating T cells. The figure is created with BioRender.com.

AMPK AND TUMOR CELLS

Currently, the exact roles of AMPK in tumor development and progression remain unclear. However, AMPK is often described as a "double-edged sword," whose action depends on the metabolic milieu (Jeon and Hay, 2015). The mixed effects of AMPK signaling in cancer remain controversial. Prior to the onset of cancer, AMPK acts as a tumor suppressor; however, following the onset of cancer, AMPK either suppresses or promotes cancer depending on the cell type, status, and metabolic milieu (Sadria *et al*., 2022). This review primarily discusses the effects and roles of AMPK activation in key metabolic signaling pathways involved in tumor suppression.

AMPK as a tumor suppressor

Cancer cells undergo metabolic reprogramming to support their growth by increasing glucose uptake and biasing energy production toward glycolysis rather than mitochondrial metabolism (Koppenol and Bounds, 2009). As this metabolic rewiring is supported by dysregulated mTOR/AMPK activity ($mTOR^{high}/AMPK^{low}$), reversing these signaling pathways may be a promising cancer treatment strategy (Shackelford and Shaw, 2009). LKB1, a positive regulator of AMPK1, acts as a tumor suppressor, as dysfunctional LKB1 exacerbates the growth of gastrointestinal malignancies in humans and mice (Shackelford and Shaw, 2009). In this context, several studies have reported that AMPK recapitulates the tumor-restraining effect of LKB1 in various cancers, including liver cancer (Lee *et al*., 2012), lung cancer (Storozhuk *et al*., 2013), colorectal cancer (Sugiyama *et al*., 2009), melanoma (Cerezo *et al*., 2013; Pokhrel *et al*., 2021; Pandit *et al*., 2023), and prostate cancer (Zadra *et al*., 2014; Li *et al*., 2015). Furthermore, AMPK activators, metformin and AICAR, delay tumorigenesis in some cancer types (Zhou *et al*., 2001; Cha *et al*., 2018; Su *et al*., 2019), indicating that AMPK may also act as a tumor suppressor. Mechanistically, AMPK activation inhibits tumorigenesis by targeting several signaling pathways related to cell cycle progression, metabolism, proliferation, and survival (Fig. 5, Table 1).

Inhibition of aerobic glycolysis (Warburg effect) via mTOR downregulation

The Warburg Effect is a phenomenon in which cancer cells exhibit a higher rate of glucose uptake and glycolysis, fol-

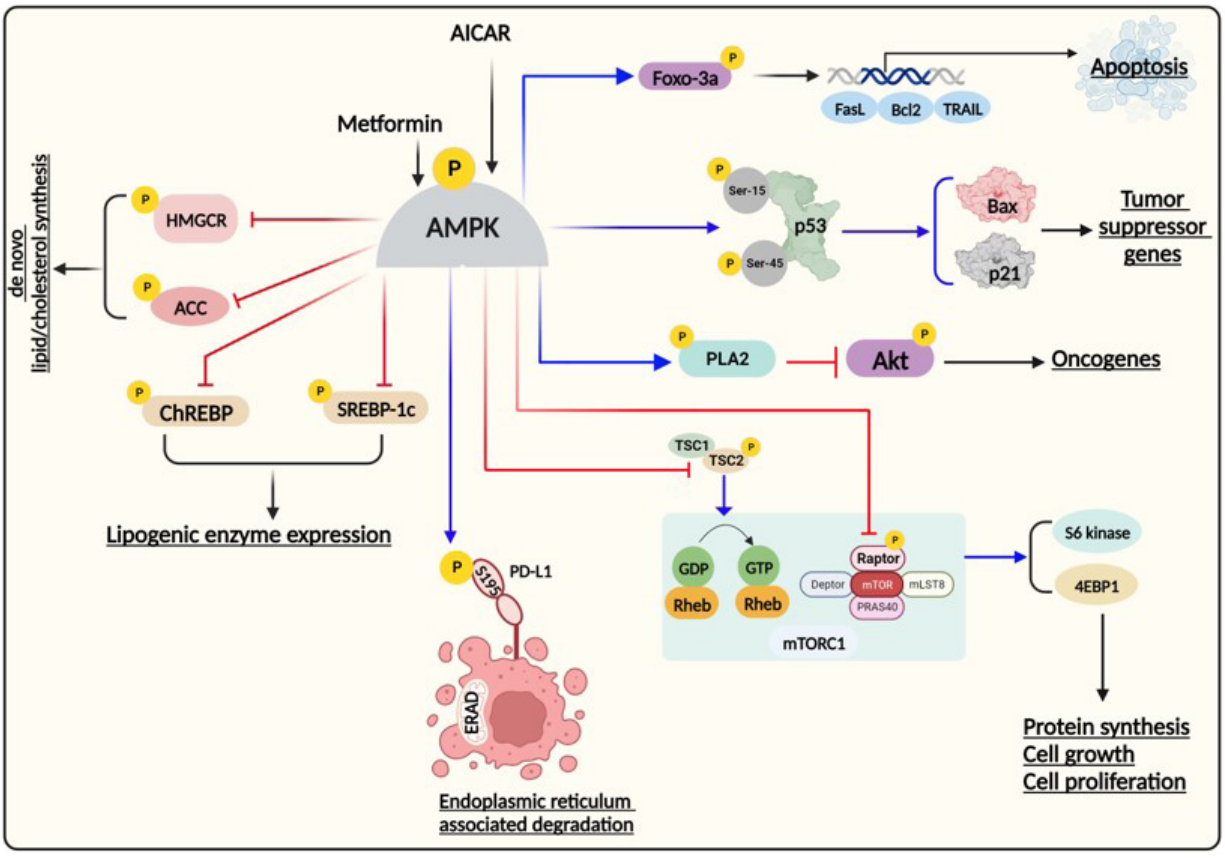

Fig. 5. AMPK plays a central role as a tumor suppressor. AMPK inhibits *de novo* lipid/cholesterol synthesis through inhibiting ACC and HMGCR to dampen tumor cell proliferation. It also represses SREBP-1c and ChREBP that induce ACC and fatty acid synthase. AMPK also induces aberrant glycosylation of PD-L1 by phosphorylating at S195 of PD-L1, leading to ER-associated protein degradation (ERAD). In context of mTORC1, AMPK inhibits TSC2 to prevent Rheb from GTP binding. AMPK also hinders Raptor, which reduce the activity of 4EBP1 and S6 kinases. Oncogenic AKT is inhibited by AMPK-induced phosphatase A2. In other aspect, AMPK activates tumor suppressor genes. AMPK phosphorylates p53 at Ser-15 and -46, then it activates p21 and Bax to arrest tumor cell proliferation. another tumor suppressor FOXO3a is phosphorylated by AMPK. This leads to apoptotic genes such as Fas ligand, TRAIL, and Bcl-2 to induce tumor cell death. The figure is created with BioRender.com.

lowed by lactate production, even under aerobic conditions, in contrast to normal cells, which primarily rely on oxidative phosphorylation for energy production (Liberti and Locasale, 2016). This metabolic preference for glycolysis over oxidative phosphorylation is less efficient in terms of ATP production but provides cancer cells with several advantages, such as rapid energy production and accumulation and diversion of glycolytic intermediates to biosynthetic pathways. These intermediates provide the building blocks for the synthesis of lipids, nucleic acids, and amino acids to meet the high biomass demand of rapidly proliferating cancer cells. Furthermore, lactate buildup in the tumor microenvironment causes the reduction of extracellular pH, stifling anti-tumor immunity and promoting cancer development (Palsson-McDermott and O'neill, 2013).

Notably, mTOR is a major regulator of the Warburg effect (Sun *et al*., 2011). mTOR is a key component of two protein complexes, mTORC1 and mTORC2 (Inoki *et al*., 2003; Zong *et al*., 2014). In particular, mTORC1 regulates the growth and survival of tumor cells upon integration of nutrient/growth factor signals via the phosphoinositide 3-kinase (PI3K)/AKT and Ras/MAPK pathways (Guertin and Sabatini, 2007; Laplante and Sabatini, 2012; Dibble and Cantley, 2015). AMPK inhibits mTORC1 via two molecular mechanisms. First, AMPK phosphorylates the tuberous sclerosis complex protein-2 (TSC-2), preventing the GTP binding of small G protein Rheb (Inoki *et al*., 2003). Second, AMPK phosphorylates the regulation-associated protein of mTOR, the regulatory subunit of mTORC1 (Gwinn *et al*., 2008), inhibiting mTOR function and blocking the activation of the S6 kinase/eukaryotic translation initiation factor, 4E -binding protein 1 (4EBP1). This negatively regulates protein synthesis, retarding tumor progression (Inoki *et al*., 2003; Tsakiridis *et al*., 2021).

Downregulation of the hypoxia-inducible factor 1-alpha (HIF-1α)

Hypoxia is a hallmark of the tumor environment and promotes tumor growth by facilitating pro-tumoral stimuli, such as angiogenesis, stemness, epithelial–mesenchymal transition, and metastasis (Semenza *et al*., 1991). Hypoxic effects in the tumor environment are driven by the HIF family. HIFs exist in three isoforms: HIF-1, HIF-2, and HIF-3. Among these, HIF-1 is the most notorious for accelerating tumor growth. Under normoxic conditions, HIF-1α is inactivated by the prolyl hydroxylase enzymes, prolyl hydroxylase domain-containing proteins

Table 1. Inhibition of different cancer types via AMP-activated protein kinase (AMPK) activation and the underlying mechanisms

Cancer types	AMPK activation compounds	Mechanisms	References
Breast cancer	Honokiol	Inhibits the invasiveness and migration of breast cancer via the liver kinase B1 (LKB1)/AMP-activated protein kinase (AMPK)/pS6K axis in MCF7 and MDA-MB-231 cells	Nagalingam *et al*., 2012
Breast cancer	Demethoxycurcumin and nordihydroguaiaretic acid	Inhibit the AMPK/mammalian target of rapamycin complex 1 (mTORC1) signaling pathway in MDA-MB-231, MCF-7, and Bcap37 cells	Zhang *et al*., 2012; Shieh *et al*., 2013
Hepatocellular carcinoma (HCC)	Antroquinonol	Inhibits mTOR translational pathway leading to the G1 arrest of cell cycle and subsequent cell apoptosis via the AMPK/mTOR/p70-S6 kinase and 4EBP1 pathways in HepG2 cells	Chiang *et al*., 2010
Esophageal Cancer	Cordycepin	Increases chemosensitivity to cisplatin by activating AMPK and inhibiting the AKT signaling pathway in HK, K180, K70, and ECA109 cells	Gao *et al*., 2020
Colon cancer	Curcumin	Inhibits tumor growth via the AMPK/pAKT/cyclooxygenase 2 (COX-2) pathway in HT-29 cells	Lee *et al*., 2009
Colon cancer	Magnolol and quercetin	Induce apoptosis via the AMPK/p53/Bax pathway in HCT-116 and HT-29 cells	Kim *et al*., 2010; Park *et al*., 2012
Colon cancer	Widdrol	Induces apoptosis via the activation of caspase-3/7 and caspase-9 through AMPK activation in HT-29 cells	Kang *et al*., 2012
Ovarian cancer	GANT61	Elevates chemosensitivity to cisplatin by regulating the AMPK pathway in Caov-3 and SKOV-3 cells	Zhu *et al*., 2022
Ovarian and colon cancers	Curcumin	Induces cell death via the AMPK/p53 pathway in CaOV3 cells and HT-29 cells	Song *et al*., 2005; Pan *et al*., 2008
Lung cancer	Metformin-salicylate	Phosphorylates ACC and inhibits de novo lipogenesis via AMPK activation in A549 and H1299 cells	O'Brien *et al*., 2015
Hepatoma and colon cancer	Cryptotanshinone	Induces autophagic cell death via the AMPK/mTOR axis in HepG2 and HCT116 cells	Park *et al*., 2014
Breast cancer	Ginsenoside-Rg2	Induces the ROS-AMPK signaling pathway and inhibits extracellular signal-regulated kinase (ERK)1/2 and AKT activation-mediated cell proliferation and cell cycle progression in MCF-7 breast cancer cells	Jeon *et al*., 2021
Melanoma	Berberine	Inhibits metastasis via the AMPK/ERK/COX2 pathway in B16F10 murine melanoma and A375 human melanoma cells	Kim *et al*., 2012
Melanoma	Ginsenoside 20-O-β-D-Glucopyranosyl-20(S)-Protopanaxadiol	Induces autophagic cell death via AMPK/Janus kinase (JNK) pathway activation in SK-MEL-28 cells	Kang *et al*., 2014
Leukemia	Tanshinone IIA	Induces autophagic cell death via AMPK/mTOR/p70-S6 kinase in KBM-5 cells	Yun *et al*., 2014
Breast cancer, melanoma, and colon cancer	Metformin	Endoplasmic reticulum (ER)-associated programmed cell death ligand-1 (PDL1) glycosylation and degradation by metformin-activated AMPK in 4T1, B16F10, and CT26 cells	Cha *et al*., 2018
Renal cancer	Hispidulin	Sensitizes cancer cells to TNF-related apoptosis-inducing ligand (TRAIL)-induced apoptosis via the AMPK/USP51 axis in CC-2559 cells	Woo *et al*., 2019
Prostate cancer	BI-9774, MT 63-78	Inhibits lipogenesis via AMPK activation in C4–2, C4–2b, LNCaP cells	Zadra *et al*., 2014; Penfold *et al*., 2023
Prostate cancer	Metformin-salicylate	Suppresses the ACC-DNL, mTOR-p70s6k/4EBP1, and HIF1α pathways	Tsakiridis *et al*., 2021
Thyroid cancer	AICAR	Inhibits C-X-C motif chemokine ligand 8 (CXCL8) secretion and suppresses CXCL8-induced neoplastic cell migration	Awwad *et al*., 2018

1–3 (Maxwell *et al*., 1999). After hydroxylation, HIF-1α binds to the Von Hippel Lindau protein-containing E3 ubiquitin ligase complex and gets ubiquitinated, subsequently undergoing proteasomal degradation. Under hypoxic conditions, HIF-1α translocates into the nucleus and stabilizes itself by binding to the partner protein, HIF-1β, promoting the transcription of oncogenes, such as *c-Myc*, *p53*, vascular endothelial growth factor, and organic cation transporter 1 (Maynard and Ohh, 2007; Ward and Thompson, 2012; Cairns and Mak, 2017). HIF-1α overexpression is commonly observed in many cancer types, including brain, breast, lung, and stomach cancers (Semenza, 2003; Weidemann and Johnson, 2008). In this context, the association between HIF-1α and AMPK has been investigated by Faubert *et al*. (2013). They showed that loss of AMPKα increases HIF-1α expression, promoting lymphoma development in AMPKα-deficient mice (Faubert *et al*., 2013). This indicates that AMPK hinders tumor formation by opposing HIF-1α activation. Additionally, AMPK activation promotes hydroxylation of HIF1α, resulting in HIF1α degradation and suppression of hepatocellular carcinoma (Tseng *et al*., 2022).

Inhibition of lipogenesis

To meet the massive growth requirements, tumor cells require tremendous resources to produce newly proliferated cells. Lipids/cholesterol are key components of the plasma membrane and signaling molecules that are supplied by acetyl ACC- and HMGCR-mediated *de novo* lipid/cholesterol synthesis (Swinnen *et al*., 2006). AMPK limits lipid and cholesterol synthesis in tumor cells by inhibiting the lipogenic enzymes. AMPK inactivates ACC and HMGCR, thereby suppressing malonyl-CoA-mediated fatty acid synthesis and mevalonate production, respectively. Furthermore, AMPK inhibits the sterol regulatory element-binding transcription factor 1c and carbohydrate-response element-binding protein, which are upstream inducers of ACC and fatty acid synthase, suggesting that at the transcriptional level, AMPK negatively regulates lipogenesis in an indirect manner (Chuang *et al*., 2014). *In vivo* AMPK activation inhibits prostate cancer development by suppressing *de novo* lipogenesis (Zadra *et al*., 2014). Additionally, AMPK activation suppresses prostate cancer progression and metastasis by decreasing lipogenesis via PGC1α activation (Penfold *et al*., 2023).

ER-associated degradation of PD-L1

PD-L1 is a key immune checkpoint molecule produced by cancer cells that evades immune surveillance (Pardoll, 2012). When PD-L1 on cancer cells binds to PD-1 on activated cytotoxic T lymphocyte-infiltrating tumors, it shuts down LCK-mediated TCR signaling, thereby inhibiting the antitumor activity (Chen *et al*., 2004). Therefore, blocking the PD-L1/PD-1 axis may be an attractive strategy for cancer immunotherapy. Recently, metformin has been reported to diminish PD-L1 expression in tumor cells. Metformin-induced AMPK directly phosphorylates S195 of PD-L1 in tumor cells, leading to the aberrant glycosylation of PD-L1. Abnormal PD-L1 accumulates in ER, resulting in ER-associated protein degradation (Cha *et al*., 2018). In clinical settings, diabetic patients with breast cancer treated with metformin show a higher rate of complete response to chemotherapy than the untreated patients. Tumor tissues in the metformin-treated patients exhibit strong AMPK activation, indicating that AMPK-driven PD-L1 degradation probably improves the patient prognosis (Cha *et al*., 2018).

Inactivation of AKT signaling

PI3K/AKT signaling is a vital pro-tumor pathway in many cancer types (Arcaro and Guerreiro, 2007). Notably, AKT regulation is associated with AMPK expression in tumor cells in a mutually antagonistic manner. For example, activated AKT negatively regulates AMPK by reducing the cellular AMP:ATP ratio (Kovacic *et al*., 2003; Hahn-Windgassen *et al*., 2005), whereas adiponectin-activated AMPK inhibits AKT function by stimulating phosphatase 2A activity (Kim *et al*., 2009; Lee *et al*., 2011). Mechanistically distinct AMPK activators, OSU-53 and AICAR, inhibit AKT activity, leading to the S-phase growth arrest of tumor cells (Rattan *et al*., 2005; Kim *et al*., 2009; Lee *et al*., 2011). Moreover, cordycepin induces AMPK activation and suppresses the AKT signaling pathway to enhance the chemosensitivity of esophageal cancer cells to cisplatin (Gao *et al*., 2020).

Upregulation of p53

p53 is a transcription factor that transactivates several genes involved in cell cycle arrest and apoptosis (Prives and Hall, 1999). Under normal conditions, p53 is present at low levels because of its gradual proteasomal degradation. However, when DNA damage occurs, p53 escapes degradation and transactivates the target genes, inducing cell cycle arrest and apoptosis (Ozaki and Nakagawara, 2011). p53 suppresses tumor development in response to several oncogenic stresses, such as hypoxia, DNA damage, and senescence (Vogelstein *et al*., 2000; Vousden and Prives, 2009). Approximately 50% of human cancers consistently harbor loss-of-function mutations in the p53 alleles (Lee *et al*., 2010). AMPK phosphorylates p53 at Ser-15 and Ser-46 to activate its function in mouse embryonic fibroblasts (Jones *et al*., 2005) and osteosarcoma cells (Okoshi *et al*., 2008), respectively. AMPK-induced p53 activates the expression of p21 and Bax to arrest cell proliferation under glucose-deficient conditions, ultimately causing tumor cell death (Okoshi *et al*., 2008; Lee *et al*., 2012).

Inhibition of cyclooxygenase 2 (COX2)

COX2 enhances stemness, apoptotic resistance, and angiogenesis to promote tumor development (Williams *et al*., 1999; Prescott and Fitzpatrick, 2000). AMPK activation by synthetic or natural agents inhibits COX2 expression in colorectal cancer (Williams *et al*., 1999) and melanoma cell lines (Kim *et al*., 2012), thereby inhibiting tumor growth. In contrast, AMPK inhibition by compound C increases the growth of human colorectal adenocarcinoma cells (HT-29) by elevating the expression levels of COX2 and AKT (Lee *et al*., 2009), implying that AMPK is a negative regulator of COX2 in tumor cells.

Activation of FoxO3a

FoxO3a is a well-established tumor suppressor in various cancers, including breast, lung, and colon cancers (Shoeb *et al*., 2013; Yang *et al*., 2014; Zhang *et al*., 2017). Mechanistically, FoxO3a activates apoptosis-inducing genes, such as the Fas ligand, TNF-related apoptosis-inducing ligand (*TRAIL*), and B-cell lymphoma 2 (*Bcl-2*) members (*Bim*, *bNIP3*, and *Bcl-xL*), and shifts the metabolic status to tumor-unfavorable conditions (Fu and Tindall, 2008). FoxO3a is commonly inactivated in cancer cell lines via allelic mutations or protein

sequestration in the cytosol, causing the uncontrolled growth of tumor cells (Liu *et al*., 2018). AMPK activation upregulates FoxO3a expression in tumor cells under various cellular stresses. AMPK phosphorylates FoxO3a and regulates its nuclear localization (Greer *et al*., 2007b; He *et al*., 2009; Chiacchiera and Simone, 2010); however, the underlying mechanisms remain unclear (Chiacchiera and Simone, 2010).

CONCLUSION

Many studies have extensively investigated AMPK, but in this review, we focused on specific aspects, such as the roles of AMPK in T cells and cancer. AMPK plays crucial roles in metabolic regulation, detection of energy/nutrient deprivation, and maintenance of metabolic balance in organisms. Therefore, precise control of the AMPK pathway is vital as it determines the fate of both T and tumor cells under nutrient-restricted conditions.

Inhibition of anabolic pathways by AMPK hampers mTORC1 and ACC, further hindering the growth and functions of actively proliferating cells, such as the effector T and tumor cells (Keerthana *et al*., 2023). In quiescent cells, such as naïve, memory, and Tregs, AMPK promotes fatty acid oxidation, supporting their survival and functions (Sun *et al*., 2017). Owing to the intricate consequences of AMPK activation depending on the cell type and status, whether targeting AMPK is beneficial remains controversial (Chang and Lai, 2020). Our review provides significant insights into the roles of AMPK in T and tumor cells to facilitate the development of effective therapeutics. However, more comprehensive studies are needed to develop novel AMPK-targeting intervention strategies for various diseases.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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