Critical role of mTOR in regulating aerobic glycolysis in carcinogenesis (Review)

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Abstract. Mammalian target of rapamycin (mTOR) serves an important role in regulating various biological processes, including cell proliferation, metabolism, apoptosis and autophagy. Among these processes, energy metabolism is the dominant process. The metabolism of not only amino acids, fatty acids and lipids, but also that of nucleotides and glucose has been indicated to be regulated by mTOR. Aerobic glycolysis, which is a specific form of glucose metabolism, is prevalent in carcinomas, and it has been considered to be a potential target for cancer therapy. In reviewing the complexity of the mTOR pathway, it is important to elucidate the central role and detailed pathway via which mTOR regulates glycolysis. In the present study, the complex mechanisms via which mTOR regulates aerobic glycolysis were comprehensively reviewed to highlight the potential of drug development via targeting the molecules associated with mTOR and glycolysis and to further provide strategies for the clinical treatment of cancer.

Contents

1. Introduction

To adapt to the severe nutrient deficient tumor microenvironment, cancer cells have been indicated to adjust their metabolic processes, including the abnormal function of signaling pathways and cellular metabolism (1). Cancer cells can express certain key glycolysis enzymes that act on the mammalian target of rapamycin (mTOR) signaling pathway to maintain clonality and promote migration (2,3). In recent years, increasing evidence has suggested that mTOR is a core network in cancer cells, regulating several key enzymes to maintain the balance between tumor growth and nutrition outside the cancer cells (4) (Fig. 1). The activation of mTOR has been indicated to promote mRNA transcription, protein synthesis, glucose metabolism and lipid synthesis that is necessary for cell growth (5,6). mTOR is an essential serine/threonine protein kinase that belongs to the PI3K family, and it includes two different catalytic subunit protein complexes, mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2) (7-9). Both complexes have been revealed to serve important roles in regulating the metabolism of cancer cells (9).

2. mTOR is central to metabolism in cancer

Carcinomas are often accompanied by metabolic alterations that are recognized as hallmarks of cancer during tumor development, and mTOR has been indicated to serve a vital role in cancer metabolism (4). There are several types of metabolism

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Abbreviations: AMPK, AMP kinase; CRC, colorectal cancer; FOXO6, forkhead box protein O6; GLUT, glucose transporter; HIF, hypoxia inducible factor; HK, hexokinase; KLF5, krüppel-like factor 5; LAD, lung adenocarcinoma; LAT, L-type amino acid transporter; LDH, lactate dehydrogenase; MCT, monocarboxylate transporter; mTOR, mammalian target of rapamycin; NSCLC, non-small cell lung cancer; PAK2, p21-activated kinase 2; PEP, phosphoenolpyruvate; PFK, phosphofructokinase; PK, pyruvate kinase; PKM, PK isozyme M; TSC, tuberous sclerosis complex

Key words: mTOR, aerobic glycolysis, carcinogenesis

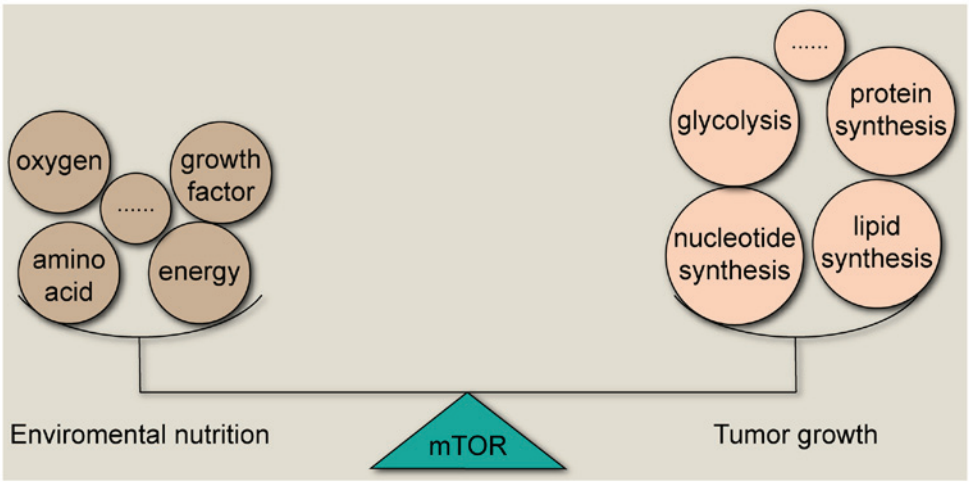

Figure 1. mTOR maintains a balance between the external environment and internal metabolic activity in cancer cells. Cancer cells need to balance the external environment, including oxygen, energy, amino acids and growth factors, with their own metabolic needs, including glycolysis, protein synthesis, nucleotide synthesis and lipid synthesis, and mTOR serves a vital role in this balance. mTOR, mammalian target of rapamycin.

in cancer cells, including amino acid, glucose, nucleotide and lipid metabolism (10) (Fig. 2).

Amino acid metabolism. Amino acids are vital nutrient substrates for protein synthesis, and this process has been indicated to be closely regulated by mTOR in cancer cells. Both essential and nonessential amino acid metabolism has been associated with the mTOR signaling pathway (4). L-type amino acid transporter (LAT) 1, which transports the essential amino acid leucine, has been associated with the activation of mTOR pathway in colorectal cancer (11). Glutamine, a nonessential amino acid, contributes to the synthesis of other amino acids, lipids and nucleotides (4), and glutaminolysis has been indicated to be promoted by the mTORC1 and mTORC2 pathways (12,13).

Nucleotide metabolism. Cancer cells necessitate nucleic acids to support their own proliferation (14). mTOR promotes purine synthesis by regulating enzymes that mediate the synthetic process. For example, phosphoribosyl pyrophosphate synthase 2 is the rate-limiting enzyme in purine synthesis, and its expression has been revealed to be upregulated by the mTORC2/AKT signaling pathway (4). Pyrimidine synthesis is also regulated by mTOR, as the mTORC1/S6 kinase pathway has been indicated to regulate implicated enzymes, including carbamoyl phosphate synthetase II, phosphorylation and oligomerization of aspartate transcarbamylase and dihydroorotase (4).

Lipid metabolism. Cancer cells can synthesize fatty acids intracellularly or incorporate extracellular fatty acids, and mTOR has been indicated to regulate fatty acid transporters, such as CD36 and synthesis enzymes, including ATP citrate lyase and fatty acid synthase (4). The transmembrane glycoprotein CD147 has been reported to reprogram fatty acid metabolism via the AKT/mTOR/sterol regulatory element binding protein-1c and p38/peroxisome proliferator-activated receptor α pathways in hepatocellular carcinoma cells (15).

Glucose metabolism. Glucose, which is the main cellular energy source, has been demonstrated to promote growth, proliferation and metastasis of cancer cells; therefore, the sense, uptake and utilization of glucose are essential for maintaining life, and the mTOR signaling pathway has been indicated to participate in these processes (16). Otto Warburg has revealed that cancer cells often rely on glycolysis even in the presence of oxygen, and this phenomenon is also called aerobic glycolysis or the Warburg effect (17).

Given the significance and complexity of aerobic glycolysis and mTOR in cancer cells, it is necessary to review the relationship between mTOR and aerobic glycolysis to suggest a potential novel strategy for clinical cancer therapy that depends on both these factors.

3. Glycolysis is a complex process

Glycolysis is a process in which glucose is metabolized into several products, including pyruvate, lactate and hydrogen ions, via multistep enzymatic reactions in the cytoplasm (18). The detailed glycolytic process is depicted in Figs. 2 and 3. Glycolytic enzymes have been indicated to be closely associated with the mTOR signaling pathway (4,19). In a first step, cancer cells overexpress glucose transporters, such as glucose transporter (GLUT)1 and sodium-glucose linked transporter 1, transporting glucose into the cytoplasm to maintain high levels of glucose consumption during glycolysis (20,21). Subsequently, hexokinase (HK) phosphorylates intracellular glucose to form glucose 6-phosphate (22,23). In a second step, glucose 6-phosphate isomerase catalyzes the production of fructose-6-phosphate (24). In a third step, fructose-6-phosphate is phosphorylated by phosphofructokinase (PFK)-1 and PFK-2 into the unstable fructose-1,6-biphosphate and the relatively stable fructose-2,6-biphosphate (19), respectively. Glucose 6-phosphate is also converted into glyceraldehyde-3-phosphate (25), which is subsequently converted into glycerate-1,3-biphosphate, and glycerate-1,3-biphosphate is converted into 3-phosphoglycerate by phosphoglycerate kinase (19). Subsequently, phosphoglyceromutase drives the isomerization of 3-phosphoglycerate to phosphoglycerate 2-phosphate, followed by the formation of phosphoenolpyruvate

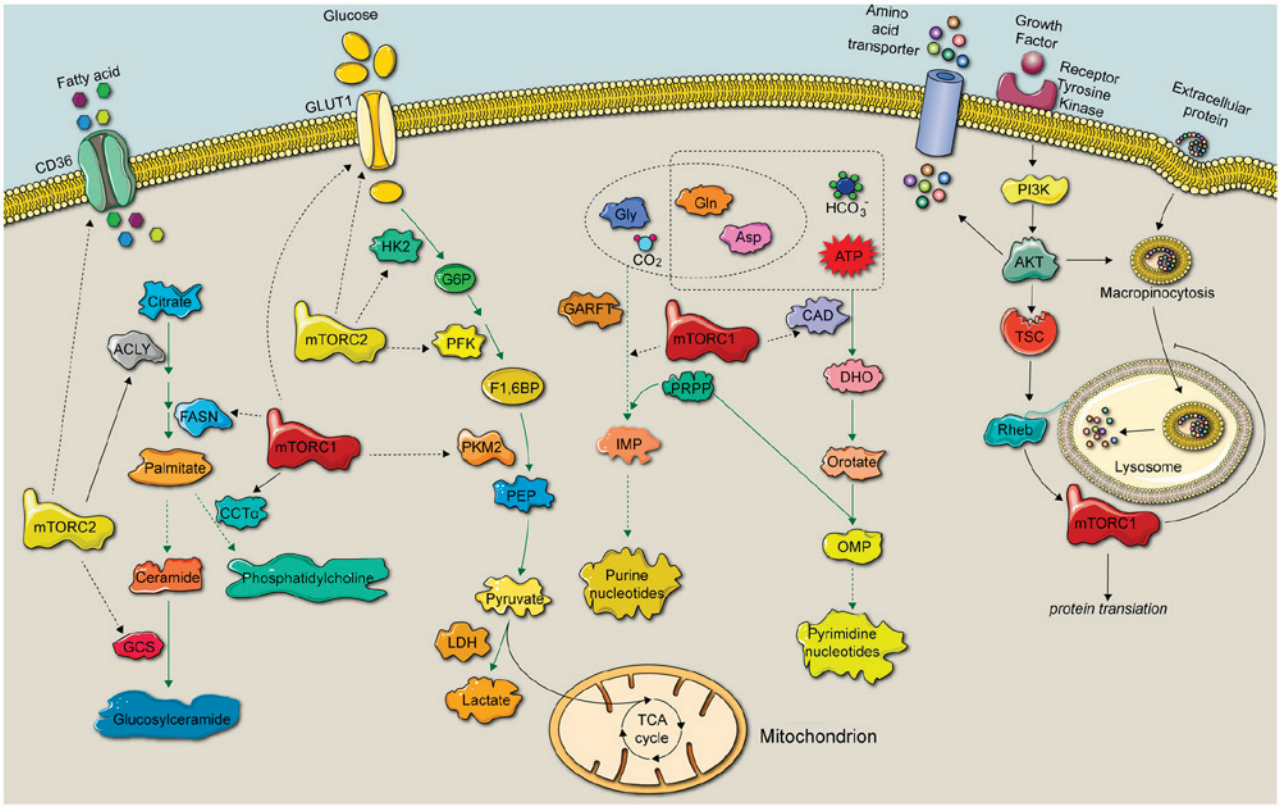

Figure 2. mTOR signaling pathway regulates cancer cell metabolism. mTOR regulates the metabolism of fatty acids and lipids, mediating the uptake of fatty acids via CD36. Citrate is converted to palmitate via multiple steps that are catalyzed by ACLY and FASN, which are both regulated by mTOR signaling. Palmitate serves as a pre-substrate of phosphatidylcholine by catalyzing the formation of phosphocholine CCTα or glucosylceramide through GCS. Both CCTα and GCS are regulated by mTOR signaling. mTOR regulates glycolysis, a complex process that involves glucose transporters and various catalytic enzymes, including HK2, PFK, PKM2 and LDH. Gln, Gly, Asp and CO_2 react with PRPP via GARFT catalysis to form the pre-substrate of purine nucleotides. Gln, Asp, HCO_3^- and ATP are converted to DHO by CAD, and after several steps pyrimidine nucleotides are produced. On the one hand, mTOR signaling regulates various amino acid transporters to increase the uptake of amino acids; on the other hand, mTOR aids in the acquisition of amino acids via macropinocytosis of extracellular proteins to synthesize the required proteins. mTOR, mammalian target of rapamycin; mTORC, mTOR complex; ACLY, ATP citrate lyase; FASN, fatty acid synthase; CCTα, cytidylyltransferase-α; GCS, glucosylceramide synthase; HK2, hexokinase 2; PFK, phosphofructokinase; PKM2, pyruvate kinase muscle isoform 2; LDH, lactate dehydrogenase; Gln, glutamine; Gly, glycine; Asp, aspartate; PRPP, ribose-5-phosphoribosyl-1-pyrophosphate; GARFT, glycinamide ribonucleotide formyltransferase; DHO, dihydroorotase; CAD, aspartate transcarbamylase and dihydroorotase; G6P, glucose-6-phosphate; F1,6BP, fructose-1,6-bisphosphate; PEP, phosphoenolpyruvate; GLUT1, glucose transporter 1; TSC, tuberous sclerosis complex; OMP, orotidine monophosphate; Rheb, Ras homolog enriched in brain.

(PEP). In the last step of glycolysis, PEP is converted into pyruvate by pyruvate kinase (PK) (26).

4. mTOR signaling pathway regulates glycolysis

As aforementioned, mTOR has been associated with several fundamental cellular processes (4), such as protein synthesis (27), autophagy (28) and cancer (29). Moreover, glycolysis is considered a principal driver of carcinoma metastasis (30) due to the energy support provided by glycolysis (30). Ka *et al* (28) revealed that pharmacological inhibition of phosphofructokinase-2/fructose-2,6-bisphosphatase 3 suppressed tumor growth and alleviated metastasis in head and neck squamous cell carcinoma. *In vitro* and *in vivo* experiments have demonstrated that glycolysis promoted breast cancer growth and metastasis via the regulation of miR-30a-5p (31). These results suggested that targeting glycolysis may be a promising strategy to inhibit cancer growth. The present review subsequently focused on the effects of the mTOR signaling pathway on energy metabolism, especially cancer cell glycolysis (Fig. 3).

Upstream pathways of mTORC1 and glycolysis. mTORC1 integrates four major regulatory inputs: Nutrients, growth factors, energy and stress (32). mTORC1 has been indicated to be frequently overactivated in glycolytic cancer cells, suggesting that the inhibition of factors upstream of mTORC1 may be more effective compared with the inhibition of downstream factors to inhibit glycolysis in cancer cells (4).

Nutrients, mTORC1 and glycolysis. Previous evidence has suggested that amino acids are critical to cancer cell growth by stimulating the mTORC1 signaling pathway, and among these, leucine and glutamine have been revealed to be the most important amino acids (33). Therefore, targeting transporters may be a reasonable strategy to inhibit tumor growth. LAT2, which mainly imports neutral amino acids, including leucine and glutamine, has been indicated to bind to phosphorylated (p)-mTOR^{Ser2448} and regulate the glutamine/p-mTOR^{Ser2448}/glutamine synthetase feedback loop, maintaining mTORC1 activation, which activates glycolysis (34).

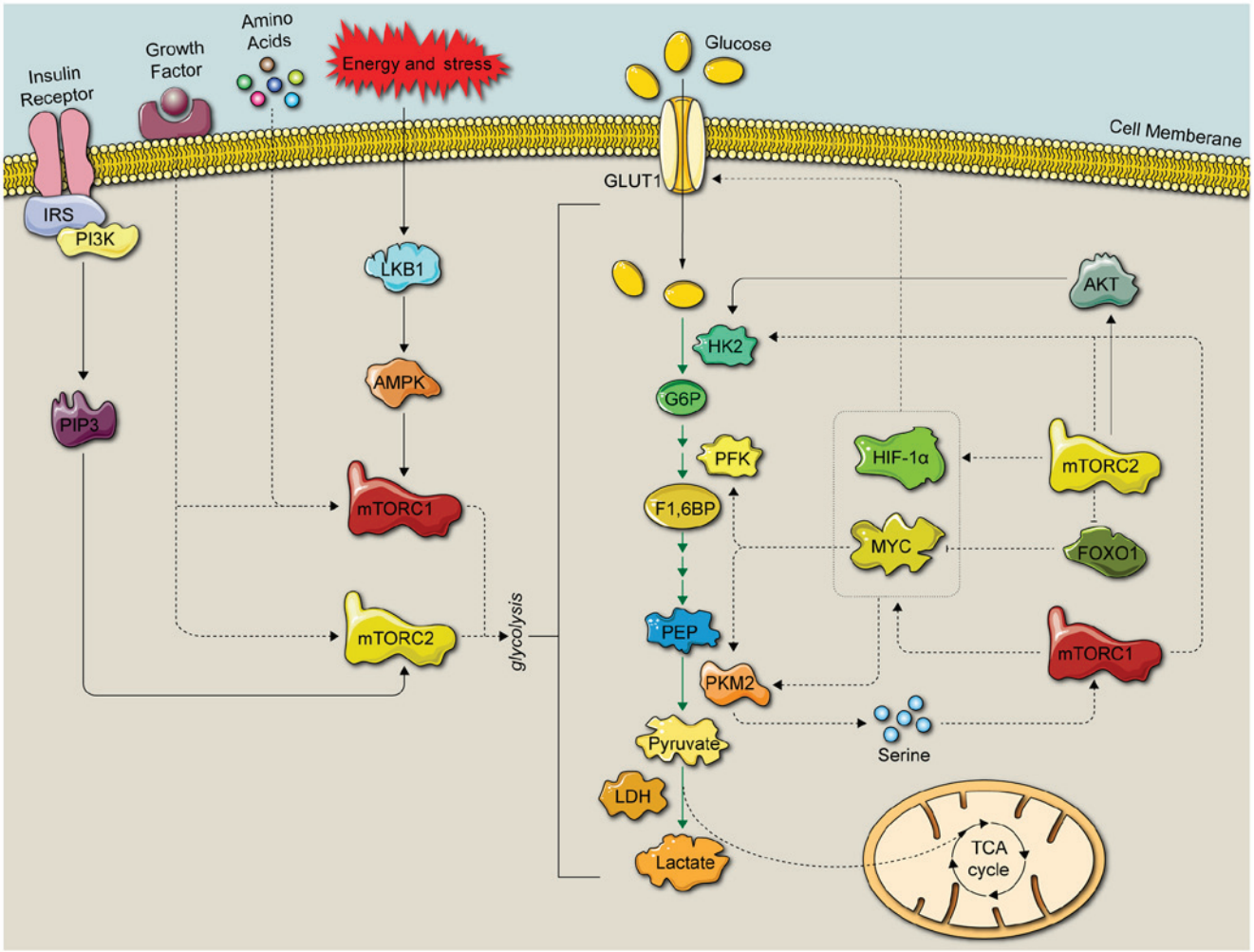

Figure 3. Upstream and downstream signaling pathways of mTOR and mTOR-mediated regulation of glycolysis. mTORC1 can be activated by growth factors, amino acids, energy and stress, while mTORC2 can only be activated by growth factors, such as insulin receptor signal transduction. Both mTORC1 and mTORC2 have regulatory effects on glycolysis via direct or indirect mechanisms. GLUT1 transports extracellular glucose into the cell. HK2 phosphorylates glucose and converts it into G6P. After several steps, G6P is converted to F1,6BP by PFK. F1,6BP is converted to PEP through several steps, and PKM2 converts PEP to pyruvate. LDH interconverts pyruvate and lactate in the last step. HK2, PFK and PKM2 are rate-limiting enzymes, and all of them are directly or indirectly regulated by the mTOR signaling pathway mainly via HIF-1α and MYC. mTOR, mammalian target of rapamycin; mTORC, mTOR complex; GLUT1, glucose transporter 1; HK2, hexokinase 2; G6P, glucose-6-phosphate; F1,6BP, fructose-1,6-bisphosphate; PFK, phosphofructokinase; PEP, phosphoenolpyruvate; PKM2, pyruvate kinase isozyme type 2; LDH, lactate dehydrogenase; HIF-1α, hypoxia-inducible factor-1α; FOXO, forkhead box protein O; AMPK, AMP kinase; IRS, insulin receptor substrate; PIP3, phosphatidylinositol-3,4,5-trisphosphate; LKB1, liver kinase B1.

Growth factors, mTORC1 and glycolysis. Previous studies have revealed that mTORC1 is a downstream mediator of growth factors (9,35). Insulin, one of these growth factors, has been indicated to upregulate pyruvate kinase M (PKM)2 expression via the PI3K/mTOR-mediated hypoxia inducible factor-1α (HIF-1α) induction, but reduce PKM2 activity independent of this pathway (36,37). Insulin-induced PKM2 upregulation has been revealed to enhance aerobic glycolysis, but the reduction in PKM2 activity may result in a characteristic pooling of glycolytic intermediates and the accumulation of NADPH (37).

Energy and stress regulate mTORC1. mTORC1 can be activated by stress (9), such as low ATP levels (38), hypoxia (39) and DNA damage (40). Mitosis serves a vital role in cellular maintenance and metabolism, and DNA replication is the most vital step of mitosis (41), as cells should check for any DNA damage before proceeding to the subsequent step. mTORC1 has been identified as the determinant for G_2/M checkpoint recovery (42) and has been indicated to be required to induce DNA damage repair and cell survival, resulting in increased cancer cell survival in the presence of DNA damage (43). These findings suggested that checkpoint inhibitors present great potential in the treatment of mTORC1-hyperactivated carcinoma.

Upstream pathways of mTORC2. A previous study has indicated that mTORC2 can be activated by growth factors, such as insulin (32). Recent studies have revealed that mTORC2 can also be stimulated by glucose (44), glutamine and mTORC1 (9,45). The mTORC2 pathway is essential for normal glucose homeostasis and metabolic regulation in the body, and the overactivation of mTORC2 may be linked to tumor growth (46). The activation of insulin-like growth factor 1-TORC2 has been indicated to drive the metastasis of nasopharyngeal carcinoma with reprogrammed glucose metabolism (47).

Two facets of AMP kinase (AMPK) and glycolysis. AMPK serves as an energy sensitive receptor in the context of energy stress and can be viewed as a negative regulator of the Warburg effect in human cancers, suggesting that a high level of AMPK indicates a better prognosis (48). Given that both AMPK and mTOR serve important roles in regulating glucose metabolism, it has been demonstrated that AMPK is indeed a regulator of mTOR and phosphorylates regulatory-associated protein of mTOR, which is a component of mTORC1, inhibiting its activity (49). The levels of aerobic glycolysis and tumor growth were indicated to be downregulated by AMPK *in vivo*, and Myc-induced lymphomagenesis was accelerated when the α1 catalytic subunit of AMPK was ablated (50). Moreover, a metabolic shift to aerobic glycolysis has been observed in both transformed and untransformed cells when AMPK was inactivated, which increased the allocation of glucose-derived carbon into lipids and biomass accumulation (50). However, the role of AMPK in regulating glycolysis may be different in other contexts. For example, tamoxifen has been indicated to inhibit oxygen consumption via inhibiting mitochondrial complex I, increasing the AMP/ATP ratio and activating the AMPK signaling pathway, thereby promoting glycolysis (51).

Moreover, glucose promotes glycolysis by regulating the AMPK/AKT/mTOR/S6 kinase and MAPK pathways (52). The small polyphenol resveratrol has been indicated to inhibit glycolysis in female ovarian cancer cells via activating the AMPK/mTOR signaling pathway (53). However, AMPK has also been demonstrated to regulate glycolysis via phosphorylating and activating 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase (PFKFB)3, thereby increasing the level of fructose-2,6-bisphosphate (54).

PI3K/AKT/mTOR signaling pathway regulates glycolysis in cancer. Glycolysis, which is a hallmark of cancer cells (4), exhibits a faster ATP production rate compared with oxidative phosphorylation to provide a carbon source for anabolic processes, including the synthesis of amino acids, lipids and nucleotides, although glycolysis produces less energy compared with oxidative phosphorylation (17). The PI3K/AKT/mTOR signaling pathway has been indicated to be a critical pathway during the process of cancer glycolysis (55). It has been demonstrated that targeting the PI3K/AKT/mTOR signaling pathway during metabolic processes presents great potential as an anticancer strategy (55). The expression of glycolysis-related genes, including GLUT1, GLUT3, lactic dehydrogenase (LDH)A, LDHB, HK1, HK2, PKM and HIF-1α, has been indicated to be higher in carcinoma compared with surrounding tissues in bladder cancer (56). Moreover, inhibition of miR-21, which has been revealed to regulate aerobic glycolysis in bladder cancer cells via the PTEN/PI3K/AKT/mTOR pathway (57,58), resulted in a reduction in aerobic glycolysis in cancer cells (56). It has been also demonstrated that inhibitors of PI3K/mTOR suppressed the glycolysis level of EGFR-mutant lung adenocarcinoma (LAD) cells and the levels of early metabolites of glycolysis (59). Moreover, 6-phosphogluconate was revealed to be decreased in response to PI3K/AKT/mTOR pathway inhibition, indicating that PI3K/AKT/mTOR signaling is indispensable for the regulation of aerobic glycolysis in EGFR-mutant LAD cells (59). Furthermore, inhibition of PI3K/mTOR has been indicated to effectively suppress the membrane localization of GLUT1, which is critical for glycolysis (59). However, the molecular mechanism by which PI3K/AKT/mTOR regulates GLUT1 remains to be further elucidated (60).

The upstream and downstream pathways of the PI3K/AKT/mTOR signaling pathway have been revealed to regulate cancer cell glycolysis. For example, knockdown of Forkhead box protein O (FOXO)6, a FOXO family member, has been indicated to inhibit PI3K/AKT/mTOR pathway activation and alter cellular metabolism via inhibiting glycolysis and promoting mitochondrial respiration in colorectal cancer (CRC), indicating that FOXO6 may serve as a potential mTOR-dependent target for CRC therapy (61). Krüppel-like factor 5 (KLF5) silencing has been reported to suppress HIF-1α-dependent glycolysis in non-small cell lung cancer (NSCLC) via inactivating the PI3K/AKT/mTOR pathway (62). Knockdown of glutamate receptor, ionotropic, N-methyl D-aspartate-associated protein 1, which is also known as GRINA, has been demonstrated to inhibit PI3K/AKT/mTOR signaling and glycolytic metabolism in gastric cancer cells (63). CD147 has been indicated to promote glycolytic metabolism in hepatocellular carcinoma cells via the PI3K/AKT/mTOR signaling pathway (64). CD276 has been reported to enhance the Warburg effect via promoting the PI3K/AKT/mTOR/HIF-1α pathway, as well as its downstream targets GLUT1 and PFKFB3, in oral squamous carcinoma (65). Tripartite motif-containing protein 59 may enhance glycolysis via the PI3K/AKT/mTOR signaling pathway, ultimately contributing to pancreatic cancer progression (66). Type Iγ phosphatidylinositol phosphate kinase has been indicated to upregulate c-Myc and HIF-1α levels by stimulating the PI3K/AKT/mTOR signaling pathway, thereby regulating the expression of glycolytic enzymes to enhance glycolysis in CRC (67).

PI3K/AKT/mTOR signaling pathway and drug resistance. The PI3K/AKT/mTOR signaling pathway is one of the most commonly activated signaling pathways associated with drug resistance in various cancers, such as breast cancer, ovarian cancer and NSCLC (62,68,69). A recent study on the drug resistance of breast cancer has revealed that the PI3K/AKT/mTOR signaling pathway serves an important role in endocrine resistance, since it was indicated to be activated in response to CC-chemokine ligand 2 secreted by tumor-associated macrophages, which promoted an endocrine resistance feedback loop in the tumor microenvironment (68). In addition to breast cancer, the PI3K/AKT/mTOR signaling pathway has also been revealed to facilitate the chemoresistance of ovarian cancer. For example, this pathway has been indicated to trigger the expression of cancer stem cell markers, including CD44v6, CD117, aldehyde dehydrogenase 1 family member A1 and Snail, resulting in cisplatin resistance in epithelial ovarian cancer (70). Hypoxia-induced cisplatin resistance in NSCLC has been demonstrated to be suppressed after knockdown of KLF5, which may occur following inhibition of HIF-1α-dependent glycolysis via PI3K/AKT/mTOR inactivation (62).

Key steps in glycolysis: One input and three processing tools. There are various types of glucose transporters and three key

rate-limiting enzymes in glycolysis, HK, PFK and PK (71), and all of these transporters and enzymes have been reported to be associated with the mTOR signaling pathway (23,72).

mTOR signaling pathway and glucose transporters. Glucose transporters act as gatekeepers of glycolysis and have been reported to be elevated to facilitate glucose uptake due to the low efficiency of glycolysis in various types of cancers, such as NSCLC (73), hepatocellular carcinoma and breast cancer (74). A previous study has revealed that glucose uptake and GLUT1 expression were increased in multiple cell types due to the absence of the downstream target protein of mTOR, tuberous sclerosis (TSC)2 protein (75). Moreover, mTORC1 has been indicated to be activated in renal angiomyolipomas as a result of the loss of TSC1/2 function, and TSC2 has been reported to regulate the membrane localization of various glucose transporter proteins, such as GLUT1, GLUT2 and GLUT4, ultimately affecting glucose uptake (76). In addition, the proliferation of CRC has been indicated to be inhibited following GLUT1 gene silencing, which was mediated by the TGF-β/PI3K/AKT/mTOR signaling pathway, providing a novel basis for targeted therapy and the development of novel drugs to treat CRC (77). It has been demonstrated that GLUT1 translocation may be regulated by the PI3K/AKT/mTOR-mediated activation of the RhoA/Rho-associated protein kinase 1 pathway or by stimulating glycolysis, but this remains to be elucidated in the future (59). Certain researchers have focused on the effects of oncogenes that are downstream of the mTOR signaling pathway, including c-Myc and HIF-1α, on the expression of glucose transporters (78,79). In addition to GLUT1, the effects of other members of the glucose family, such as GLUT2 and GLUT5, have also been examined in the context of cancer (74). In studying the role of microRNA (miRNA/miR)-21 in glycolysis and tumorigenesis in T24 bladder cancer cells, it has been revealed that GLUT3 was downregulated when miRNA-21 was sponged and that the associated mechanism may implicate the PI3K/AKT/mTOR signaling pathway (56). Similarly, the expression of GLUT3 has been indicated to be positively regulated by mTORC1 via the activation of IKK/NF-κB signaling, and reduction in aerobic glycolysis, inhibition of cell proliferation, suppression of colony formation and delay in tumor growth have been revealed to occur following GLUT3 knockdown (80).

mTOR signaling pathway and HK2. Glucose phosphorylation, which is the first step in glucose metabolism, is under the control of HK (81). There are five different types of hexokinase isoforms that have been discovered in mammalian cells (82). HK1 is widely expressed in human cells and is considered to be a housekeeping isoform, while HK2 is only expressed in certain tissues, including skeletal muscle, cardiac muscle and adipose tissues (83,84), as well as in cancer cells (85). HK3 is less characterized compared with the other isoforms due to its low levels, and it is considered to be inhibited by glucose under physiological conditions (86). Moreover, recent research has indicated that the upregulation of HK3 is closely associated with the occurrence of EMT in CRC and may be of importance in metabolic adaptation for the rapid proliferation, survival and metastasis of CRC cells (87). HK4, which is also called glucokinase, is expressed in the liver and pancreas (88) and is involved in the migration of regulatory T cells via a PI3K-mTORC2-mediated pathway (89). The importance of HK2 in cancer cells and its relationship with mTOR is highlighted below. HK2 has also been indicated to bind to mitochondrial porins and catalyze the first step of glycolysis (90). AKT can activate HK2 associated with mitochondria, thereby promoting glycolysis (91). In addition, HK2 expression has been revealed to be enhanced by HIF-1α (92,93), which is regulated by the PI3K/AKT/mTORC1 pathway (4,94). To investigate the contributions of c-Src, a proto-oncogene closely associated with mTOR (95,96), to the metabolic reprogramming of cancer cells, Conde *et al* (92) demonstrated that c-Src phosphorylated HK1 at Tyr732 and HK2 at Tyr686, strengthening their catalytic activity and enhancing glycolysis. Cell glycolysis, proliferation and metastasis were diminished when the c-Src phosphorylation site of either HK1 or HK2 was mutated (97). In addition, HK may be affected by miRNAs. miR-214 downregulation has been revealed to inhibit glycolysis by decreasing the expression of both HK2 and PKM2 via the PTEN/AKT/mTOR pathway in NSCLC cells, revealing the significance of miR-214 and the importance of mTOR-mediated HK-regulated glycolysis in NSCLC treatment (98).

mTOR signaling pathway and PFK. HIF-1 and c-Myc, which are both downstream mediators of the mTOR signaling pathway, are two major regulators of glycolytic enzymes, including HK2, PFK and LDHA (96,99). Fructose 6-phosphate is converted to fructose 1,6-bisphosphate by PFK-1, which is a well-known 'gatekeeper' of glycolysis, and this constitutes the commitment step of glycolysis (100). PFK-1 is considered to be a key regulator of metabolic reprogramming in various types of cancers (101,102), including glioblastoma (103), lung cancer (104) and breast cancer (105). It has been indicated that c-Myc directly transactivated genes encoding PFK and increased glucose uptake in Rat-1 fibroblasts (106). A previous study has revealed that PFK-1 platelet isoform (PFKP), which is the main PFK-1 isoform, was overexpressed in human glioblastoma due to the loss of PTEN- and EGFR-mediated PI3K activation, contributing to glycolysis and tumorigenesis (103). These results highlighted the potential role and regulation of PFKP and mTOR-related AKT signaling in human glioblastoma development (103). It has been revealed that PFKFB is a key glycolysis regulator that modulates fructose 2,6-bisphosphate levels and glucose uptake (107). PFKFB3 has been reported to contribute to the development, metastasis and chemotherapy resistance of cancer cells (108-111). Previous studies have indicated that mTORC2 activated AKT by phosphorylating S473, leading to the allosteric activation of PFK-1 (108,110). Moreover, PFKFB3 has been demonstrated to be upregulated by mTORC1, which was dependent on HIF-1α in acute myeloid leukemia (112), and has been indicated to be activated by AKT in another study, which was downstream of mTORC2, thereby contributing to tumor angiogenesis (113). In addition to PFKFB3, PFKFB4 has also been reported to be associated with certain malignancies (114,115). PFKFB4 expression in human bladder cancer has been demonstrated to be associated with hypoxia via HIF-1α (116). The aforementioned results

have indicated that mTOR-mediated PFK signaling is tightly associated with carcinogenesis.

mTOR signaling pathway and PK. There are two genes encoding four PK isoforms, where two PK isoforms correspond to each gene (117). The PKLR gene encodes PKL and PKR, while PKM1 and PKM2 are encoded by the PKM gene (118). It has been indicated that there is a potential relationship between PK and mTOR. The final step of glycolysis is catalyzed by PKM2, which converts PEP to pyruvate via the transfer of a phosphate group to ADP (4). PKM2 has been widely studied in past decades, and both inhibitors and activators have been developed for anticancer purposes in different contexts due to the multifaceted characteristics of cancers (119,120). Certain PKM2 activators have been developed to induce the tetramerization of PKM2, causing PKM2 to function as PKM1, which is the dominant glycolytic enzyme in healthy adult tissues (121,122). A number of scientists believe that the inhibition of PKM2 occurs as a result of its high expression in various types of cancers, including lung (123), breast (124) and gastric cancer (125). The PI3K/AKT/mTOR pathway has been implicated in regulating PKM2 expression levels, and evidence has indicated that rapamycin decreased PKM2 expression, highlighting the role of mTOR in regulating PKM2 (126,127). HIF-1α and c-Myc have also both been closely associated with the activity of PKM2 (128,129). It has been demonstrated that when mTOR was activated or inhibited, the expression levels of PKM2 and HIF-1α, as well as glycolysis, were altered in esophageal squamous cell carcinoma, indicating that mTOR promoted aerobic glycolysis in esophageal squamous cell carcinoma by upregulating PKM2 expression (130). Yes-associated protein is a powerful regulator that has been indicated to be overexpressed in various types of cancers, such as hepatocellular carcinoma (131), binds to HIF-1α in the nucleus to maintain the stability of HIF-1α protein and also binds to PKM2 gene and directly activates PKM2 transcription to accelerate glycolysis, providing a novel therapeutic target based on HIF-1α (131). Moreover, the interaction of PKM2 with the HIF-1α subunit stimulates PKM2 transactivation via a feedback loop (132). Following ligand stimulation and post-translational modification, PKM2 is transferred into the nucleus activating HIF-1α, thereby promoting the glycolytic pathway (122). The correlation between c-Myc expression and increased PKM2 synthesis in various cancers, such as gastric (133), head and neck (129), liver (134) and breast cancer (135), highlights the possible role of c-Myc in PKM2 expression (134). A recent study has revealed that c-Myc expression was upregulated by p21-activated kinase 2 (PAK2) and that c-Myc bound to the PKM promoter to induce PKM2 expression, which provided a potential framework for head and neck cancer therapy by targeting the PAK2-cMyc-PKM2 axis (129). Furthermore, mTOR has been indicated to regulate TSC1/2 to control the expression of PAK2, but the regulation of glycolysis via PKM2 remains to be explored (136).

mTOR, monocarboxylate transporters (MCTs) and metabolic symbiosis. After the bidirectional enzyme LDH converts pyruvate to lactate, certain cancer cells have been indicated to retain lactate as a metabolic substrate, although others secrete it (4,137,138). Glycolytic cancer cells have been revealed to overexpress MCT-4 to export lactate, maintaining a proper pH for tumor growth, while MCT-1 has been indicated to be highly expressed in normoxic cancer cells in close proximity to blood vessels to import lactate for the synthesis of amino acids (139,140). The phenomenon of lactate re-use in two different types of cells is called metabolic symbiosis, and it is regarded as a potent therapeutic target for cancer (139,141,142). Notably, MCT-1 and MCT-4 have been demonstrated to be critical in metabolic symbiosis (143,144). In arsenite-induced carcinogenesis, it has been reported that arsenite caused high HIF-1α-mediated expression of MCT-4 in liver cells, enhancing glycolysis and resulting in hepatoxicity (145).

5. Perspectives

Cancer cell metabolism shifts from oxidative phosphorylation to glycolysis even in the presence of oxygen, which is also called the Warburg effect, to accommodate the rapid increase in the energy requirements of cancer cells (4). Cancer cells often overexpress catalytic glycolysis enzymes to promote energy production, which is often associated with the abnormal activation of the mTOR signaling pathway (146). All molecules of the entire glycolytic pathway from GLUT to PK are indispensable for glycolysis, and disruption of any factor can lead to glycolysis disorders (4). More importantly, the molecules involved in glycolysis do not function alone, but are regulated by other molecules (147). mTOR-mediated pathways have been revealed to act as central regulators to control the entire glycolytic process (4). Currently, several drugs have been indicated to affect glycolytic proteins, and certain of these drugs will undergo clinical testing (148). Although the Warburg effect has been identified in the past century, its application in cancer has been investigated until recent decades (149). mTOR inhibitors that have been used in the clinic to treat cancer have also been revealed to exert unsatisfactory effects (148). Therefore, in reviewing the importance of aerobic glycolysis and mTOR in carcinogenesis and the limitations of a single application in cancer treatment, we hypothesize that simultaneously blocking glycolysis-associated proteins and the mTOR pathway may be a better alternative for cancer therapy compared with the single-agent inhibition of glycolysis.

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Availability of data and materials

Data sharing is not applicable to this article, as no datasets were generated or analyzed during the current study.

Authors' contributions

WXC, YL and SJW conceived and supervised the study; HF and YYW wrote the original draft; HF, SYY, XML and AYW wrote and edited the review; HF prepared the figures; WXC and YL acquired funding. All the authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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