WORLD ACADEMY OF SCIENCES JOURNAL 7: 103, 2025

Deciphering the critical roles of the AMPK/mTOR signaling pathway in cancer cell metabolism (Review)

AMER ALASADI[1,2], NOOR FADHIL[3] and SEAN CHEN[4]

[1]Department of Pharmacology, Rutgers, The State University of New Jersey, Piscataway, NJ 08854, USA;
[2]Department of Medical Basic Science, Collage of Nursing, University of Thi-Qar, Nasiriyah, Thi Qar Governorate 00964, Iraq;
[3]Department of Nutrition Science, Rutgers, The State University of New Jersey, New Brunswick, NJ 08901, USA;
[4]Ernest Mario School of Pharmacy, Rutgers, The State University of New Jersey, Piscataway, NJ 08854, USA

Received June 19, 2025; Accepted August 22, 2025

DOI: 10.3892/wasj.2025.391

Abstract. AMP-activated protein kinase (AMPK) and mechanistic target of rapamycin complexes (mTORCs; mTORC1 and mTORC2) have critical functions in controlling tumor cell metabolism, reciprocally affecting the anabolic and catabolic pathways that control cell growth, proliferation and survival. AMPK serves as a key energy sensor, activated in response to low cellular energy levels, while the action of mTORCs becomes evident under conditions with high nutrient and growth factors. The dysregulation of these cascades is notably detected in a number of types of cancer, where reduced AMPK activity and unrestrained mTOR signaling pathways accelerate metabolic shifts that support carcinogenesis. The connection between AMPK and mTOR is significant. AMPK plays a role in hindering mTOR signaling, thus diminishing protein biosynthesis and stimulating autophagy. This strengthens cellular homeostasis, progression and survival during severe metabolic distress. Nevertheless, the function of AMPK in tumors is multifaceted. At the same time, it commonly functions as a tumor suppressor; evidence suggests that in specific environments, AMPK may stimulate tumor development by supporting the survival of tumor cells under adverse conditions, such as metabolic deprivation. This dualism highlights that the therapeutic targeting of AMPK/mTOR signaling pathways needs to be addressed carefully, as the consequences may vary, depending on the specific cancer microenvironment and nutrient state. The present review summarizes evidence from the literature in an aim to shed light onto the complex balance of the actions, regulation and critical role of AMPK and mTORCs in cancer cell metabolism. The present review aimed to provide insight that may lead to the development of novel targeted therapies that diminish the threat of unfavorable consequences associated with modified metabolic control.

Contents

1. Introduction

Mammalian target of rapamycin (mTOR) plays a critical role in regulating cellular metabolism by integrating signals from nutrients, growth factors and the environment. mTOR exists in two distinct mTOR complexes (mTORCs), mTORC1 and mTORC2, which are conserved across species from yeast to humans. mTORC1 is a protein complex that consists of mTOR,

---

Correspondence to: Dr Amer Alasadi, Department of Pharmacology, Rutgers, The State University of New Jersey, 675 Hoes Lane West, Piscataway, NJ 08854, USA
E-mail: aha36@scarletmail.rutgers.edu

Abbreviations: AMPK, AMP-activated protein kinase; mTOR, mammalian target of rapamycin; mTORCs, mammalian target of rapamycin complexes; OXPHOS, oxidative phosphorylation; ATP, adenosine triphosphate; NADPH, nicotinamide adenine dinucleotide phosphate; PPP, pentose phosphate pathway; R5P, ribose-5-phosphate; HIF, hypoxia inducible factor; GLUT, glucose transporter; PFK, phosphofructokinase; TSC, tuberous sclerosis complex; GS, glutamine synthetase; ASNS, asparagine synthetase; FAs, fatty acids; SREBP1, sterol regulatory element-binding protein 1; CAD, carbamoyl-phosphate synthetase 2, aspartate transcarbamylase, and dihydroorotase; AML, acute myeloid leukemia

Key words: glycolysis, AMPK, mTOR kinase, cancer cell metabolism, dual roles

Raptor, Deptor, mLST8, and PRAS40. It is the primary target of the drug rapamycin that allosterically reduces its activity, while mTORC2 consists of mTOR, Debtor, Raptor, mLST8, mSIN1 and Protor, and its inhibition occurs indirectly (1-4) (Fig. 1A). Rapamycin and its analogs are currently utilized in clinical settings. They are being tested for various conditions, including cancer, immune disorders, metabolic syndromes and neurodegenerative diseases, exhibiting potential as anti-aging agents that may enhance human and animal health. Insight into mTOR-mediated metabolic shifting in target cells, such as tumors and immune cells in their microenvironments, can significantly advance the development of targeted therapeutic approaches. The proper functioning of mTORC1 and mTORC2 is essential for maintaining metabolic equilibrium, preventing diseases and extending the health area (5). Studies have revealed that AMP-activated protein kinase (AMPK) affects cancer cell metabolism through several mechanisms. The activation of AMPK has been correlated with the inhibition of aerobic glycolysis which is well-known as the Warburg Effect. The Warburg effect has been known as one of the cancer hallmarks and is characterized by enhanced glycolysis even in the presence of oxygen (5-7). This pathway stimulates the catabolic metabolic processes, which promote cancer cell metabolism to switch to energy preservation under severe stress conditions. AMPK stimulation has been shown to utilize anti-proliferation and propagation effects in various tumor types (6).

The importance of cancer cell metabolism orchestrated through AMPK/mTOR cascades is an attractive avenue for innovative cancer therapies and highlights the need for the understanding of these signaling pathways further to advance wide-ranging combination therapy approaches. AMPK and mTORCs have critical functions in controlling the cell metabolism in a number of types of cancer, shaping the anabolic and catabolic pathways that regulate cell growth, proliferation and survival. AMPK serves as a key energy sensor, activated in response to low cellular energy levels, while the action of mTOR becomes evident under high nutrient conditions (3-7).

AMPK deploys dual roles in controlling the intracellular environment of tumor immunity, affecting both immune and tumor cells. AMPK is the key factor between the immune cell microenvironment and the metabolism energy of tumor cells (8). Recently, it has been shown that AMPK exhibits anticancer immune activity by cooperating with dominant components at the cancer microenvironment, affecting the roles of T-lymphocytes, myeloid suppressor cells and macrophages (9). Furthermore, AMPK can inhibit the production of chemokines and cytokines (10). Taken together, AMPK plays a master role in the modulation of tumor microenvironment.

Moreover, the mTOR signaling pathway plays a critical role in the regulation of the tumor microenvironment (11). The mTOR cascade plays regulatory roles in the growth, differentiation, survival and function of adaptive and innate immune cells (12). It controls the phenotypic, the functional, and direct reprogram in tumor-immune cells microenvironment. In addition, mTOR stimulates the inflammatory process and promotes the replenishment of the immune cell to tumor environment, resulting in stimulating anticancer effects or supporting tumor cell development, proliferation and metastasis (13). Therefore, misregulated mTOR pathways in tumors can modify the tumor microenvironment, disrupting the cancer immune microenvironment.

Research has demonstrated critical associations between the AMPK/mTOR signaling pathway and ferroptosis in carcinogenesis (14). Ferroptosis is an iron dependent programmed cell death process that has gained increasing attention from researchers for targeting cancer growth (15). Ferroptosis is closely associated with mTOR, and utilizing mTOR-related therapy has the potential to stimulate the rate of ferroptosis in the targeting of several types of cancer (16). It has also been demonstrated that AMPK confines the stimulation of ferroptosis and subsequently, the inhibition of AMPK therapy restores the treatment and restores the responsiveness to ferroptosis activators (17). Moreover, it has been demonstrated that amentoflavone stimulates ferroptosis by stimulating the ROS/AMPK/mTOR signaling axis to reduce the uterine cell cancer viability and prorogation by stimulating the ferroptosis and apoptosis (18). Thus, AMPK/mTOR signaling pathway is the central player in ferroptosis process.

Furthermore, AMPK and mTOR have been recently shown to be involved in mitochondrial dynamics in cancer progression (19). AMPK plays a crucial role in the regulation of mitochondrial activity and cytoskeleton modification, with an increased AMPK activity in cells with a low migratory ability; this induces the mitochondrial fission, leading to reduced oxidative phosphorylation (OXPHOS), low adenosine triphosphate (ATP) biogenesis and the reduction of ameboid myosin II-dependent cell migration (20). Moreover, the abnormal expression of MTERF1 in colorectal cancer cells modulates the p-AMPK/mTOR pathway of mitochondrial dysfunction (21). Therefore, the AMPK/mTOR axis can be a good way to treat different mitochondrial-related diseases such as cancer and metabolic syndromes.

The AMPK/mTOR signaling pathway has also recently been shown to be involved metabolically in condensate formation. Developments (condensates) are a mutual strategy for cells to complete various functions, such as DNA repair, chromatin association, transcriptional activity and signal transduction (22). Recently, abnormal phase separation and alteration have been stated to be associated with cancer and other neurodegenerative diseases (23). AMPK activation occurs during metabolic stress; this activation stimulates the formation of condensate and stress particles that promote cancer cell survival and progression under different nutrients deficiency (24). In addition, condensate development organizes the necessary metabolic enzymes to stimulate the metabolic switching in the tumor microenvironment (25). Moreover, a recent study demonstrated that the formation of EMT supports carcinogenesis, and metastasis is notably initiated and governed by phase separation (condensate formation) (26). These data highlight the critical role of the AMPK/mTOR pathway in regulating condensate particle formation; these data may provide a novel approach for cancer treatment by targeting these metabolic vulnerabilities.

Disruptions in these signaling pathways may inadvertently cause tumor progression, emphasizing the importance of novel therapeutic interventions targeting this complex network. Moreover, understanding the complex balance of the action between AMPK and mTORCs can lead to the development of novel approaches to combat cancer growth, while diminishing

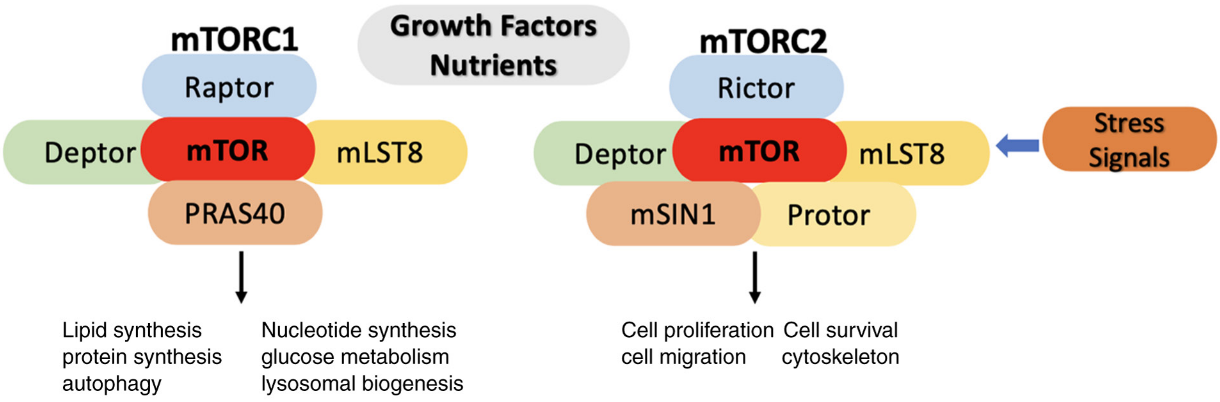

Figure 1. The mTOR pathway is organized as two unique mTOR complexes, termed mTORC1 and mTORC2. mTORC1 is a protein complex of mTOR, Raptor, Deptor, mLST8 and PRAS40. mTORC1 phosphorylates downstream targets to control protein and lipid biosynthesis, lysosomal biogenesis, autophagy, glucose metabolism, and nucleotide synthesis. mTORC2 is a protein complex of mTOR, Debtor, Raptor, mLST8, mSIN1, and Protor. mTORC2 regulates cell proliferation, survival, cytoskeleton and cell migration. mTOR, mammalian target of rapamycin; mTORC, mammalian target of rapamycin complex.

the threat of unintentional consequences associated with modifying metabolic switches.

2. Critical role of mTOR in the glucose metabolism of cancer cells

Both mTORCs function as central regulators of the use of glucose in normal and cancer cells, markedly contributing to metabolic rewiring, which describes different malignancies. mTOR1 and mTOR2 can regulate the expression of glycolytic enzymes, glucose transporters and transcription machinery that stimulate the expression of various genes related to glycolysis pathway effectors (27).

Decades ago, Otto Warburg found that cancer cells use aerobic glycolysis as fuel source to keep the building blocks that are required for cell growth and propagation. This specific characteristic of tumor cells is well-known as the Warburg effect, whereas OXPHOS is the main energy source for the maintenance of the development and proliferation of normal cells (27-30). Warburg's discovery was recognized and confirmed in various human tumors with radioactive glucose analogs using (fluorodeoxyglucose) to examine glucose utilization in normal and tumor tissues (30). Currently, the Warburg effect is one of the cancer hallmarks, in addition to other characteristics, such as immortality, resistance to cell death, avoiding growth defeat, stimulating invasion, angiogenesis and metastasis (28-30). Additionally, a high mutation rate with genomic variability, escaping the immune defense and tumor-increasing inflammation are up-and-coming hallmarks that are related to carcinogenesis. Modified glucose uptake over aerobic glycolysis is an ineffective mode to generate energy, as it provides two ATPs per glucose molecule. By contrast, OXPHOS provides 36 ATPs from glucose oxidation via the Krebs cycle (30-33). Previous studies have confirmed that the majority of tumor cells shift the glucose metabolism from OXPHOS to aerobic glycolysis even in the presence of O_2. Tumor cells convey glucose metabolic intermediates to biosynthetic macromolecule new building blocks pathways. This activity sustains tumor development by providing metabolic intermediates to refill cancer cells and producing reducing molecules, such as nicotinamide adenine dinucleotide phosphate (NADPH) for different metabolic activities (33-35).

In differentiated cells, glucose oxidation is an oxygen-dependent process, either through OXPHOS (with O_2) or fermentation (without O_2) (35-38). In expanding cells, mainly tumor cells, pyruvate from the oxidation of glucose is transformed into lactic acid through aerobic glycolysis, also known as the Warburg effect, even in the presence of oxygen. In addition, glucose oxidation provides the intermediate substrates for the pentose phosphate pathway (PPP) to generate ribose-5-phosphate (R5P) required for nucleotide synthesis and NADPH to sustain cellular redox homeostasis (39). Furthermore, glycolytic substrates are essential for synthesis 3-phosphoglycerate, a precursor for the serine synthesis cascade, providing the crucial molecules for the biosynthesis of various (non-essential) amino acids. Moreover, the transamination reaction converts pyruvate to alanine and citrate transfers the mitochondria into the cytoplasmic matrix for the biogenesis of fatty acids (FAs) (35,40-42). This indicates that tumor cells efficiently use different glucose metabolism to maintenance progression and survival.

mTORC1 stimulates glycolysis by promoting and regulating two main transcription factors [hypoxia inducible factor (HIF)1a and Myc] (Fig. 2). mTORC1 similarly stimulates the upregulation of glycolytic gene through the transcriptional controller of Myc (43,44). Myc is mutated in >50% of human cancers, and its increased expression is frequently associated with enhanced glycolysis and glutamine metabolism (45,46). mTORC1 stimulation of S6K and 4EBP1 is essential for Myc-stimulated carcinogenesis (47). Researchers have demonstrated that genes are sensitive to rapamycin and are controlled by Myc (48). The metabolic shift of glucose metabolism is mainly orchestrated across the mTOR1 activation, which reacts to external growth signals such as insulin, amino acids and glucose (49-52). mTORC1 boosts the glycolysis pathway and enhances the transcription and translation activities for crucial enzymes that participate in glycolytic and lactic acid production, such as hexokinase II and pyruvate kinase M2, that is produced in dividing and cancer cells. In addition, the mTOR2 pathway stimulates the

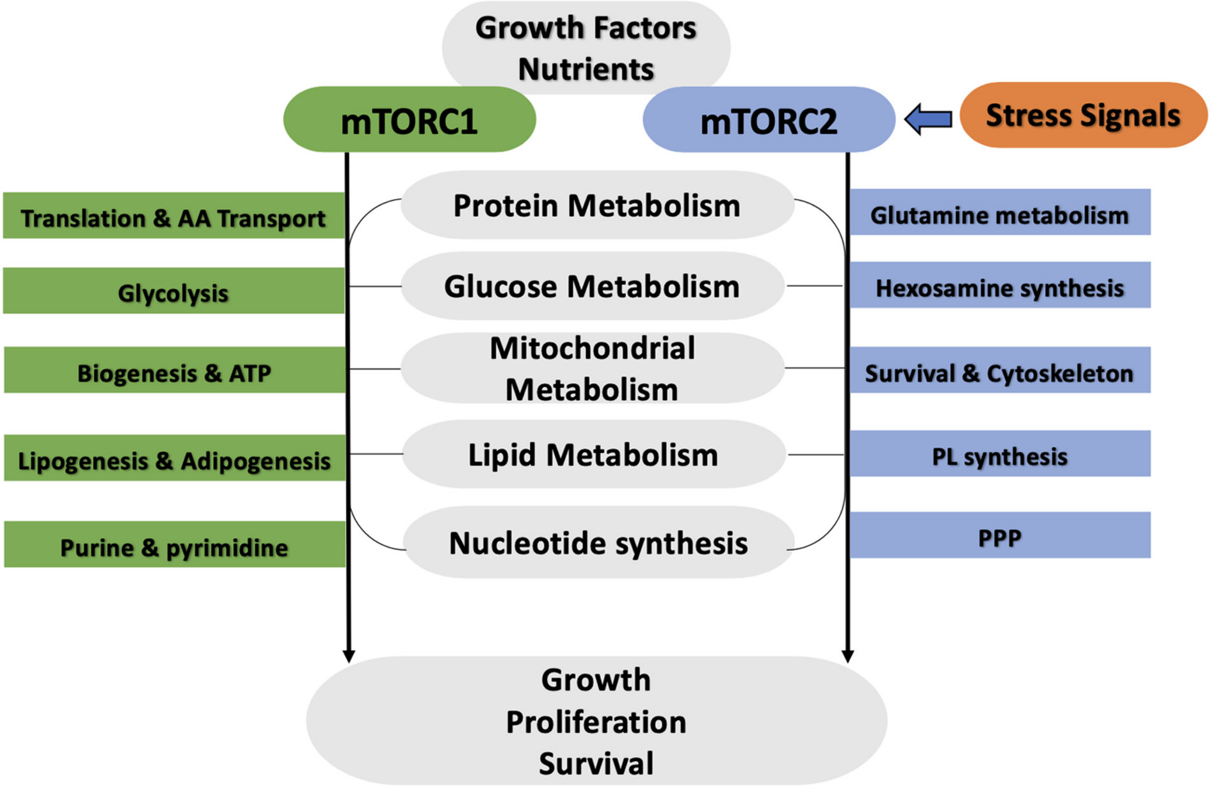

Figure 2. With sufficient nutrients and growth factors, mTORCs stimulate cancer cell growth, propagation and survival. mTORC1 and mTORC2 control the metabolic sources for protein biosynthesis through translation and amino acid transport and glutamine metabolism, respectively. Both complexes are participated in metabolism of glucose via glycolysis and hexosamine synthesis. Mitochondrial metabolism is controlled by mTORC1 and mTORC2 by regulating biogenesis, ATP synthesis, cell survival, and cytoskeleton organization. mTORCs modulate lipid metabolism by promoting lipogenesis, adipogenesis, and phospholipid synthesis. mTORC1 and mTORC2 significantly regulate the synthesis of purine, pyrimidine and PPP, essential biomolecules for cancer cell proliferation and survival. AA, amino acid; PL, phospholipid synthesis; mTOR, mammalian target of rapamycin; mTORC, mammalian target of rapamycin complex; PPP, pentose phosphate pathway.

expression of glucose transporter (GLUT)1 and phosphofructokinase (PFK) under the transcription machinery of these factors, thereby accelerating the glucose uptake in various types of cancer, such as colon, pancreatic, hepatic, lung and breast cancers (53-56). This step is essential for maintaining the excessive ATP levels necessary for energy-intensive activities, such as cell development and division. Furthermore, mTOR1 stimulates the expression level of several glycolytic enzymes by enhancing the translation of HIF1a (57). Evidence indicates that the role of mTOR is to regulate the gene expression of the enzymes for the glycolysis pathway and modulate the enzymatic activity through phosphorylation, promoting the appropriate microenvironment for cancer cell growth and development (58). Furthermore, the upregulation of this enzyme by mTOR1 is regulated through the aforementioned mechanism. In addition, the upregulated mTOR1 pathway due to tuberous sclerosis complex (TSC)2 mutation specifically stimulates the one isoform of PFK in acute myeloid leukemia (AML) (59). Moreover, the connection between the mTOR cascade and the PI3K/AKT signaling cascades has been demonstrated as the central axis for the glycolysis signaling pathway. Activated AKT induces the activity of the glycolytic signaling pathway under hypoxic environments and downregulates the expression of large non-coding RNA, further enriching tumor cell adaptation and development (60-62).

mTORC2 increases glycolysis that stimulates class IIa histone deacetylase phosphorylation, thus inhibiting them, promoting Fox O1 and O3 acetylation, resulting in the downregulation of c-Myc in glioblastoma (63). A better understanding of the function of the mTOR pathway in glycolysis and cancer cell metabolism will open a new avenue for targeting this pathway therapeutically, allowing the modification of glycolysis to impede cancer growth. Targeting the mTOR pathway using an mTOR inhibitor has shown promising results in clinical breast cancer models by decreasing glycolytic activity and enhancing metabolic deprivation in tumor cells (64).

3. Critical role of mTOR in the stimulation of glutamine in cancer cells

mTOR plays a substantial role in the dependence of cancer cell on glutamine breakdown, which is increasingly recognized as a crucial factor in cancer biology and therapeutic approaches. mTOR is an evolutionarily conserved serine/threonine kinase that is in two different complexes, mTORC1 and mTORC2; mTOR plays regulatory roles in numerous biological processes, such as cell glucose metabolism, growth, lysosome biogenesis, survival, autophagy and migration, that are required for cell development (Fig. 2). Therefore, its equilibriums between the anabolic and catabolic activities consistent to different bioenvironmental elements (65,66). One of the crucial roles of mTOR is its role in the metabolism of glutamine, which has been raised as a critical source of nitrogen and energy for rapidly proliferating cancer cells. Tumor cells use glutamine also as an energy source apart from the utilization of glucose; glutamine is conditionally an essential amino acid, and it is free in human blood. Therefore, its production may be decreased under specific different pathophysiological situations and metabolic conditions (67). Glutamine synthetase (GS) accelerates the linking reaction between glutamate and ammonia to procedure glutamine (68). Glutamine has functions in lipid and protein synthesis, precisely in tumor cells and energy redox homeostasis such s glucose. It is a precursor for glutamate citric acid and carbon synthesis (69). Moreover, glutamine is a nitrogen atom donor for purines, pyrimidines, and asparagine. Notably, it is also a precursor of (NAD) and is a source of glucosamine synthesis (67). In addition to the function of glucose in stimulating tumor cell proliferation, tumor cells are dependent and addicted to glutamine use to support different anabolic signaling pathways for constant cell persistence (70).

The activity of mTOR is essential in this metabolic flexibility, as it functions as a nutrient sensor, sensing the activity of a number of amino acids, including glutamine, and controlling subsequent signaling pathways accordingly. Research reveals that metabolic glutamine triggers mTORC1 activity through intermediates produced during its breakdown. For example, glutamate is subsequently converted to α-ketoglutarate (α-KG), a key metabolite that stimulates mTORC1 via its interaction with prolyl hydroxylases, which increases the GTP loading of Rag GTPases responsible for mTORC1 activation; this controlling mechanism elucidates how glutamine not only stores energy, but also performs as an agonist for mTOR metabolic pathway, developing a pro-growth microenvironment that boosts cancer cell growth and survival (71).

The mTORC1 pathway stimulates glutamine metabolism through the c-Myc transcription factor, which controls the expression of genes required for glutaminolysis, such as glutaminase 2 and other enzymes in c-Myc-stimulated T-cells (72). A feedback cycle exists between mTORC1 activation and glutamine metabolism through Myc (73,74). In addition, mTORC1 stimulates glutaminolysis by controlling the activity of cAMP-responsive element binding 2 (CREB2) by enhancing its degradation (75). These results indicate that mTORC1 stimulates glutamine uptake via negative feedback mechanism of CREB2, finally leading to GDH stimulation.

Additionally, the association between the mTOR pathway and glutamine metabolism extends to controlling autophagy and cellular stress reactions. Under a rich nutrient situation, mTORC1 stimulates protein production, while hindering autophagy, a safe process for degrading excessive or malfunctional proteins and damaged cellular components. When cellular glutamine levels are low, mTORC1 action is reduced, stimulating autophagy to reutilize cellular components and maintain metabolic cellular homeostasis (76).

Notably, the role of mTOR in glutamine use has a number of clinical implications, as various studies have investigated the targeting of this signaling pathway with mTOR inhibitors as a novel therapeutic approach. For example, it has been demonstrated that some cancers can adapt to mTOR inhibitors by enhancing glutamine metabolism to promote cancer growth and resist treatment. In addition, it has also been demonstrated that glutamine deprivation plus mTOR inhibition can be more effective in eradicating tumor growth and survival (72-76). Cancers with highly upregulated mTOR activity are frequently challenging to standard therapies, and reducing mTOR activity significantly impairs cancer growth by breaking their metabolic flexibility. Moreover, mTORC2 is rising as a critical player in glutamine cellular metabolism as it controls the expression of Myc (77). It has been shown that the knockdown of Rictor reduces α-KG levels, which are expected to have originated from glutaminolysis, indicating that mTORC2 can control this process (78). Earlier findings have demonstrated that the mTORC2/AKT axis may not affect glutamine metabolism or consumption (79). A recent study suggested a connection between stimulated mTORC2-facilitated AKT phosphorylation and glutaminolysis through different mechanisms. In addition, low levels of glutamine or its substrate activate mTORC2, as revealed by the phosphorylation of AKT. Moreover, low levels of glutamine reduce the activity of mTORC1, whereas mTORC2 activity increases (80). Inhibiting the activity of mTORCs stimulates glutaminolysis, signifying an additional multifaceted feedback loop, possibly to confirm TCA replenishing as mTOR signaling declines.

mTORCs play a crucial role in controlling glutamine metabolism in cancer cells. By serving as a sensor of metabolic nutrient accessibility, mTORCs not only affect cellular development and propagation, but are also tortuously associated with the metabolic needs of tumor cells to promote a favorable microenvironment for tumor progression. Further studies are required to elucidate the precise mechanisms behind the regulatory role of mTORCs for glutamine use. It is crucial to develop effective therapies that disturb the metabolic routes that tumor cells manipulate to accomplish their rapacious energy requirements.

4. Critical role of mTOR in the protein metabolism of cancer cells

mTOR has a central function in controlling protein metabolism in cancer cells, functioning as a central hub that combines numerous signaling cascades, the availability of nutrients, and energy situations to regulate cellular growth, propagation and metabolic variation. Understanding the importance of mTOR in protein biosynthesis and metabolism is necessary for illustrating how malignant cells achieve their elevated need for proteins, crucial constituents for cell structure, role, and signaling during cancer propagation. Protein biosynthesis is correctly regulated and requires essential and nonessential amino acids. Cancer and non-cancer cells obtain these molecules through growth factor signaling by providing surface transporters, which allow them to direct these molecules from external sources and maintain mTOR-signaling networks (81,82).

mTORC1 is mainly involved in stimulating protein biosynthesis across its effector molecules (Fig. 2). mTORC1 phosphorylates the two main effecters for protein translation, 4E-BP1- and S6K1. S6K1 phosphorylates a number of factors that are directly or indirectly involved in protein biosynthesis, such as PDCD4, SKAR eIF4B and eIF3 (83,84). Notably, mTORC1 is stimulated by amino acids to promotes protein biosynthesis through its active functions in translation and ribosome synthesis, phosphorylating S6K and the initiation factor 4E-BP for eukaryotic translation (85-87). This phosphorylation cascade enhances the translation of mRNAs involved in ribosome biogenesis and protein synthesis (88-91). A crucial aspect of the role of mTORC1 is that it enhances ribosomal protein synthesis, which is necessary for cellular growth and proliferation. A previous study revealed that mTORC1 notably affects ribosome biosynthesis in lung cancer cells, emphasizing its function in supporting tumor cell growth through enhanced protein biogenesis (92). With the increase in ribosome biosynthesis, mTORC1 accelerates the total protein biosynthesis rate, thus driving energetic tumor cell metabolism towards progression and malignant behavior. Furthermore, the interplay between mTOR roles and oncogenic cascade is crucial for understanding the function of mTOR in cancer development (93).

mTORC1 activation is related to the oncogenic action of Myc. Myc enhances the expression of genes involved in protein biogenesis, and its activity is mainly mTOR-dependent, demonstrating that mTOR inhibitor drugs may be an efficient therapeutic approach in Myc-dependent tumors (94,95). In contrast to the above, the dysregulation of mTOR signaling triggers the abnormal metabolism of protein, causative of tumor cell persistence and drug challenge, as demonstrated in research investigating the effects of mTOR inhibitors in several tumor models, including renal adenocarcinoma (96). Recent developments in cancer research biology have shown that the function of mTOR is not merely the regulation of protein biogenesis. Still, it extends to controlling the balance of the anabolic and catabolic pathways, such as autophagy. Under high nutrient availability, mTORC1 stimulates protein production while hindering autophagy, a safe process for degrading excessive or malfunctioning proteins and damaged cellular components. Genomic data showed that treatment with rapamycin was related to a decline in the transporters of neutral amino acids (97). Suppressing either Raptor or Rictor reduces, whereas their mutual knockdown blocks transport action for alanine and leucine amino acids (98). In addition, mTORC1 controls the transfer of the aforementioned transporters through the inhibition of Nedd4-2 ubiquitin ligase activity, which stimulates ubiquitination and diminished expression levels of the mentioned transporters (99). Moreover, the inhibition of mTOR activity with Torin 1 diminishes the transcription of the gene for amino acid enzymes and transporters essential for amino acid and protein metabolism (100).

Furthermore, mTORC2 is directly engaged in the metabolism and transport of amino acids through Ser26 phosphorylation of cysteine-glutamate antiporter, which impedes the glutamate output and cysteine input (101). Therefore, the aforementioned data support the critical roles of mTORC1 and mTORC2 in modulating protein metabolism and synthesis by regulating the transporter activity and/or level of amino acids. mTOR regulates asparagine synthetase (ASNS) expression levels (102,103). mTORC1 controls the ASNS expression level (104). In lung adenocarcinoma, the elevated level of KRAS promotes ASNS activity that occurs through AKT and Nrf2, facilitating the stimulation of ATF4. Mutually AKT inhibition with the reduction of cellular asparagine inhibits cancer growth (105). Rapamycin stimulates the gene machinery of argininosuccinate synthetase-1 (ASS1), the crucial enzyme for arginine synthesis (98). Arginine-deficient cancers, for example hepatocellular carcinoma and melanoma, are resistant to arginine deiminase therapy that reduces the cellular arginine and increases ASS. These tumors become primarily sensitive to dual inhibitors of PI3K and AKT (106); thus, mTORC2 is involved in arginine biosynthesis. *De novo* serine and glycine synthesis are also increased by mTORC1 via ATF4, the transcription factor (107). Ultimately, the mTORCs, through an indirect pathway, may be involved in protein and amino acid synthesis via their activity in other metabolic signaling cascades.

This paradox is critical for appreciating the metabolic modification of tumor cells, as a high mTOR activity can increase survival by inhibiting the autophagy pathway, permitting an accumulation of the necessary proteins for fast cell progression and proliferation (108). Therefore, targeting mTORC1 and mTORC2 therapeutically interrupts this balance, stimulating autophagy to fight carcinogenesis efficiently.

5. Critical role of mTOR in the fatty acid metabolism of cancer cells

The importance of the mTOR pathway in controlling FA metabolism is a primary mechanism enabling tumor growth and persistence Fig. 2. Cancer cells create fatty acids for lipid membrane, lipid alterations, and signaling cascade action (103-109). FA synthesis requires acetyl-CoA and cytosolic form (NADPH) of the reducing agents. Dynamic FA synthesis relies on the incorporation of additional carbon metabolic signaling pathways and oxidation-reduction reactions. Glucose is the main precursor of acetyl-CoA for FA synthesis in the majority of culture media (110-112).

In hypoxic and mitochondrial malfunction, acetate glutamine and leucine breakdown are another resource for acetyl-CoA (113-117). Additionally, study revealed that FAs synthesis is controlled by the sterol regulatory element-binding protein 1 (SREBP-1) transcription factor (118). SREBP-1 regulates the enzymes needed to transfer the acetyl-CoA into fatty acid and the PPP enzymes needed to convert acetate and glutamine to acetyl-CoA. Thus, SREBP-1 controls genes that help or catalyze FA synthesis (119). In tumor cells with an abnormal rate of FA synthesis, the mTOR pathway, across its subsequent target S6 Kinase (S6K), stimulates and promotes the transcription activity of both SREBP-1 and SREBP 2. The ultimate proteins regulate the transcription activity of different genes that relate to sterol biosynthesis (120). Therefore, SREBP-1 and SREBP-2 are essential for mTOR to promote and stimulate cell growth and proliferation. Tumor and normal cells take FAs and lipids from the extracellular sources to use them to maintain the synthesis of cell membranes. In presence of growth factors, PI3K increases FAs and lipid use and downregulates oxidation of lipid through (β-oxidation) within the mitochondrial matrix to continue cell growth and proliferation (121).

In tumor cells and under hypoxic conditions, the mTOR pathway enhances endoplasmic reticulum action to sustain protein biosynthesis via an extracellular resource of unsaturated FAs. Moreover, ATP citrate lyase, the final enzyme that alters acetate to acetyl-CoA, inhibits tumor cell growth and propagation (122). Thus, targeting FA synthesis and transport can reduce tumor cell growth and proliferation. mTOR is a critical regulator of various metabolic pathways in cancer cells, including fatty acid metabolism, which is essential for understanding tumor biology and therapeutic interventions. mTOR modulates metabolic processes by integrating nutrient signals, growth factors, and stressors. Given that cancer cells exhibit altered metabolism, often adapting to exploit various substrates, the importance of mTOR in controlling the metabolism of fatty acids stands out as a primary mechanism enabling tumor growth and persistence.

Cancer cells have a reprogrammed metabolism to meet the increased requirements for fuel and building blocks required for fast proliferation. In this context, FAs function as primary energy resources and synthesize different biomolecules, including cell membranes and signaling biomolecules. mTOR plays a central role in FA synthesis by controlling the expression and activity of lipogenic enzymes. It has been demonstrated that mTORC1 directly activates SREBP1, causing an increase in the expression of FA synthase and subsequent FA synthesis (123). Consequently, the activating mTORC1 pathway enhances lipogenesis, which is particularly relevant in cancer types characterized by increased demand for lipids.

Moreover, PI3K/AKT/mTOR oncogenic cascade pathways are frequently dysregulated in several types of cancer, further enhancing lipogenic activities. For example, in thyroid gland cancer, pyruvate carboxylase, an enzyme key for transferring pyruvate to oxaloacetate, stimulates aggressive cancer action partially through increased lipogenesis, which is controlled through mTORC2 signaling (124). This reveals that mTOR signaling not only accelerates the uptake of FA, but also vigorously provides for their biosynthesis, providing cancer cells with an adaptable energy source to acclimate under unusual physiological stresses. Recent research suggests a growing interest in how specific FAs influence mTOR signaling and metabolic reprogramming in cancer cells through the high expression of several enzymes that are essential for FAs metabolism, such as carnitine transporter, CPT isoforms and CD36 in several types of cancer, such as gastric and prostate cancer, and triple-negative breast cancer (TNBC) (125). Some researchers have investigated the function of omega-3 FAs that have been shown to reduce mTORC1 signaling activity, theoretically leading to diminished FA synthesis and boosting apoptosis in tumor cells (126). This provides prospective opportunities for a therapeutic approach, as combining mTOR inhibitors with dietary FA variation could provide a dual-target system to hinder tumor cell growth and stimulate metabolic susceptibility.

6. Critical role of mTOR in nucleotide biosynthesis and cancer cell growth

mTORCs are key regulators of cell metabolism, specifically from the perspective of nucleotide biosynthesis, which is necessary for tumor cell development and proliferation (Fig. 2). Nucleotide biosynthesis (purine and pyrimidine) is critical in rapidly-dividing cells, particularly, in cancer cells with sufficient precursors for RNA and DNA synthesis. The nucleotide biosynthesis is a complex process, demanding enormous support from additional metabolic signaling pathways in a specific manner. R5P is the intermediate product of the PPP that provides the main sources for phosphoribosylamine and glutamine. R5P also functions as an amide precursor for nucleotide biosynthesis (127,128). In addition, one carbon cascade is an additional resource for different non-methyl-group and non-essential amino acids that are involved in pyrimidine purine biosynthesis. Moreover, the TCA cycle supplies the oxaloacetate that is transaminated to aspartate, and its vital element that is necessary for nucleotides base synthesis (129-131). Therefore, the inhibition of nucleotide biosynthesis by pharmacological therapies may be an effective approach for eradicating specific tumors, such as antifolates and nucleosides that have been used in the treatment of cancer for a number of years (132).

The activation of the mTORC1 pathway has been shown to stimulate pyrimidine biosynthesis (132). Ribosomal K6S stimulates the phosphorylation of carbamoyl-phosphate synthetase 2, aspartate transcarbamylase, and dihydroorotase (CAD), a specific enzyme that stimulates the first reaction of pyrimidine synthesis (133,134). mTORC1 actively stimulates nucleotide breakdown by controlling the upregulation of central enzymes in de novo nucleotide biosynthesis. Research has revealed that mTORC1 stimulation boosts the biosynthesis of phosphoribosyl pyrophosphate amidotransferase, a key enzyme in the purine biosynthesis pathway. This control enhances the purine nucleotide level that supports tumor cell growth and progression (135).

Moreover, mTORC1 incorporates signals from different nutrient availability, mainly amino acids, to certify that nucleotide synthesis is associated with the metabolic requests of rapidly growing cancers. In addition to supporting nucleotide biosynthesis, the mTORC1 pathway is highly linked to controlling metabolic cascades that produce R5P, a key factor for the biosynthesis of nucleotides. The PPP produces R5P from glucose-6-phosphate, emphasizing the interconnection between the glycolytic pathway, mTOR signaling, and metabolism of nucleotides (136-138). When glucose freely exists, mTORC1 triggers cellular propagation by increasing glycolysis and nucleotide biosynthesis signaling pathways, assisting tumor cells to proliferate quickly.

Furthermore, the communication between mTORC2 and oncogenic cascades, such as the PI3K/AKT signaling pathway, further highlights the importance of mTORC2 in nucleotide synthesis and tumorigenesis. For example, PI3K/AKT pathway activation triggers mTORC2, stimulating fat and nucleotide biosynthesis that is critical for cancer cell growth. mTORC2 signaling is often dysregulated in breast cancer; targeting this pathway can impede nucleotide synthesis, impairing cancer growth (139-143).

7. Significance of the interplay between AMPK and mTOR complexes to cancer cell metabolism

The mTOR complexes, mTORC1 and mTORC2, are pivotal regulators of cancer cell metabolism by integrating nutrient availability with signals that drive cell growth and proliferation (Fig. 3). AMPK is an intracellular sensor for energy equilibrium, which is presented in each eukaryotic cell.

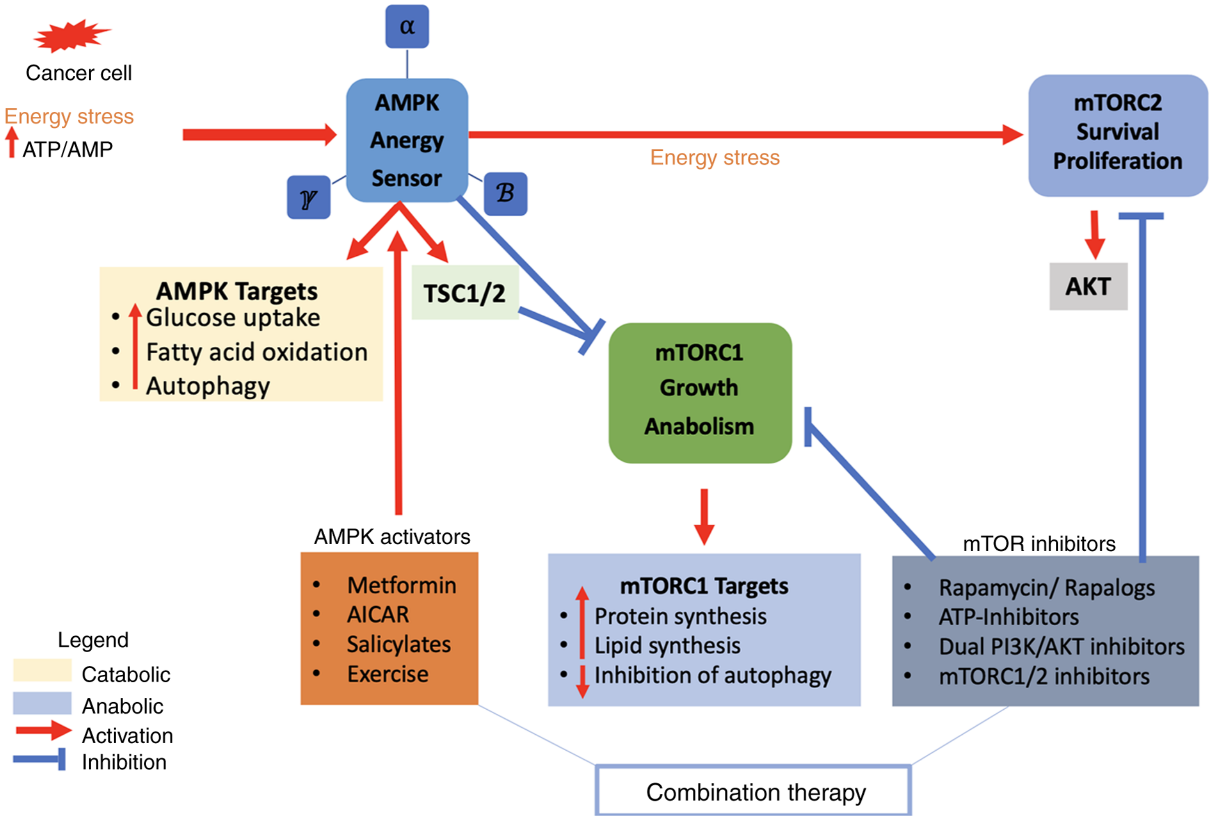

Figure 3. Combination therapy strategy. Under energy stress, AMPK is activated, inhibiting mTORC1 through direct and indirect inhibition by TSC1/2 activation and activating mTORC2. AMPK inhibits the anabolic pathways that are under mTORC1 activation. AMPK activators and mTORC1/2 inhibitors stimulate the catabolic pathways and reduce the cell growth, survival, and propagation of cancer cells. mTOR, mammalian target of rapamycin; mTORC, mammalian target of rapamycin complex; AMPK, AMP-activated protein kinase; TSC1/2, tuberous sclerosis protein 1/2.

AMPK consists of three subunits; (α) is the enzymatic subunit and (β and γ) are the controlling subunits. Different isoforms have been encoded by certain genes for each submit in humans (144). AMP/ATP and ADP/ATP ratios stimulate AMPK during severe energy stresses. The activation of AMPK restores energy redox hemostasis by turning on the catabolic cascade and turning off the anabolic cascades to increase ATP production and maintain the energy equilibrium (145,146). Moreover, AMPK stimulates glucose consumption through the oxidation process in low proliferative cells rather than rapid glucose utilization and glycolysis that are employed in high proliferative cells (147,148). In yeast, the AMPK analog is essential to shift the metabolism of yeast from fermentation (glycolysis) to OXPHOS metabolism under severe starvation situations. This rewired metabolism is similar to the reversal of aerobic glycolysis (Warburg effect) that occurs in a number of rapidly-growing cells, such as cancer cells (128). Salicylate and metformin are the pharmacological activators of AMPK (149,150). They activate AMPK through threonine residue (Thr172) phosphorylation and AMP binding (151-153). The actions of AMPK occur through three different mechanisms: i) The enhanced phosphorylation of Thr 172 via LKB1; LKB1 is a tumor suppressor, and it is the main upstream target of AMPK; ii) reduced Thr172 dephosphorylation by a phosphatase; and iii) activated allosteric stimulation. All AMPK activations occur due to AMP binding to itself and not due to the upstream kinase outcome or phosphatase (152-154). Together, the complex interaction between mTORCs and AMPK signaling cascades signifies a crucial metabolic step that guides cells to anabolic processes that stimulate cancer development or turn to catabolic process pathways that may defeat carcinogenesis.

AMPK redeems the energy balance following its activation via energy stress by activating the catabolic signaling cascade to produce sufficient ATP and by reducing the anabolic cascades that use ATP (154,155). The loss of a single allele of AMPK-α increases the development of B-cell lymphoma in mice with c-Myc transgenic expression in B-cells, whereas the loss of both alleles prompts a severe outcome (156). Therefore, this reveals that AMPK may serve as a tumor suppressor, and any mutation in the genes of AMPK subunits is uncommon in human tumors. Consequently, diminished AMPK actions may be necessary for cancer cell survival and malignancy by constraining the specific effects of AMPK on cell development and propagation (157). The activation of AMPK is a suitable approach to decrease tumor cell metabolism by hindering the anabolic cascades and stimulating the catabolic cascades. Histological slides from a human breast tumor study indicated that the phosphorylation ratio of AMPK-α enzymatic subunits was less than that of adjacent normal tissue (158). Another study revealed that the phosphorylation of AMPK-α is a common occurrence in patients with hepatocellular carcinoma (159). Additionally, another study demonstrated that AMPK is a negative switch of the Warburg effect in cell and animal models (160). Several mechanisms have been suggested to elucidate the reduction of AMPK activity. For example, the genetic damage of LKB1 is relatively common in cervical and non-small cell lung tumors but not in other tumors (161-163). The activation of insulin/IGF1 controls the protein kinase AKT/PKB is additional machinery for downregulation of AMPK, gain function genes mutations of AKT and loss-of-function mutations of PTEN (tumor suppressor) that happen in various tumors (164-166). Collectively, the regular arrangement of AMPK inactivation across various tumor types through several biomolecular mechanisms such as downregulation of LKB1, loss of PTEN and Akt/PKB upregulation, highlights the basic roles of AMPK as an energy and metabolic master, which represents a hopeful therapeutic approach for correcting the unusual energy status that supports cancer cell persistence and propagation.

In addition, AMPK has an essential pro-survival function in hepatocellular carcinoma, pancreatic ductal adenocarcinoma (PDAC) and AML through various mechanisms. A key feature of AMPK is its role in buffering ROS, which are frequently raised in tumor cells due to high metabolic requirements to support tumorigenesis characters. The activation of AMPK enhances the antioxidant ability by stimulating the main enzymes for antioxidant activity, such as superoxide dismutase and glutathione (GSH; specifically, by modifications of the regulatory metabolism of GSH and regeneration pathways of NADPH), thus reducing oxidative stress and supporting cell survival (167,168). Additionally, in the cancer microenvironment, AMPK stimulates metabolic modifications, such as increasing the oxidation of FA and downregulating the mTOR cascade by phosphorylating acetyl-CoA carboxylase and fatty acid synthase, allowing tumor cells to generate a sufficient amount of ATP under different unfavorable and stressful conditions (169). Moreover, AMPK stimulates cell cycle progression in hepatocellular carcinoma by modifying the essential enzymes that are necessary for cell-cycle checkpoints system, mainly the transition of G1/S (170). Under different stress conditions, AMPK stimulates the phosphorylation of the p53-p21 axis, and PERK-eIF2α in hepatocellular carcinoma, PDAC and AML respectively, thus promoting cell cycle arrests, preventing DNA damage and promoting cell survival (170-172). PDAC, hepatocellular carcinoma and AML cells utilize the activation of AMPK to support cancer progression under severe metabolic stress by stimulating the autophagy regulators, such as beclin 1(BECN1), unc-51 like autophagy activating kinase 1(ULK1) and transcription factor EB (TFEB), promoting the degradation of protein aggregates and damaged microgranules that would then stimulate the apoptotic pathway (173). Recently, a previous study have revealed that the activation of AMPK in AML cells induces the downregulation of mTOR and increases autophagy, generating a metabolically challenging phenotype that leads to drug resistance (172). AMPK also controls mitochondrial dynamics and biogenesis, confirming that leukemic cells preserve adequate bioenergetic ability for survival and cancer progression (174). Taken together, these mechanisms emphasize the roles of AMPK in regulating tumor cell survival, proposing its prospective approach as a therapeutic strategy in hepatocellular carcinoma, PDAC and AML.

Furthermore, the roles of AMPK depend on the mechanistic foundation for this functional shift that present inside cellular microenvironment such as nutrients levels and hypoxia (175). Through the early steps of cancer transformation, when cells preserve sufficient nutrients and oxygen, AMPK stimulation functions as an energy check that inhibits uncontrolled propagation by preventing main anabolic cascade, such as FA biosynthesis, protein transformation and the biosynthesis of nucleotides. The oppressive function of AMPK is facilitated across the phosphorylation of acetyl-CoA carboxylase, leading to reduced FA biosynthesis, and mTORC1 inhibition, which diminishes protein biosynthesis and cell progression (176). Moreover, AMPK stimulates mitochondrial genesis and autophagy processes that typically helps the cellular microenvironment, but can ironically help established cancers facing sever nutrient stress (177). Therefore, the shifting from cancer suppressor to cancer promoter occurs when tumor cells face metabolic restrictions through the cellular environment, where the pro-survival roles of AMPK become beneficial for cancer growth and development.

In breast cancer, AMPK displays perhaps the most well-known dual roles, with its function determined mainly by tumor stage, phenotype and microenvironmental situations (178). In hormone receptor-positive breast cancers, AMPK stimulation is associated with improved patient outcomes and minimized tumorigenesis (179). The tumor suppressive properties are facilitated through the ability of AMPK to inhibit the mevalonate cascade, decreasing cholesterol biosynthesis that is critical for ER-receptor stimulation, and through the direct suppression of FAS, constraining cell membrane biogenesis required for rapid cell proliferation and division (180). Metformin, as indirect activator of AMPK, exhibits significant anti-tumor roles in this situation by stimulating metabolic stress and increasing insulin sensitivity (181).

Conversely, in TNBC, AMPK mainly has an oncogenic function and promotes metastasis. Under sever low O_2 conditions, commonly observed in severe aggressive breast cancers, AMPK enables metabolic switching to glycolysis and supports autophagy-mediated persistence. This is mainly evident in drug-resistant TNBC cells, where the activation of AMPK assists survival during nutrients stress induced by cytotoxic compounds (182). The protein biosynthesis promotes cancer cell metastasis through controlling the dynamics of cytoskeletal and stimulates blood vessels growth via HIF-1α maintenance (183). Moreover, in $HER2^+$ breast cancers treated with trastuzumab, AMPK-induced autophagy provides a resistance mechanism by reusing cellular element to sustain energy equilibrium during targeted drug-promoted stress (184).

In addition, lung adenocarcinoma presents a special model for acknowledging the dual roles of AMPK due to the high mutation rate pf LKB1, the main upstream signaling kinase that controls the activation of AMPK (185). In the presence of wild-type LKB1, AMPK sustains its tumor suppressive roles across traditional mechanisms, such as the activation of TSC2 and the final inhibition of mTORC1 (186). Lung cancer reacts positively to severe metabolic stress and exhibits a response to AMPK activators, such as metformin and AICAR (187). The tumor inhibition features are highlighted through the inhibition of glycolysis flux, increased oxidative metabolism, and sustained cell cycle checkpoints that stimulate apoptosis in response to oncogenic burden and stress (188). Nevertheless, ~30% of non-small lung cancer (NSLCS) cases harbor LKB1 mutations, primarily shifting the functions of AMPK and removing its tumor suppressive ability. In these cancers, different signaling cascades compensate for the damage of AMPK-facilitated metabolic controlling, leading to increase in addiction on glutamine and glucose metabolism (189). Paradoxically, while AMPK is activated in LKB1-mutant lung adenocarcinoma, it can stimulate tumor propagation by accelerating metabolic modification to nutrient restriction and oxidative stress (190). This is mainly significant in KRAS-dependent lung adenocarcinoma, where AMPK supports maintain redox balance during oncogene-mediated metabolic stress (191). Moreover, hypoxic areas within lung cancers manipulate AMPK to stimulate VEGF upregulation and increase angiogenesis, promoting cancer vascularization and progression (192).

Moreover, AMPK displays a dual role in colorectal cancer progression through its complex connections with different inflammatory and metabolic signaling pathways (193). In the initial stages of colorectal cancer, mainly in the stage of inflammatory intestine disease and abnormal polyposis, AMPK plays a protective role by inhibiting the chronic inflammatory reaction inside bowel and decreasing oxidative damage by inhibiting the NF-κB pathway activity, thus decreasing assembly of pro-inflammatory elements such as cytokines that trigger cancer initiation and development (194). AMPK also inhibits the Wnt/β-catenin pathway in APC-mutant colorectal tumors, reducing one of the main drivers of colorectal cancer growth (195). As colorectal cancer proceeds to more advanced phases, the function of AMPK changes towards cancer promotion, specifically in the mediating of hepatic metastases where metabolic needs are enhanced. In the advanced stages of colorectal cancer, cells use AMPK-drive metabolic reprograming to modify to the liver microenvironment that differs drastically from the colonic tissue in terms of metabolic availability and nutrients requirements (196). Hypoxic areas within colorectal tumors employ AMPK to sustain glycolysis bioproducts and stimulate autophagy-promote survival during periods of hypoxic angiogenesis. Additionally, AMPK accelerates resistance to regular drugs such as 5-fluorouracil by increasing nucleotide salvage cascades and supporting cellular energy equilibrium through treatment-mediated metabolic stress (197).

Additionally, hepatocellular carcinoma provides a convincing model of how AMPK functions under different metabolic stress conditions. In the pre-carcinogenesis stage of fatty liver and steatohepatitis, AMPK functions as an essential tumor suppressor by inhibiting fatty liver accumulation and decreasing oxidative damage. AMPK inhibits SREBP-1C to trigger lipogenesis and β-oxidation, thus diminishing the inflammatory environment that prompts the progression of hepatocellular carcinoma (198). This protective role is mainly evident in patients with diabetes mellitus, when AMPK is activated through metformin and provides hepatoprotective benefits, decreasing the risk of developing hepatocellular carcinoma (199). Once hepatocellular carcinoma develops, particularly in conditions of chronic hepatic diseases and cirrhosis, AMPK shifts to a tumor-accelerator role. In the microenvironment with severe metabolic deprivation and hypoxia, the metabolic modifications of AMPK become beneficial for carcinogenesis (200). In hepatocellular carcinoma, AMPK reprograms glutamine metabolism as the main energy source when glucose sources become limited, stimulating autophagy-enhanced persistence during sorafenib treatment (201). AMPK also accelerates modification to the unique metabolic difficulties of the liver microenvironment, where competition for metabolic elements with adjacent hepatocytes and immune cells generates selective pressure for metabolically adaptable cancer cells (202,203).

The mechanistic interaction between the redox metabolic roles of AMPK and hormonal signaling pathways to regulate cancer behavior has also been observed in prostate cancer (PC). In hormone-sensitive prostate cancer, AMPK displays well-defined tumor suppressive roles through its connections with the AR signaling pathway in androgen-sensitive PC (204). The activation of AMPK decreases AR transcription directly and indirectly through phosphorylation-trigger inhibition and via the suppression of mTORC1 activity, respectively, which is necessary for AR protein biosynthesis (205). AMPK also reduces lipid biosynthesis cascade, which are necessary for building blocks to support high PC proliferation and arrest the cell cycle through p21 stimulation (206). These results provide good outcomes for patients with identified PC who sustain usual metabolic function. During the transition to castration resistance, PC marks an important shift in the function of AMPK towards a tumor developer (207). AMPK become an essential player in metabolic reprograming and tumor survival in the AR-depleted milieu formed by AR deprivation chemotherapy. In the androgen-depleted environment created by androgen deprivation therapy, AMPK becomes essential for metabolic adaptation and survival. PC cells manipulate AMPK to stimulate AR-VS splicing (alternative splicing of AR variants) that maintain main activity in the absence of AR, accelerating hormone-independent progression (208). Under the low O_2 conditions normally established in advanced-stage PC, AMPK stimulates metabolic switching from OXPHOS to glycolysis and increases autophagy-facilitated survival in docetaxel resistance PC patients. Survival function is particularly evident in docetaxel resistant (207,208).

A number of anabolic signaling pathways are activated by the mTORC1 pathway, which, in the end, inhibits AMPK activation (209). This inhibition occurs through various mechanisms, such as TSCs phosphorylation or the phosphorylation of Raptor, a regulatory part of mTORC1 (210,211). Thus, AMPK activation inhibits the biosynthesis of lipids, nucleotide, and proteins, reducing cell growth and proliferation. Moreover, it arrests the cell cycle at the G0/G1 phase by stimulating p53 phosphorylation, thus preventing DNA biosynthesis (212-214). Conversely, it has been demonstrated that AMPK can directly stimulate mTORC2 by phosphorylating its parts, supporting cell growth and survival during severe energetic stress (215,216). Therefore, both roles of the AMPK regulator with the inhibition of mTORC1 stimulate anabolic pathways; the potential stimulation of mTORC2 highlights a multifaceted association that should be cautiously modified to accomplish efficient tumor therapy.

In various types of malignancies, such as colorectal, PDAC and glioblastoma, the association between mTORC1 and AMPK is necessary for cell progression under metabolic stress environments. Data from hepatocellular carcinoma study have established that the deprivation of amino acids and the later re-addition of leucine lead to a specific alteration in mTORC1 activity, with the consequent stimulation of AMPK during glutamine deficiency, promoting the inhibition of the mTORC1 cascade (217). This suggests that the glutamine level and nitrogen source, which modify the metabolic environment, can significantly regulate mTORC1 stimulation across the AMPK signaling pathway, suggesting a feasible therapeutic area for tumor glutamine-dependent metabolism. Furthermore, data from T-cell acute lymphoblastic leukemia studies have revealed that AMPK stimulation is crucial for glycolytic intermediates ratio/mitochondrial function and metabolism, consequently accelerating the downregulation of mTORC1 in situations of severe metabolic stress (218,219). Additionally, emerging data from an AML study have revealed a complex association between the role of AMPK and mTORC1; these appear to function through two parallel essential cascades that connect the activation of mTORC1 and glucose metabolism to control the complete cellular homeostasis (220). The co-activation of AMPK and mTORC1 within specific leukemia cells demonstrates the paradoxical landscape of these metabolic pathways, with AMPK fostering OXPHOS, whereas mTORC1 mainly triggers glycolysis. This indicates that controlling AMPK activity could produce distinctive effects in metabolic reprogramming, conditional on the specific cancer environment (221,222). Furthermore, the link between mTORC2 and AMPK is progressively acknowledged as a critical factor in regulating the metabolism of several cancers and treatment responses. While mTORC1 has been significantly studied for its function in growth signaling, mTORC2 is more strictly connected with cell survival and metabolism through switching, as for example, metabolic deprivation and the withdrawal of growth factors. Data from recent project on colorectal cancer have demonstrated that AMPK stimulation can boost mTORC2 signaling, stimulating cell growth and survival under different nutrient deprivations (223). This association suggests a complex response mechanism. At the same time, AMPK usually serves to impede mTORC1 activities in a low energy environment. Still, it can also maintain mTORC2, thus permitting the stimulation of pro-survival metabolic pathways throughout AKT phosphorylation, finally modifying cancer aggressiveness (224). Study on lung cancer that are resistant to EGFR inhibitor therapy have demonstrated that mTORC2 is necessary for mediating resistance against the aforementioned inhibitors. Upregulated mTORC2 helps to sustain lung cancer cell propagation despite EGFR inhibitors (225). AMPK shapes cellular reactions in such models, theoretically stimulating a shift towards an aerobic glycolysis pathway to meet energy demands under therapy-induced stress. The role of AMPK not only affects mTORC2, but also overlaps with additional oncogenic cascades, encouraging metabolic switches that maintain cell growth and proliferation (226). These data mutually demonstrated that the AMPK/mTORC1 signaling pathway functions as a in adynamic and metabolic control, where the stability between these two contrasting cascades regulate tumor cell outcome and metabolic elasticity, emphasizing the essential for accuracy therapeutic methods that need for cancer-specific metabolic addictions and microenvironmental restrictions.

Moreover, from the perspective of pancreatic cancer, the mTORC2 pathway has been connected to modifying metabolic flexibility and response to different therapies, such as PARP inhibitors. A study in this area has confirmed that mTORC2 signaling controls DNA repair by regulating BRCA1 (227). The precise interaction between AMPK and BRCA1-dependent processes is still being disclosed. However, it highlights the possibility of the AMPK-regulated modulation of mTORC2 increasing therapeutic sensitivity, possibly providing dual therapies that control these signaling pathways. Furthermore, the notion that mTORC2 provides glycolytic switching in response to elevated glutamine levels underlines the necessity to appreciate the dynamic interaction between metabolic availability and mTORC2 action through AMPK (228). In a study on glioblastoma, the AMPK/mTORC2 axis displayed its functions in stimulating cell survival during nutrient deprivation, which is critical as these tumor cells frequently encounter shifting metabolic environments within tumors. The upregulation of mTORC2 by AMPK increased AKT signaling, which helps support cellular stability and functions and escape apoptosis when the growth factor is diminished (229). This role of AMPK may appear paradoxical given its established function in inhibiting mTORC1; however, it affirms the importance of context-dependent signaling where AMPK activation can favor survival by engaging mTORC2 while simultaneously restraining excessive mTORC1 activity.

The clinical efficiency of mTOR inhibitors is dependent on the progress of developed resistance; there are numerous connected molecular mechanisms that have been significantly described. The PI3K/AKT/mTOR signaling pathway is a highly conserved signal transduction pathway in eukaryotic cells that stimulates cell survival, cell progression, and cell cycle events, and any malfunction of this signaling pathway can prompt to tumor development (230). Tumor cells can modify their response against mTOR inhibitors by stimulating compensatory persistence pathways that overcome the therapeutic blockade through various key processes.

The stimulation of receptor tyrosine kinases, such as IGF-1R, HER2/neu and EGFR is one of the highest prominent resistance mechanisms against mTOR inhibitors. These receptors can be overactivated in response to mTOR inhibitors, generating other signaling pathways that maintain cellular growth and development (231). Another study has confirmed that resistance to PI3Kβ/AKT inhibition in PTEN-null breast cancer cells is conferred by the loss of specific genes in the PI3K/AKT/mTOR pathway, including TSC1/2, INPPL1 and PIK3R2 relatively than genes connected with different signaling cascades (232). This result emphasizes there is an intrinsic pathway of resistance.

Moreover, mutations of S6K1 and 4E-BP1 can reduce cell dependence on the mTOR pathway for protein biosynthesis and development regulation. Cancer cells have a special metabolic shifting that represents another critical feature of developed resistance, where persistent mTOR inhibition pushes tumor cells to increase their dependance on different metabolic signaling pathways, such as GLUT1 stimulation to increase glucose usage through, aerobic glycolysis, and stimulation of autophagy for prorogation purpose (233). Additionally, histone modification, DNA methylation are epigenetic modifications that significantly contribute to the secure resistance for several phenotypes, making these modifications mainly challenging to available chemotherapy (234).

PI3K/AKT rebound activation can be the highest clinically important limitation of mTOR inhibitors. This phenomenon occurs through the disturbance of negative-feedback loops in the PI3K/AKT/mTOR axis (235). In addition, the key mechanism has been recorded in the recent literature, and it is described as the basic challenge for the single mTOR inhibitor chemotherapy (236). The activation of mTOR causes a negative feedback-loop control through S6K1 that decreases the activity of PI3K and S6K1 phosphorylation deactivates IRS-1 that is required for insulin signaling through PI3K (237). The degradation of IRS-1is required for the subsequent and constant attenuation of PI3K/AKT signaling under normal homeostasis conditions (238). Conversely, once mTOR is inhibited using a single mTOR inhibitor, this negative loop is perturbed, causing IRS-1 stabilization and accumulation. In addition, use of mTOR inhibitor will prompt IRS-1stimulation releasing the negative loop, resulting in paradoxical cascade restimulation (239).

Mechanistically, recent studies have specified more details about the dynamic of the rebound activation phenomenon. Inhibition of PI3K cascade blocks phosphorylation of 4E-BP1 through mTOR which then inhibits translation of PTEN, causing a rebound of AKT phosphorylation 2-4 h after-treatment (240). This rapid reactivation displays that the compensatory reaction occurs within hours of treatment initiation, efficiently reducing the therapeutic margin of mTOR inhibitors. The accumulated IRS-1 then serves as an effective upstream activator for PI3K, causing a strong phosphorylation and activation for PI3K that can surpass the initial level detected pretreatment (241). The effective stimulation of PI3K helps to avoid the pro-apoptotic action of mTOR inhibition, promote cell survival, propagation and metabolic switching. The consequences of this challenge phenomena it modifies the cytotoxic or cytostatic intervention effect into a mysterious progression stimulating signal (242).

Imminent studies aim to employ the connections between AMPK and mTORC2, mainly focusing on understanding how this connection can be manipulated to improve treatment efficiency and cope with resistance mechanisms in tumor cells (243). These adverse dual roles of AMPK concurrently restraining mTORC1 whereas hypothetically boosting mTORC2 cascades discloses a new metabolic persistence way that supports tumor cells to sustain the cellular homeostasis under metabolic stress, suggesting that efficient therapeutic approach must hit both mTORCs in combination with AMPK signaling to stop redeeming persistence mechanisms and shifting metabolic routes.

Targeting the AMPK/mTORC2 signaling cascade opens a new avenue for groundbreaking tumor therapies and emphasizes clarifying these complexes' signaling pathways to develop wide-ranging therapy approaches. The double role of AMPK in controlling both mTORCs clarifies new opportunities for targeted treatment approaches in several cancers is illustrated in (Fig. 3).

8. Conclusion and future perspectives

The complex metabolic switching of cancer cells is one of the most basic features of tumorigenesis, with AMPK and mTOR complexes serving as the primary regulators of this pathological alteration. The metabolism of cancer cells is well-known for its notable flexibility, enabling tumor cells to survive and proliferate under different microenvironmental situations through a metabolic rewiring strategy. The dysregulation of the AMPK/mTOR crosstalk orchestrates a wide-ranging metabolic renovation in tumor cells, endorsing enhanced glucose utilization, modified lipid metabolism, enlarged amino acid uptake, and adjusted nucleotide biosynthesis to meet the eminent biosynthetic requirements of rapidly dividing cells. This metabolic elasticity enables tumor cells to manipulate the Warburg effect, preferring glycolysis even in oxygen-rich environment, but concurrently sustaining the ability to use alternative energy sources during nutrient paucity.

The paradoxical role of AMPK in cancer cell metabolism, acting as both a tumor suppressor through metabolic control and a survival helper under a severe stress environment, highlights the complex metabolic modification mechanisms that tumor cells utilize. Moreover, the metabolic divergence and heterogeneity detected across different tumor types and even across specific tumors reveal complex interactions between AMPK/mTOR complexes signaling pathways and tissue-specific metabolic demands.

Understanding and clarifying these metabolic complexities is critical for formulating precision innovative oncology strategies to efficiently eradicate tumor cell metabolism without damaging normal cell function. As research advances towards more sophisticated, creative therapeutic approaches, manipulating the distinctive metabolism of cancer cells across a targeted variety of AMPK/mTOR pathways provides immense promise for inventing metabolically based therapy strategies that can subdue therapeutic challenges and advance patient outcomes against cancer.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Authors' contributions

AA conceived and supervised the review. AA wrote the draft of the review. SC reviewed and edited the review. AA and NF revised the review and prepared the figures. All the authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Fan H, Wu Y, Yu S, Li X, Wang A, Wang S, Chen W and Lu Y: Critical role of mTOR in regulating aerobic glycolysis in carcinogenesis (review). Int J Oncol 58: 9-19, 2021.
2. Hua H, Kong Q, Zhang H, Wang J, Luo T and Jiang Y: Targeting mTOR for cancer therapy. J Hematol Oncol 12: 71, 2019.
3. Zarogoulidis P, Lampaki S, Turner JF, Huang H, Kakolyris S, Syrigos K and Zarogoulidis K: mTOR pathway: A current, up-to-date mini-review (review). Oncol Lett 8: 2367-2370, 2014.
4. Lien EC, Lyssiotis CA and Cantley LC: Metabolic reprogramming by the PI3K-Akt-mTOR pathway in cancer. Recent Results Cancer Res 207: 39-72, 2016.
5. Mossmann D, Park S and Hall MN: mTOR signaling and cellular metabolism are mutual determinants in cancer. Nat Rev Cancer 18: 744-757, 2018.
6. Ramanathan A and Schreiber SL: Direct control of mitochondrial function by mTOR. Proc Natl Acad Sci USA 106: 22229-22232, 2009.
7. Warburg O: On the origin of cancer cells. Science 123: 309-314, 1956.
8. Wang N, Wang B, Maswikiti EP, Yu Y, Song K, Ma C, Han X, Ma H, Deng X, Yu R and Chen H: AMPK-a key factor in crosstalk between tumor cell energy metabolism and immune microenvironment? Cell Death Discov 10: 237, 2024.
9. Torres Acosta MA, Gurkan JK, Liu Q, Mambetsariev N, Reyes Flores C, Helmin KA, Joudi AM, Morales-Nebreda L, Cheng K, Abdala-Valencia H, *et al*: AMPK is necessary for Treg functional adaptation to microenvironmental stress during malignancy and viral pneumonia. J Clin Invest 135: e179572, 2025.
10. Marafie SK, Al-Mulla F and Abubaker J: mTOR: Its critical role in metabolic diseases, cancer, and the aging process. Int J Mol Sci 25: 6141, 2024.
11. Smiles WJ, Ovens AJ, Kemp BE, Galic S, Petersen J and Oakhill JS: New developments in AMPK and mTORC1 cross-talk. Essays Biochem 68: 321-336, 2024.
12. Keerthana CK, Rayginia TP, Shifana SC, Anto NP, Kalimuthu K, Isakov N and Anto RJ: The role of AMPK in cancer metabolism and its impact on the immunomodulation of the tumor microenvironment. Front Immunol 14: 1114582, 2023.
13. Zhang T, Wang X, Alexander PG, Feng P and Zhang J: An analysis of AMPK and ferroptosis in cancer: A potential regulatory axis. Front Biosci (Landmark Ed) 30: 36618, 2025.
14. Liao H, Wang Y, Zou L, Fan Y, Wang X, Tu X, Zhu Q, Wang J, Liu X and Dong C: Relationship of mTORC1 and ferroptosis in tumors. Discov Oncol 15: 107, 2024.
15. Sun Z, Liu L, Liang H and Zhang L: Nicotinamide mononucleotide induces autophagy and ferroptosis via AMPK/mTOR pathway in hepatocellular carcinoma. Mol Carcinog 63: 577-588, 2024.
16. Wang X, Tan X, Zhang J, Wu J and Shi H: The emerging roles of MAPK-AMPK in ferroptosis regulatory network. Cell Commun Signal 21: 200, 2023.
17. Lee H, Zandkarimi F, Zhang Y, Meena JK, Kim J, Zhuang L, Tyagi S, Ma L, Westbrook TF, Steinberg GR, *et al*: Energy-stress-mediated AMPK activation inhibits ferroptosis. Nat Cell Biol 22: 225-234, 2020.
18. Sun Q, Zhen P, Li D, Liu X, Ding X and Liu H: Amentoflavone promotes ferroptosis by regulating reactive oxygen species (ROS)/5'AMP-activated protein kinase (AMPK)/mammalian target of rapamycin (mTOR) to inhibit the malignant progression of endometrial carcinoma cells. Bioengineered 13: 13269-13279, 2022.
19. Chen W, Zhao H and Li Y: Mitochondrial dynamics in health and disease: Mechanisms and potential targets. Signal Transduct Target Ther 8: 333, 2023.
20. Crosas-Molist E, Graziani V, Maiques O, Pandya P, Monger J, Samain R, George SL, Malik S, Salise J, Morales V, *et al*: AMPK is a mechano-metabolic sensor linking cell adhesion and mitochondrial dynamics to Myosin-dependent cell migration. Nat Commun 14: 2740, 2023.
21. Liu Q, Zhang L, Zou Y, Tao Y, Wang B, Li B, Liu R, Wang B, Ding L, Cui Q, *et al*: Modulating p-AMPK/mTOR pathway of mitochondrial dysfunction caused by MTERF1 abnormal expression in colorectal cancer cells. Int J Mol Sci 23: 12354, 2022.
22. Liu A, Lu X, Song Y, Pei J and Wei R: ACK1 condensates promote STAT5 signaling in lung squamous cell carcinoma. Cancer Cell Int 25: 237, 2025.
23. Mehta S and Zhang J: Liquid-liquid phase separation drives cellular function and dysfunction in cancer. Nat Rev Cancer 22: 239-252, 2022.
24. Peng Q, Tan S, Xia L, Wu N, Oyang L, Tang Y, Su M, Luo X, Wang Y, Sheng X, *et al*: Phase separation in cancer: From the impacts and mechanisms to treatment potentials. Int J Biol Sci 18: 5103-5122, 2022.
25. Maqsood Q, Sumrin A, Saleem MZ, Perveen R, Hussain N, Mahnoor M, Akhtar MW, Wajid A and Ameen E: An insight into cancer from biomolecular condensates. Cancer Screen Prev 2: 177-190, 2023.
26. Li Y, Feng Y, Geng S, Xu F and Guo H: The role of liquid-liquid phase separation in defining cancer EMT. Life Sci 353: 122931, 2024.
27. Vander Heiden MG, Cantley LC and Thompson CB: Understanding the Warburg effect: The metabolic requirements of cell proliferation. Science 324: 1029-1033, 2009.
28. Warburg O and Minami S: Versuche an Überlebendem carcinom-gewebe. Klin Wochenschr 2: 776-777, 1923.
29. Lunt SY and Vander Heiden MG: Aerobic glycolysis: Meeting the metabolic requirements of cell proliferation. Annu Rev Cell Dev Biol 27: 441-464, 2011.
30. Koppenol WH, Bounds PL and Dang CV: Otto Warburg's contributions to current concepts of cancer metabolism. Nat Rev Cancer 11: 325-337, 2011.
31. Tochigi T, Shuto K, Kono T, Ohira G, Tohma T, Gunji H, Hayano K, Narushima K, Fujishiro T, Hanaoka T, *et al*: Heterogeneity of glucose metabolism in esophageal cancer measured by fractal analysis of fluorodeoxyglucose positron emission tomography image: Correlation between metabolic heterogeneity and survival. Dig Surg 34: 186-191, 2017.
32. Larson SM: Positron emission tomography-based molecular imaging in human cancer: Exploring the link between hypoxia and accelerated glucose metabolism. Clin Cancer Res 10: 2203-2204, 2004.
33. DeBerardinis RJ and Chandel NS: Fundamentals of cancer metabolism. Sci Adv 2: e1600200, 2016.
34. Ward PS and Thompson CB: Metabolic reprogramming: A cancer hallmark even Warburg did not anticipate. Cancer Cell 21: 297-308, 2012.
35. Hsu PP and Sabatini DM: Cancer cell metabolism: Warburg and beyond. Cell 134: 703-707, 2008.
36. Li ZY and Zhang HF: Reprogramming of glucose, fatty acid and amino acid metabolism for cancer progression. Cell Mol Life Sci 73: 377-392, 2016.
37. Kim SY: Cancer energy metabolism: Shutting power off cancer factory. Biomol Ther (Seoul) 26: 39-44, 2018.
38. Corbet C and Feron O: Cancer cell metabolism and mitochondria: Nutrient plasticity for TCA cycle fueling. Biochim Biophys Acta Rev Cancer 1868: 7-15, 2017.
39. Weinberg F and Chandel NS: Mitochondrial metabolism and cancer. Ann NY Acad Sci 1177: 66-73, 2009.
40. Zhao L, Mao Y, Zhao Y, Cao Y and Chen X: Role of multifaceted regulators in cancer glucose metabolism and their clinical significance. Oncotarget 7: 31572-31585, 2016.
41. Finley LWS: What is cancer metabolism? Cell 186: 1670-1688, 2023.
42. Stine ZE, Schug ZT, Salvino JM and Dang CV: Targeting cancer metabolism in the era of precision oncology. Nat Rev Drug Discov 21: 141-162, 2022.
43. Vander Heiden MG, Locasale JW, Swanson KD, Sharfi H, Heffron GJ, Amador-Noguez D, Christofk HR, Wagner G, Rabinowitz JD, Asara JM and Cantley LC: Evidence for an alternative glycolytic pathway in rapidly proliferating cells. Science 329: 1492-1499, 2010.
44. Kalyanaraman B, Cheng G, Hardy M, Ouari O, Lopez M, Joseph J, Zielonka J and Dwinell MB: A review of the basics of mitochondrial bioenergetics, metabolism, and related signaling pathways in cancer cells: Therapeutic targeting of tumor mitochondria with lipophilic cationic compounds. Redox Biol 14: 316-327, 2016.

45. Stepien M, Duarte-Salles T, Fedirko V, Floegel A, Barupal DK, Rinaldi S, Achaintre D, Assi N, Tjønneland A, Overvad K, *et al*: Alteration of amino acid and biogenic amine metabolism in hepatobiliary cancers: Findings from a prospective cohort study. Int J Cancer 138: 348-360, 2016.
46. Frezza C: Cancer metabolism: Addicted to serine. Nat Chem Biol 12: 389-390, 2016.
47. Gordan JD, Thompson CB and Simon MC: HIF and c-Myc: Sibling rivals for control of cancer cell metabolism and proliferation. Cancer Cell 12: 108-113, 2007.
48. West MJ, Stoneley M and Willis AE: Translational induction of the c-myc oncogene via activation of the FRAP/TOR signalling pathway. Oncogene 17: 769-780, 1998.
49. Kalkat M, De Melo J, Hickman KA, Lourenco C, Redel C, Resetca D, Tamachi A, Tu WB and Penn LZ: MYC deregulation in primary human cancers. Genes (Basel) 8: 151, 2017.
50. Goetzman ES and Prochownik EV: The role for Myc in coordinating glycolysis, oxidative phosphorylation, glutaminolysis, and fatty acid metabolism in normal and neoplastic tissues. Front Endocrinol (Lausanne) 9: 129, 2018.
51. Pourdehnad M, Truitt ML, Siddiqi IN, Ducker GS, Shokat KM and Ruggero D: Myc and mTOR converge on a common node in protein synthesis control that confers synthetic lethality in Myc-driven cancers. Proc Natl Acad Sci USA 110: 11988-11993, 2013.
52. Sukumaran A, Choi K and Dasgupta B: Insight on transcriptional regulation of the energy sensing AMPK and biosynthetic mTOR pathway genes. Front Cell Dev Biol 8: 671, 2020.
53. Khan MW, Biswas D, Ghosh M, Mandloi S, Chakrabarti S and Chakrabarti P: mTORC2 controls cancer cell survival by modulating gluconeogenesis. Cell Death Discov 1: 15016, 2015.
54. Sun Q, Chen X, Ma J, Peng H, Wang F, Zha X, Wang Y, Jing Y, Yang H, Chen R, *et al*: Mammalian target of rapamycin up-regulation of pyruvate kinase isoenzyme type M2 is critical for aerobic glycolysis and tumor growth. Proc Natl Acad Sci USA 108: 4129-4134, 2011.
55. Wei H, Dong C and Shen Z: Kallikrein-related peptidase (KLK10) cessation blunts colorectal cancer cell growth and glucose metabolism by regulating the PI3K/Akt/mTOR pathway. Neoplasma 67: 889-897, 2020.
56. Iqbal MA, Siddiqui FA, Gupta V, Chattopadhyay S, Gopinath P, Kumar B, Manvati S, Chaman N and Bamezai RN: Insulin enhances metabolic capacities of cancer cells by dual regulation of glycolytic enzyme pyruvate kinase M2. Mol Cancer 12: 72, 2013.
57. Buller CL, Loberg RD, Fan MH, Zhu Q, Park JL, Vesely E, Inoki K, Guan KL and Brosius FC III: A GSK-3/TSC2/mTOR pathway regulates glucose uptake and GLUT1 glucose transporter expression. Am J Physiol Cell Physiol 295: C836-C843, 2008.
58. Shi LZ, Wang R, Huang G, Vogel P, Neale G, Green DR and Chi H: HIF1alpha-dependent glycolytic pathway orchestrates a metabolic checkpoint for the differentiation of TH17 and Treg cells. J Exp Med 208: 1367-1376, 2011.
59. Siska PJ, van der Windt GJW, Kishton RJ, Cohen S, Eisner W, MacIver NJ, Kater AP, Weinberg JB and Rathmell JC: Suppression of Glut1 and glucose metabolism by decreased Akt/mTORC1 signaling drives T cell impairment in B cell leukemia. J Immunol 197: 2532-2540, 2016.
60. Feng Y and Wu L: mTOR up-regulation of PFKFB3 is essential for acute myeloid leukemia cell survival. Biochem Biophys Res Commun 483: 897-903, 2017.
61. Finlay DK, Rosenzweig E, Sinclair LV, Feijoo-Carnero C, Hukelmann JL, Rolf J, Panteleyev AA, Okkenhaug K and Cantrell DA: PDK1 regulation of mTOR and hypoxia-inducible factor 1 integrate metabolism and migration of CD8+ T cells. J Exp Med 209: 2441-2453, 2012.
62. Chen X, Zhu Y, Wang Z, Zhu H, Pan Q, Su S, Dong Y, Li L, Zhang H, Wu L, *et al*: mTORC1 alters the expression of glycolytic genes by regulating KPNA2 abundances. J Proteomics 136: 13-24, 2016.
63. Li Y, He ZC, Liu Q, Zhou K, Shi Y, Yao XH, Zhang X, Kung HF, Ping YF and Bian XW: Large intergenic non-coding RNA-RoR inhibits aerobic glycolysis of glioblastoma cells via Akt pathway. J Cancer 9: 880-889, 2018.
64. Holloway RW and Marignani PA: Targeting mTOR and glycolysis in HER2-positive breast cancer. Cancers (Basel) 13: 2922, 2021.
65. Dibble CC and Manning BD: Signal integration by mTORC1 coordinates nutrient input with biosynthetic output. Nat Cell Biol 15: 555-564, 2013.
66. Kullmann L and Krahn MP: Controlling the master-upstream regulation of the tumor suppressor LKB1. Oncogene 37: 3045-3057, 2018.
67. Zhang J, Pavlova NN and Thompson CB: Cancer cell metabolism: The essential role of the nonessential amino acid, glutamine. EMBO J 36: 1302-1315, 2017.
68. Altman BJ, Stine ZE and Dang CV: From Krebs to clinic: Glutamine metabolism to cancer therapy. Nat Rev Cancer 16: 619-634, 2016.
69. Choi YK and Park KG: Targeting glutamine metabolism for cancer treatment. Biomol Ther (Seoul) 26: 19-28, 2018.
70. Masui K, Tanaka K, Akhavan D, Babic I, Gini B, Matsutani T, Iwanami A, Liu F, Villa GR, Gu Y, *et al*: mTOR complex 2 controls glycolytic metabolism in glioblastoma through FoxO acetylation and upregulation of c-Myc. Cell Metab 18: 726-739, 2013.
71. Prieto J, García-Cañaveras JC, León M, Sendra R, Ponsoda X, Izpisúa Belmonte JC, Lahoz A and Torres J: c-MYC triggers lipid remodelling during early somatic cell reprogramming to pluripotency. Stem Cell Rev Rep 17: 2245-2261, 2021.
72. Khan MW, Layden BT and Chakrabarti P: Inhibition of mTOR complexes protects cancer cells from glutamine starvation induced cell death by restoring Akt stability. Biochim Biophys Acta Mol Basis Dis 1864: 2040-2052, 2018.
73. Csibi A, Lee G, Yoon SO, Tong H, Ilter D, Elia I, Fendt SM, Roberts TM and Blenis J: The mTORC1/S6K1 pathway regulates glutamine metabolism through the eIF4B-dependent control of c-Myc translation. Curr Biol 24: 2274-2280, 2014.
74. Shaw E, Talwadekar M, Rashida Z, Mohan N, Acharya A, Khatri S, Laxman S and Kolthur-Seetharam U: Anabolic SIRT4 exerts retrograde control over TORC1 signaling by glutamine sparing in the mitochondria. Mol Cell Biol 40: e00212-19, 2020.
75. Wang D, He J, Huang B, Liu S, Zhu H and Xu T: Emerging role of the Hippo pathway in autophagy. Cell Death Dis 11: 880, 2020.
76. Trejo-Solís C, Serrano-García N, Castillo-Rodríguez RA, Robledo-Cadena DX, Jimenez-Farfan D, Marín-Hernández Á, Silva-Adaya D, Rodríguez-Pérez CE and Gallardo-Pérez JC: Metabolic dysregulation of tricarboxylic acid cycle and oxidative phosphorylation in glioblastoma. Rev Neurosci 35: 813-838, 2024.
77. Morita M, Gravel SP, Chénard V, Sikström K, Zheng L, Alain T, Gandin V, Avizonis D, Arguello M, Zakaria C, *et al*: mTORC1 controls mitochondrial activity and biogenesis through 4E-BP-dependent translational regulation. Cell Metab 18: 698-711, 2013.
78. Wise DR, DeBerardinis RJ, Mancuso A, Sayed N, Zhang XY, Pfeiffer HK, Nissim I, Daikhin E, Yudkoff M, McMahon SB and Thompson CB: Myc regulates a transcriptional program that stimulates mitochondrial glutaminolysis and leads to glutamine addiction. Proc Natl Acad Sci USA 105: 18782-18787, 2008.
79. Byun JK, Choi YK, Kim JH, Jeong JY, Jeon HJ, Kim MK, Hwang I, Lee SY, Lee YM, Lee IK and Park KG: A positive feedback loop between Sestrin2 and mTORC2 is required for the survival of glutamine-depleted lung cancer cells. Cell Rep 20: 586-599, 2017.
80. Durán RV, Oppliger W, Robitaille AM, Heiserich L, Skendaj R, Gottlieb E and Hall MN: Glutaminolysis activates Rag-mTORC1 signaling. Mol Cell 47: 349-358, 2012.
81. Chiu M, Tardito S, Barilli A, Bianchi MG, Dall'Asta V and Bussolati O: Glutamine stimulates mTORC1 independent of the cell content of essential amino acids. Amino Acids 43: 2561-2567, 2012.
82. Bodineau C, Tomé M, Courtois S, Costa ASH, Sciacovelli M, Rousseau B, Richard E, Vacher P, Parejo-Pérez C, Bessede E, *et al*: Two parallel pathways connect glutamine metabolism and mTORC1 activity to regulate glutamoptosis. Nat Commun 12: 4814, 2021.
83. Dennis MD, Jefferson LS and Kimball SR: Role of p70S6K1-mediated phosphorylation of eIF4B and PDCD4 proteins in the regulation of protein synthesis. J Biol Chem 287: 42890-42899, 2012.
84. Dalle Pezze P, Ruf S, Sonntag AG, Langelaar-Makkinje M, Hall P, Heberle AM, Razquin Navas P, van Eunen K, Tölle RC, Schwarz JJ, *et al*: A systems study reveals concurrent activation of AMPK and mTOR by amino acids. Nat Commun 7: 13254, 2016.
85. Nicklin P, Bergman P, Zhang B, Triantafellow E, Wang H, Nyfeler B, Yang H, Hild M, Kung C, Wilson C, *et al*: Bidirectional transport of amino acids regulates mTOR and autophagy. Cell 136: 521-534, 2009.

86. Selwan EM and Edinger AL: Branched chain amino acid metabolism and cancer: The importance of keeping things in context. Transl Cancer Res 6 (Suppl 3): S578-S584, 2017.
87. McCracken AN and Edinger AL: Nutrient transporters: The Achilles' heel of anabolism. Trends Endocrin Met 24: 200-208, 2013.
88. Kawasome H, Papst P, Webb S, Keller GM, Johnson GL, Gelfand EW and Terada N: Targeted disruption of p70(s6k) defines its role in protein synthesis and rapamycin sensitivity. Proc Natl Acad Sci USA 95: 5033-5038, 1998.
89. Martineau Y, Wang X, Alain T, Petroulakis E, Shahbazian D, Fabre B, Bousquet-Dubouch MP, Monsarrat B, Pyronnet S and Sonenberg N: Control of Paip1-eukaryotic translation initiation factor 3 interaction by amino acids through S6 kinase. Mol Cell Biol 34: 1046-1053, 2014.
90. Iadevaia V, Liu R and Proud CG: mTORC1 signaling controls multiple steps in ribosome biogenesis. Semin Cell Dev Biol 36: 113-120, 2014.
91. Abetov DA, Kiyan VS, Zhylkibayev AA, Sarbassova DA, Alybayev SD, Spooner E, Song MS, Bersimbaev RI and Sarbassov DD: Formation of mammalian preribosomes proceeds from intermediate to composed state during ribosome maturation. J Biol Chem 294: 10746-10757, 2019.
92. Gentilella A, Kozma SC and Thomas G: A liaison between mTOR signaling, ribosome biogenesis and cancer. Biochim Biophys Acta 1849: 812-820, 2015.
93. He J, Yang Y, Zhang J, Chen J, Wei X, He J and Luo L: Ribosome biogenesis protein Urb1 acts downstream of mTOR complex 1 to modulate digestive organ development in zebrafish. J Genet Genomics 44: 567-576, 2017.
94. Rad E, Murray JT and Tee AR: Oncogenic signalling through mechanistic target of rapamycin (mTOR): A driver of metabolic transformation and cancer progression. Cancers (Basel) 10: 5, 2018.
95. Qin L, Cheng X, Wang S, Gong G, Su H, Huang H, Chen T, Damdinjav D, Dorjsuren B, Li Z, *et al*: Discovery of novel aminobutanoic acid-based ASCT2 inhibitors for the treatment of non-small-cell lung cancer. J Med Chem 67: 988-1007, 2024.
96. Leibowitz BJ, Zhao G, Xia W, Wang Y, Ruan H, Zhang L and Yu J: mTOR inhibition suppresses Myc-driven polyposis by inducing immunogenic cell death. Oncogene 42: 2007-2016, 2023.
97. Elkon R, Loayza-Puch F, Korkmaz G, Lopes R, van Breugel PC, Bleijerveld OB, Altelaar AF, Wolf E, Lorenzin F, Eilers M and Agami R: Myc coordinates transcription and translation to enhance transformation and suppress invasiveness. EMBO Rep 16: 1723-1736, 2015.
98. Peng T, Golub TR and Sabatini DM: The immunosuppressant rapamycin mimics a starvation-like signal distinct from amino acid and glucose deprivation. Mol Cell Biol 22: 5575-5584, 2002.
99. Rosario FJ, Kanai Y, Powell TL and Jansson T: Mammalian target of rapamycin signalling modulates amino acid uptake by regulating transporter cell surface abundance in primary human trophoblast cells. J Physiol 591: 609-625, 2013.
100. Rosario FJ, Dimasuay KG, Kanai Y, Powell TL and Jansson T: Regulation of amino acid transporter trafficking by mTORC1 in primary human trophoblast cells is mediated by the ubiquitin ligase Nedd4-2. Clin Sci (Lond) 130: 499-512, 2016.
101. Park Y, Reyna-Neyra A, Philippe L and Thoreen CC: mTORC1 balances cellular amino acid supply with demand for protein synthesis through post-transcriptional control of ATF4. Cell Rep 19: 1083-1090, 2017.
102. Gu Y, Albuquerque CP, Braas D, Zhang W, Villa GR, Bi J, Ikegami S, Masui K, Gini B, Yang H, *et al*: mTORC2 regulates amino acid metabolism in cancer by phosphorylation of the cystine-glutamate antiporter xCT. Mol Cell 67: 128-138.e7, 2017.
103. Toda K, Kawada K, Iwamoto M, Inamoto S, Sasazuki T, Shirasawa S, Hasegawa S and Sakai Y: Metabolic alterations caused by KRAS mutations in colorectal cancer contribute to cell adaptation to glutamine depletion by upregulation of asparagine synthetase. Neoplasia 18: 654-665, 2016.
104. Pupo E, Avanzato D, Middonti E, Bussolino F and Lanzetti L: KRAS-driven metabolic rewiring reveals novel actionable targets in cancer. Front Oncol 9: 848, 2019.
105. Gwinn DM, Lee AG, Briones-Martin-Del-Campo M, Conn CS, Simpson DR, Scott AI, Le A, Cowan TM, Ruggero D and Sweet-Cordero EA: Oncogenic KRAS regulates amino acid homeostasis and asparagine biosynthesis via ATF4 and alters sensitivity to L-asparaginase. Cancer Cell 33: 91-107.e6, 2018.
106. Long Y, Tsai WB, Wangpaichitr M, Tsukamoto T, Savaraj N, Feun LG and Kuo MT: Arginine deiminase resistance in melanoma cells is associated with metabolic reprogramming, glucose dependence, and glutamine addiction. Mol Cancer Ther 12: 2581-2590, 2013.
107. Selvarajah B, Azuelos I, Platé M, Guillotin D, Forty EJ, Contento G, Woodcock HV, Redding M, Taylor A, Brunori G, *et al*: mTORC1 amplifies the ATF4-dependent de novo serine-glycine pathway to supply glycine during TGF-β_1-induced collagen biosynthesis. Sci Signal 12: eaav3048, 2019.
108. Kma L and Baruah TJ: The interplay of ROS and the PI3K/Akt pathway in autophagy regulation. Biotechnol Appl Biochem 69: 248-264, 2022.
109. Horton JD, Goldstein JL and Brown MS: SREBPs: Activators of the complete program of cholesterol and fatty acid synthesis in the liver. J Clin Invest 109: 1125-1131, 2002.
110. Randle PJ: Regulatory interactions between lipids and carbohydrates: The glucose fatty acid cycle after 35 years. Diabetes Metab Rev 14: 263-283, 1998.
111. Chen Y and Li P: Fatty acid metabolism and cancer development. Sci Bull 61: 1473-1479, 2016.
112. Alasadi A, Humaish HH and Al-hraishawi H: Evaluation the predictors of non-alcoholic fatty liver disease (NAFLD) in type 2 diabetes mellitus (T2DM) patients. Syst Rev Pharm 11: 421-430, 2020.
113. Mullen AR, Wheaton WW, Jin ES, Chen PH, Sullivan LB, Cheng T, Yang Y, Linehan WM, Chandel NS and DeBerardinis RJ: Reductive carboxylation supports growth in tumour cells with defective mitochondria. Nature 481: 385-388, 2011.
114. Metallo CM, Gameiro PA, Bell EL, Mattaini KR, Yang J, Hiller K, Jewell CM, Johnson ZR, Irvine DJ, Guarente L, *et al*: Reductive glutamine metabolism by IDH1 mediates lipogenesis under hypoxia. Nature 481: 380-384, 2011.
115. Wise DR, Ward PS, Shay JE, Cross JR, Gruber JJ, Sachdeva UM, Platt JM, DeMatteo RG, Simon MC and Thompson CB: Hypoxia promotes isocitrate dehydrogenase-dependent carboxylation of α-ketoglutarate to citrate to support cell growth and viability. Proc Natl Acad Sci USA 108: 19611-19616, 2011.
116. Schug ZT, Peck B, Jones DT, Zhang Q, Grosskurth S, Alam IS, Goodwin LM, Smethurst E, Mason S, Blyth K, *et al*: Acetyl-CoA synthetase 2 promotes acetate utilization and maintains cancer cell growth under metabolic stress. Cancer Cell 27: 57-71, 2015.
117. Green CR, Wallace M, Divakaruni AS, Phillips SA, Murphy AN, Ciaraldi TP and Metallo CM: Branched-chain amino acid catabolism fuels adipocyte differentiation and lipogenesis. Nat Chem Biol 12: 15-21, 2016.
118. Eberlé D, Hegarty B, Bossard P, Ferré P and Foufelle F: SREBP transcription factors: master regulators of lipid homeostasis. Biochimie 86: 839-848, 2004.
119. Nakamura MT, Cheon Y, Li Y and Nara TY: Mechanisms of regulation of gene expression by fatty acids. Lipids 39: 1077-1083, 2004.
120. Pégorier JP, Le May C and Girard J: Control of gene expression by fatty acids. J Nutr 134: 2444S-2449S, 2004.
121. Düvel K, Yecies JL, Menon S, Raman P, Lipovsky AI, Souza AL, Triantafellow E, Ma Q, Gorski R, Cleaver S, *et al*: Activation of a metabolic gene regulatory network downstream of mTOR complex 1. Mol Cell 39: 171-183, 2010.
122. DeBerardinis RJ, Lum JJ and Thompson CB: Phosphatidylinositol 3-kinase-dependent modulation of carnitine palmitoyltransferase 1A expression regulates lipid metabolism during hematopoietic cell growth. J Biol Chem 281: 37372-37380, 2006.
123. Hao YJ, Samuels Y, Li QL, Krokowski D, Brunengraber H, Hatzoglou M, Zhang GF, Vogelstein B and Wang Z: Abstract 1125: Oncogenic PIK3CA mutations reprogram glutamine metabolism in colorectal cancers. Cancer Res 75 (15 Suppl): S1125, 2015.
124. Liu C, Zhou X, Pan Y, Liu Y and Zhang Y: Pyruvate carboxylase promotes thyroid cancer aggressiveness through fatty acid synthesis. BMC Cancer 21: 722, 2021.
125. Schiliro C and Firestein BL: Mechanisms of metabolic reprogramming in cancer cells supporting enhanced growth and proliferation. Cells 10: 1056, 2021.
126. Andrade-Vieira R, Han JH and Marignani PA: Omega-3 polyunsaturated fatty acid promotes the inhibition of glycolytic enzymes and mTOR signaling by regulating the tumor suppressor LKB1. Cancer Biol Ther 14: 1050-1058, 2013.

127. Kuma A, Hatano M, Matsui M, Yamamoto A, Nakaya H, Yoshimori T, Ohsumi Y, Tokuhisa T and Mizushima N: The role of autophagy during the early neonatal starvation period. Nature 432: 1032-1036, 2004.
128. Alasadi AH, Guo J, Tao H and Jin S: Preventing and treating hepatic metastatic colon and pancreatic cancers by targeting cell metabolism. Cancer Res 76 (14 Suppl): S45, 2016.
129. Aird KM and Zhang R: Nucleotide metabolism, oncogene-induced senescence and cancer. Cancer Lett 356: 204-210, 2015.
130. Cantor JR and Sabatini DM: Cancer cell metabolism: One hallmark, many faces. Cancer Discov 2: 881-898, 2012.
131. Vander Heiden MG: Targeting cancer metabolism: A therapeutic window opens. Nat Rev Drug Discov 10: 671-684, 2011.
132. Ben-Sahra I, Howell JJ, Asara JM and Manning BD: Stimulation of de novo pyrimidine synthesis by growth signaling through mTOR and S6K1. Science 339: 1323-1328, 2013.
133. Robitaille AM, Christen S, Shimobayashi M, Cornu M, Fava LL, Moes S, Prescianotto-Baschong C, Sauer U, Jenoe P and Hall MN: Quantitative phosphoproteomics reveal mTORC1 activates de novo pyrimidine synthesis. Science 339: 1320-1323, 2013.
134. He L, Wei X, Ma X, Yin X, Song M, Donninger H, Yaddanapudi K, McClain CJ and Zhang X: Simultaneous quantification of nucleosides and nucleotides from biological samples. J Am Soc Mass Spectrom 30: 987-1000, 2019.
135. Qian X, Li X, Tan L, Lee JH, Xia Y, Cai Q, Zheng Y, Wang H, Lorenzi PL and Lu Z: Conversion of PRPS hexamer to monomer by AMPK-mediated phosphorylation inhibits nucleotide synthesis in response to energy stress. Cancer Discov 8: 94-107, 2018.
136. Yecies JL, Zhang HH, Menon S, Liu S, Yecies D, Lipovsky AI, Gorgun C, Kwiatkowski DJ, Hotamisligil GS, Lee CH and Manning BD: Akt stimulates hepatic SREBP1c and lipogenesis through parallel mTORC1-dependent and independent pathways. Cell Metab 14: 21-32, 2011.
137. Chen J, Yang S, Li Y, Ziwen X, Zhang P, Song Q, Yao Y and Pei H: De novo nucleotide biosynthetic pathway and cancer. Genes Dis 10: 2331-2338, 2022.
138. Qian J, Chen Y, Meng T, Ma L, Meng L, Wang X, Yu T, Zask A, Shen J and Yu K: Molecular regulation of apoptotic machinery and lipid metabolism by mTORC1/mTORC2 dual inhibitors in preclinical models of HER2+/PIK3CAmut breast cancer. Oncotarget 7: 67071-67086, 2016.
139. Evert M, Calvisi DF, Evert K, De Murtas V, Gasparetti G, Mattu S, Destefanis G, Ladu S, Zimmermann A, Delogu S, *et al*: V-AKT murine thymoma viral oncogene homolog/mammalian target of rapamycin activation induces a module of metabolic changes contributing to growth in insulin-induced hepatocarcinogenesis. Hepatology 55: 1473-1484, 2012.
140. Cheng J, Huang Y, Zhang X, Yu Y, Wu S, Jiao J, Tran L, Zhang W, Liu R, Zhang L, *et al*: TRIM21 and PHLDA3 negatively regulate the crosstalk between the PI3K/AKT pathway and PPP metabolism. Nat Commun 11: 1880, 2020.
141. Saha A, Connelly S, Jiang J, Zhuang S, Amador DT, Phan T, Pilz RB and Boss GR: Akt phosphorylation and regulation of transketolase is a nodal point for amino acid control of purine synthesis. Mol Cell 55: 264-276, 2014.
142. Wang W and Guan KL: AMP-activated protein kinase and cancer. Acta Physiol (Oxf) 196: 55-63, 2009.
143. Cantó C and Auwerx J: Calorie restriction: Is AMPK a key sensor and effector? Physiology (Bethesda) 26: 214-224, 2011.
144. Klaus S, Keipert S, Rossmeisl M and Kopecky J: Augmenting energy expenditure by mitochondrial uncoupling: A role of AMP-activated protein kinase. Genes Nutr 7: 369-386, 2012.
145. Fujii N, Aschenbach WG, Musi N, Hirshman MF and Goodyear LJ: Regulation of glucose transport by the AMP-activated protein kinase. Proc Nutr Soc 63: 205-210, 2004.
146. Haurie V, Boucherie H and Sagliocco F: The Snf1 protein kinase controls the induction of genes of the iron uptake pathway at the diauxic shift in Saccharomyces cerevisiae. J Biol Chem 278: 45391-45396, 2003.
147. Zhou G, Myers R, Li Y, Chen Y, Shen X, Fenyk-Melody J, Wu M, Ventre J, Doebber T, Fujii N, *et al*: Role of AMP-activated protein kinase in mechanism of metformin action. J Clin Invest 108: 1167-1174, 2001.
148. Hawley SA, Fullerton MD, Ross FA, Schertzer JD, Chevtzoff C, Walker KJ, Peggie MW, Zibrova D, Green KA, Mustard KJ, *et al*: The ancient drug salicylate directly activates AMP-activated protein kinase. Science 336: 918-922, 2012.
149. Daurio NA, Tuttle SW, Worth AJ, Song EY, Davis JM, Snyder NW, Blair IA and Koumenis C: AMPK activation and metabolic reprogramming by tamoxifen through estrogen receptor-independent mechanisms suggests new uses for this therapeutic modality in cancer treatment. Cancer Res 76: 3295-3306, 2016.
150. Xiao B, Heath R, Saiu P, Leiper FC, Leone P, Jing C, Walker PA, Haire L, Eccleston JF, Davis CT, *et al*: Structural basis for AMP binding to mammalian AMP-activated protein kinase. Nature 449: 496-500, 2007.
151. Scott JW, Hawley SA, Green KA, Anis M, Stewart G, Scullion GA, Norman DG and Hardie DG: CBS domains form energy-sensing modules whose binding of adenosine ligands is disrupted by disease mutations. J Clin Invest 113: 274-284, 2004.
152. Gowans GJ, Hawley SA, Ross FA and Hardie DG: AMP is a true physiological regulator of AMP-activated protein kinase by both allosteric activation and enhancing net phosphorylation. Cell Metab 18: 556-566, 2013.
153. Hardie DG: Molecular pathways: Is AMPK a friend or a foe in cancer? Clin Cancer Res 21: 3836-3840, 2015.
154. Faubert B, Vincent EE, Griss T, Samborska B, Izreig S, Svensson RU, Mamer OA, Avizonis D, Shackelford DB, Shaw RJ and Jones RG: Loss of the tumor suppressor LKB1 promotes metabolic reprogramming of cancer cells via HIF-1α. Proc Natl Acad Sci USA 111: 2554-2559, 2014.
155. El-Masry OS, Brown BL and Dobson PRM: Effects of activation of AMPK on human breast cancer cell lines with different genetic backgrounds. Oncol Lett 3: 224-228, 2012.
156. Hadad SM, Baker L, Quinlan PR, Robertson KE, Bray SE, Thomson G, Kellock D, Jordan LB, Purdie CA, Hardie DG, *et al*: Histological evaluation of AMPK signaling in primary breast cancer. BMC Cancer 9: 307, 2009.
157. Lee CW, Wong LLY, Tse EYT, Liu HF, Leong VY, Lee JM, Hardie DG, Ng IO and Ching YP: AMPK promotes p53 acetylation via phosphorylation and inactivation of SIRT1 in liver cancer cells. Cancer Res 72: 4394-4404, 2012.
158. Laderoute KR, Calaoagan JM, Chao WR, Dinh D, Denko N, Duellman S, Kalra J, Liu X, Papandreou I, Sambucetti L and Boros LG: 5'-AMP-activated protein kinase (AMPK) supports the growth of aggressive experimental human breast cancer tumors. J Biol Chem 289: 22850-22864, 2014.
159. Zheng L, Yang W, Wu F, Wang C, Yu L, Tang L, Qiu B, Li Y, Guo L, Wu M, *et al*: Prognostic significance of AMPK activation and therapeutic effects of metformin in hepatocellular carcinoma. Clin Cancer Res 19: 5372-5380, 2013.
160. Faubert B, Boily G, Izreig S, Griss T, Samborska B, Dong Z, Dupuy F, Chambers C, Fuerth BJ, Viollet B, *et al*: AMPK is a negative regulator of the Warburg effect and suppresses tumor growth in vivo. Cell Metab 17: 113-124, 2013.
161. Sanchez-Cespedes M, Parrella P, Esteller M, Nomoto S, Trink B, Engles JM, Westra WH, Herman JG and Sidransky D: Inactivation of LKB1/STK11 is a common event in adenocarcinomas of the lung. Cancer Res 62: 3659-3662, 2002.
162. Ji H, Ramsey MR, Hayes DN, Fan C, McNamara K, Kozlowski P, Torrice C, Wu MC, Shimamura T, Perera SA, *et al*: LKB1 modulates lung cancer differentiation and metastasis. Nature 448: 807-810, 2007.
163. Wingo SN, Gallardo TD, Akbay EA, Liang MC, Contreras CM, Boren T, Shimamura T, Miller DS, Sharpless NE, Bardeesy N, *et al*: Somatic LKB1 mutations promote cervical cancer progression. PLoS One 4: e5137, 2009.
164. Hawley SA, Ross FA, Gowans GJ, Tibarewal P, Leslie NR and Hardie DG: Phosphorylation by Akt within the ST loop of AMPK-α1 down-regulates its activation in tumour cells. Biochem J 459: 275-287, 2014.
165. Horman S, Vertommen D, Heath R, Neumann D, Mouton V, Woods A, Schlattner U, Wallimann T, Carling D, Hue L and Rider MH: Insulin antagonizes ischemia-induced Thr172 phosphorylation of AMP-activated protein kinase alpha-subunits in heart via hierarchical phosphorylation of Ser485/491. J Biol Chem 281: 5335-5340, 2006.
166. Hay N and Sonenberg N: Upstream and downstream of mTOR. Genes Dev 18: 1926-1945, 2004.
167. Zhang Y, Li W, Niu J, Fan Z, Li X and Zhang H: Reprogramming of glucose metabolism in pancreatic cancer: Mechanisms, implications, and therapeutic perspectives. Front Immunol 16: 1586959, 2025.
168. Du W, Xu A, Huang Y, Cao J, Zhu H, Yang B, Shao X, He Q and Ying M: The role of autophagy in targeted therapy for acute myeloid leukemia. Autophagy 17: 2665-2679, 2021.

169. Mohanty SS, Warrier S and Rangarajan A: Rethinking AMPK: A reversible switch fortifying cancer cell stress-resilience. Yale J Biol Med 98: 33-52, 2025.
170. Baek SY, Hwang UW, Suk HY and Kim YW: Hemistepsin A inhibits cell proliferation and induces G0/G1-phase arrest, cellular senescence and apoptosis via the AMPK and p53/p21 signals in human hepatocellular carcinoma. Biomolecules 10: 713, 2020.
171. Wang EM, Akasaka H, Zhao J, Varadhachary GR, Lee JE, Maitra A, Fleming JB, Hung MC, Wang H and Katz MHG: Expression and clinical significance of protein kinase RNA-like endoplasmic reticulum kinase and phosphorylated eukaryotic initiation factor 2α in pancreatic ductal adenocarcinoma. Pancreas 48: 323-328, 2019.
172. Grenier A, Poulain L, Mondesir J, Jacquel A, Bosc C, Stuani L, Mouche S, Larrue C, Sahal A, Birsen R, *et al*: AMPK-PERK axis represses oxidative metabolism and enhances apoptotic priming of mitochondria in acute myeloid leukemia. Cell Rep 38: 110197, 2022.
173. Wang S, Li H, Yuan M, Fan H and Cai Z: Role of AMPK in autophagy. Front Physiol 13: 1015500, 2022.
174. Panina SB, Pei J and Kirienko NV: Mitochondrial metabolism as a target for acute myeloid leukemia treatment. Cancer Metab 9: 17, 2021.
175. Liu Y and Ma Z: Leukemia and mitophagy: A novel perspective for understanding oncogenesis and resistance. Ann Hematol 103: 2185-2196, 2024.
176. Li Y, Sun R, Zou J, Ying Y and Luo Z: Dual roles of the AMP-activated protein kinase pathway in angiogenesis. Cells 8: 752, 2019.
177. Carling D: AMPK hierarchy: A matter of space and time. Cell Res 29: 425-426, 2019.
178. Uprety B and Abrahamse H: Targeting breast cancer and their stem cell population through AMPK activation: Novel insights. Cells 11: 576, 2022.
179. Jhaveri TZ, Woo J, Shang X, Park BH and Gabrielson E: AMP-activated kinase (AMPK) regulates activity of HER2 and EGFR in breast cancer. Oncotarget 6: 14754-14765, 2015.
180. Göbel A, Riffel RM, Hofbauer LC and Rachner TD: The mevalonate pathway in breast cancer biology. Cancer Lett 542: 215761, 2022.
181. Amengual-Cladera E, Morla-Barcelo PM, Morán-Costoya A, Sastre-Serra J, Pons DG, Valle A, Roca P and Nadal-Serrano M: Metformin: From diabetes to cancer-unveiling molecular mechanisms and therapeutic strategies. Biology (Basel) 13: 302, 2024.
182. Pei W, Dai L, Li M, Cao S, Xiao Y, Yang Y, Ma M, Deng M, Mo Y and Liu M: Targeting mitochondrial quality control for the treatment of triple-negative breast cancer: From molecular mechanisms to precision therapy. Biomolecules 15: 970, 2025.
183. Lim JS, Kim E, Song JS and Ahn S: Energy-stress-mediated activation of AMPK sensitizes MPS1 kinase inhibition in triple-negative breast cancer. Oncol Rep 52: 101, 2024.
184. Mustafa M, Abbas K, Alam M, Ahmad W, Moinuddin, Usmani N, Siddiqui SA and Habib S: Molecular pathways and therapeutic targets linked to triple-negative breast cancer (TNBC). Mol Cell Biochem 479: 895-913, 2024.
185. Li C, Syed MU, Nimbalkar A, Shen Y, Vieira MD, Fraser C, Inde Z, Qin X, Ouyang J, Kreuzer J, *et al*: LKB1 regulates JNK-dependent stress signaling and apoptotic dependency of KRAS-mutant lung cancers. Nat Commun 16: 4112, 2025.
186. Huang Q, Ren Y, Yuan P, Huang M, Liu G, Shi Y, Jia G and Chen M: Targeting the AMPK/Nrf2 pathway: A novel therapeutic approach for acute lung injury. J Inflamm Res 17: 4683-4700, 2024.
187. Fatehi Hassanabad A and MacQueen KT: Molecular mechanisms underlining the role of metformin as a therapeutic agent in lung cancer. Cell Oncol (Dordr) 44: 1-18, 2021.
188. Bernasconi R, Soodla K, Sirp A, Zovo K, Kuhtinskaja M, Lukk T, Vendelin M and Birkedal R: Higher AMPK activation in mouse oxidative compared with glycolytic muscle does not correlate with LKB1 or CaMKKβ expression. Am J Physiol Endocrinol Metab 328: E21-E33, 2025.
189. Sumbly V and Landry I: Unraveling the role of STK11/LKB1 in non-small cell lung cancer. Cureus 14: e21078, 2022.
190. Shi Y, Zheng H, Wang T, Zhou S, Zhao S, Li M and Cao B: Targeting KRAS: From metabolic regulation to cancer treatment. Mol Cancer 24: 9, 2025.
191. Liu H, Zhou D, Ou Y, Chen S, Long Y, Yuan T, Li Y and Tan Y: Multiple signaling pathways in the frontiers of lung cancer progression. Front Immunol 16: 1593793, 2025.
192. Yibcharoenporn C, Muanprasat C, Moonwiriyakit A, Satitsri S and Pathomthongtaweechai N: AMPK in intestinal health and disease: A multifaceted therapeutic target for metabolic and inflammatory disorders. Drug Des Devel Ther 19: 3029-3058, 2025.
193. Li S, Wang Y, Zhang D, Wang H, Cui X, Zhang C and Xin Y: Gliclazide reduces colitis-associated colorectal cancer formation by deceasing colonic inflammation and regulating AMPK-NF-κB signaling pathway. Dig Dis Sci 69: 453-462, 2024.
194. Su G, Wang D, Yang Q, Kong L, Ju X, Yang Q, Zhu Y, Zhang S and Li Y: Cepharanthine suppresses APC-mutant colorectal cancers by down-regulating the expression of β-catenin. Nat Prod Bioprospect 14: 18, 2024.
195. Liu JY, Liu JX, Li R, Zhang ZQ, Zhang XH, Xing SJ, Sui BD, Jin F, Ma B and Zheng CX: AMPK, a hub for the microenvironmental regulation of bone homeostasis and diseases. J Cell Physiol 239: e31393, 2024.
196. Fakhri S, Moradi SZ, Moradi SY, Piri S, Shiri Varnamkhasti B, Piri S, Khirehgesh MR, Bishayee A, Casarcia N and Bishayee A: Phytochemicals regulate cancer metabolism through modulation of the AMPK/PGC-1α signaling pathway. BMC Cancer 24: 1079, 2024.
197. Cheng D, Zhang M, Zheng Y, Wang M, Gao Y, Wang X, Liu X, Lv W, Zeng X, Belosludtsev KN, *et al*: α-Ketoglutarate prevents hyperlipidemia-induced fatty liver mitochondrial dysfunction and oxidative stress by activating the AMPK-pgc-1α/Nrf2 pathway. Redox Biol 74: 103230, 2024.
198. Naiini MR, Shahouzehi B, Azizi S, Shafiei B and Nazari-Robati M: Trehalose-induced SIRT1/AMPK activation regulates SREBP-1c/PPAR-α to alleviate lipid accumulation in aged liver. Naunyn Schmiedebergs Arch Pharmacol 397: 1061-1070, 2024.
199. Cunha V, Cotrim HP, Rocha R, Carvalho K and Lins-Kusterer L: Metformin in the prevention of hepatocellular carcinoma in diabetic patients: A systematic review. Ann Hepatol 19: 232-237, 2020.
200. Tufail M, Jiang CH and Li N: Altered metabolism in cancer: Insights into energy pathways and therapeutic targets. Mol Cancer 23: 203, 2024.
201. Liu B, Liu L and Liu Y: Targeting cell death mechanisms: The potential of autophagy and ferroptosis in hepatocellular carcinoma therapy. Front Immunol 15: 1450487, 2024.
202. Li A, Wang R, Zhao Y, Zhao P and Yang J: Crosstalk between epigenetics and metabolic reprogramming in metabolic dysfunction-associated steatotic liver disease-induced hepatocellular carcinoma: A new sight. Metabolites 14: 325, 2024.
203. Nadile M, Sze NS, Fajardo VA and Tsiani E: Inhibition of prostate cancer cell survival and proliferation by carnosic acid is associated with inhibition of Akt and activation of AMPK signaling. Nutrients 16: 1257, 2024.
204. Schooling CM, Yang G, Soliman GA and Leung GM: A hypothesis that glucagon-like peptide-1 receptor agonists exert immediate and multifaceted effects by activating adenosine monophosphate-activate protein kinase (AMPK). Life (Basel) 15: 253, 2025.
205. Manoharan R: Salt-inducible kinases (SIKs) in cancer: Mechanisms of action and therapeutic prospects. Drug Discov Today 30: 104279, 2025.
206. Espitia-Pérez PJ, Espitia-Perez LM and Negrette-Guzmán M: Targeting Prostate cancer metabolism through transcriptional and epigenetic modulation: A multi-target approach to therapeutic innovation. Int J Mol Sci 26: 6013, 2025.
207. Pujana-Vaquerizo M, Bozal-Basterra L and Carracedo A: Metabolic adaptations in prostate cancer. Br J Cancer 131: 1250-1262, 2024.
208. Feng Y, Zhang Y, Li H, Wang T, Lu F, Liu R, Xie G, Song L, Huang B, Li X, *et al*: Enzalutamide inhibits PEX10 function and sensitizes prostate cancer cells to ROS activators. Cell Death Dis 15: 559, 2024.
209. Lemos G, Fernandes CMADS, Silva FH and Calmasini FB: The role of autophagy in prostate cancer and prostatic diseases: A new therapeutic strategy. Prostate Cancer Prostatic Dis 27: 230-238, 2024.
210. Inoki K, Kim J and Guan KL: AMPK and mTOR in cellular energy homeostasis and drug targets. Annu Rev Pharmacol Toxicol 52: 381-400, 2012.
211. Choi BH and Coloff JL: The diverse functions of non-essential amino acids in cancer. Cancers (Basel) 11: 675, 2019.

212. Jin J, Byun JK, Choi YK and Park KG: Targeting glutamine metabolism as a therapeutic strategy for cancer. Exp Mol Med 55: 706-715, 2023.
213. Halama A and Suhre K: Advancing cancer treatment by targeting glutamine metabolism-A roadmap. Cancers (Basel) 14: 553, 2022.
214. Linke M, Fritsch SD, Sukhbaatar N, Hengstschläger M and Weichhart T: mTORC1 and mTORC2 as regulators of cell metabolism in immunity. FEBS Lett 591: 3089-3103, 2017.
215. Wang R, Dillon CP, Shi LZ, Milasta S, Carter R, Finkelstein D, McCormick LL, Fitzgerald P, Chi H, Munger J and Green DR: The transcription factor Myc controls metabolic reprogramming upon T lymphocyte activation. Immunity 35: 871-882, 2011.
216. Valvezan AJ and Manning BD: Molecular logic of mTORC1 signalling as a metabolic rheostat. Nat Metab 1: 321-333, 2019.
217. Nishitani S, Horie M, Ishizaki S and Yano H: Branched chain amino acid suppresses hepatocellular cancer stem cells through the activation of mammalian target of rapamycin. PLoS One 8: e82346, 2013.
218. Kazyken D, Magnuson B, Bodur C, Acosta-Jaquez HA, Zhang D, Tong X, Barnes TM, Steinl GK, Patterson NE, Altheim CH, *et al*: AMPK directly activates mTORC2 to promote cell survival during acute energetic stress. Sci Signal 12: eaav3249, 2019.
219. Sadria M and Layton AT: Interactions among mTORC, AMPK and SIRT: A computational model for cell energy balance and metabolism. Cell Commun Signal 19: 57, 2021.
220. Sujobert P, Poulain L, Paubelle E, Zylbersztejn F, Grenier A, Lambert M, Townsend EC, Brusq JM, Nicodeme E, Decrooqc J, *et al*: Co-activation of AMPK and mTORC1 induces cytotoxicity in acute myeloid leukemia. Cell Rep 11: 1446-1457, 2015.
221. Davie E, Forte GMA and Petersen J: Nitrogen regulates AMPK to control TORC1 signaling. Curr Biol 25: 445-454, 2015.
222. Lie S, Wang T, Forbes B, Proud CG and Petersen J: The ability to utilise ammonia as nitrogen source is cell type specific and intricately linked to GDH, AMPK and mTORC1. Sci Rep 9: 1461, 2019.
223. Lu T, Sun L, Wang Z, Zhang Y, He Z and Xu C: Fatty acid synthase enhances colorectal cancer cell proliferation and metastasis via regulating AMPK/mTOR pathway. Onco Targets Ther 12: 3339-3347, 2019.
224. Pereira O, Teixeira A, Sampaio-Marques B, Castro I, Girão H and Ludovico P: Signalling mechanisms that regulate metabolic profile and autophagy of acute myeloid leukaemia cells. J Cell Mol Med 22: 4807-4817, 2018.
225. Chiang CT, Demetriou AN, Ung N, Choudhury N, Ghaffarian K, Ruderman DL and Mumenthaler SM: mTORC2 contributes to the metabolic reprogramming in EGFR tyrosine-kinase inhibitor resistant cells in non-small cell lung cancer. Cancer Lett 434: 152-159, 2018.
226. Zhang P, Fu HJ, Lv LX, Liu CF, Han C, Zhao XF and Wang JX: WSSV exploits AMPK to activate mTORC2 signaling for proliferation by enhancing aerobic glycolysis. Commun Biol 6: 361, 2023.
227. He Z, Houghton PJ, Williams TM and Shen C: Regulation of DNA duplication by the mTOR signaling pathway. Cell Cycle 20: 742-751, 2021.
228. Bu C, Zhao L, Wang L, Yu Z and Zhou J: mTORC2 promotes pancreatic cancer progression and PARP inhibitor resistance. Oncol Res 31: 495-503, 2023.
229. Pournajaf S and Pourgholami MH: The mTOR pathway in Gliomas: From molecular insights to targeted therapies. Biomed Pharmacother 189: 118237, 2025.
230. Glaviano A, Foo ASC, Lam HY, Yap KCH, Jacot W, Jones RH, Eng H, Nair MG, Makvandi P, Geoerger B, *et al*: PI3K/AKT/mTOR signaling transduction pathway and targeted therapies in cancer. Mol Cancer 22: 138, 2023.
231. Carew JS, Kelly KR and Nawrocki ST: Mechanisms of mTOR inhibitor resistance in cancer therapy. Target Oncol 6: 17-27, 2011.
232. Dunn S, Eberlein C, Yu J, Gris-Oliver A, Ong SH, Yelland U, Cureton N, Staniszewska A, McEwen R, Fox M, *et al*: AKT-mTORC1 reactivation is the dominant resistance driver for PI3Kβ/AKT inhibitors in PTEN-null breast cancer and can be overcome by combining with Mcl-1 inhibitors. Oncogene 41: 5046-5060, 2022.
233. Basnet R, Basnet BB, Gupta R, Basnet T, Khadka S and Alam MS: Mammalian target of rapamycin (mTOR) signalling pathway-a potential target for cancer intervention: A short overview. Curr Mol Pharmacol 17: e310323215268, 2024.
234. Kim H, Lebeau B, Papadopoli D, Jovanovic P, Russo M, Avizonis D, Morita M, Afzali F, Ursini-Siegel J, Postovit LM, *et al*: MTOR modulation induces selective perturbations in histone methylation which influence the anti-proliferative effects of mTOR inhibitors. iScience 27: 109188, 2024.
235. Faes S, Santoro T, Troquier L, Silva OD and Dormond O: Rebound pathway overactivation by cancer cells following discontinuation of PI3K or mTOR inhibition promotes cancer cell growth. Biochem Biophys Res Commun 513: 546-552, 2019.
236. Khorasani ABS, Hafezi N, Sanaei MJ, Jafari-Raddani F, Pourbagheri-Sigaroodi A and Bashash D: The PI3K/AKT/mTOR signaling pathway in breast cancer: Review of clinical trials and latest advances. Cell Biochem Funct 42: e3998, 2024.
237. Napolitano F, Lin CC, Ahuja K, Ye D, Chica-Parrado MR, Uemoto Y, Luna P, Matsunaga Y, Mendiratta S, Unni N, *et al*: Abstract 3003: Targeting mechanisms of adaptive resistance to the PI3Kαmutant selective inhibitor RLY-2608 in HR+/PIK3CA mutant breast cancer. Cancer Res 85 (8 Suppl 1): S3003, 2025.
238. Elkanawati RY, Sumiwi SA and Levita J: Impact of lipids on insulin resistance: Insights from human and animal studies. Drug Des Devel Ther 18: 3337-3360, 2024.
239. Martínez Báez A, Ayala G, Pedroza-Saavedra A, González-Sánchez HM and Chihu Amparan L: Phosphorylation codes in IRS-1 and IRS-2 are associated with the activation/inhibition of insulin canonical signaling pathways. Curr Issues Mol Biol 46: 634-649, 2024.
240. Banjac K, Obradovic M, Zafirovic S, Essack M, Gluvic Z, Sunderic M, Nedic O and Isenovic ER: The involvement of Akt, mTOR, and S6K in the in vivo effect of IGF-1 on the regulation of rat cardiac Na^+/K^+-ATPase. Mol Biol Rep 51: 517, 2024.
241. Wright SCE, Vasilevski N, Serra V, Rodon J and Eichhorn PJA: Mechanisms of resistance to PI3K inhibitors in cancer: Adaptive responses, drug tolerance and cellular plasticity. Cancers (Basel) 13: 1538, 2021.
242. Pourbarkhordar V, Rahmani S, Roohbakhsh A, Hayes AW and Karimi G: Melatonin effect on breast and ovarian cancers by targeting the PI3K/Akt/mTOR pathway. IUBMB Life 76: 1035-1049, 2024.
243. Vadla R and Haldar D: Mammalian target of rapamycin complex 2 (mTORC2) controls glycolytic gene expression by regulating Histone H3 Lysine 56 acetylation. Cell Cycle 17: 110-123, 2018.