The Glycolytic Switch in Tumors: How Many Players Are Involved?

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Abstract

Reprogramming of cellular metabolism is a hallmark of cancers. Cancer cells more readily use glycolysis, an inefficient metabolic pathway for energy metabolism, even when sufficient oxygen is available. This reliance on aerobic glycolysis is called the Warburg effect, and promotes tumorigenesis and malignancy progression. The mechanisms of the glycolytic shift in tumors are not fully understood. Growing evidence demonstrates that many signal molecules, including oncogenes and tumor suppressors, are involved in the process, but how oncogenic signals attenuate mitochondrial function and promote the switch to glycolysis remains unclear. Here, we summarize the current information on several main mediators and discuss their possible mechanisms for triggering the Warburg effect.

Key words: the Warburg effect; reprogramming of glucose metabolism; aerobic glycolysis; tumor metabolism; glycolytic switch.

Introduction

Reprogramming of glucose metabolism is a key event in tumorigenesis. Cancer cells undergo a metabolic switch from oxidative phosphorylation (OXPHOS) to glycolysis in which a molecule of glucose is degraded to two molecules of pyruvate (Fig 1). Depending on the supply of oxygen for the cells, pyruvate is either reduced to lactate in the absence of oxygen via an anaerobic glycolysis pathway, or oxidized to yield acetyl-coenzyme A in the presence of oxygen and then oxidized completely to CO₂ and H₂O via citric acid cycle. The majority of cancer cells depend on high rates of glycolysis for growth and survival, even when there is sufficient oxygen [1, 2]. This type of aerobic glycolysis is called the Warburg effect, and the mechanisms underlying this reprogramming are not fully understood. The Warburg effect has long been linked to hypoxia, but it is not solely adaptive to hypoxia, as it also occurs under normoxic conditions [1, 2]. Although mitochondrial dysfunction in cancer cells can cause a shift in energy metabolism, a majority of tumor cells demonstrate normal mitochondrial function and OXPHOS [3-5], and the high glycolytic flux in cancer cells does not mean impairment of OXPHOS [6]. The high rates of glycolysis provide advantages for the survival and growth of cancer cells [7]. Three possible explanations for tumor cell use of the glycolysis pathway, an inefficient metabolic pathway, have been proposed [8, 9]. First, compared to OXPHOS, the rate of ATP production through glycolysis is much more rapid [10]. Secondly, high glycolytic flux provides sufficient glycolytic intermediates to meet the biosynthesis needs of the rapidly proliferating cells [11-13]. Finally, NADPH, derived from the enhanced

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pentose phosphate pathway (PPP) due to the accumulation of glycolytic intermediates, enables cancer cells to maintain adequate levels of reduced forms of glutathione for resistance to chemotherapeutic agents.

Several mechanisms have been proposed to enable cancer cells to maintain high glycolytic flux [11]. First, phosphofructokinase-1 (PFK1) serves as a critical driver of glycolytic flux. The expression of PFK2 is upregulated in cancer cells and promotes the production of fructose-2,6-bisphosphate, which acts as a potent allosteric activator of PFK1 to overcome negative allosteric feedback inhibition of PFK1 by high ATP levels. Second, re-generation of NAD+ and lactate production mediated by lactate dehydrogenase (LDH) is instrumental in maintaining glycolysis. In addition, the expression of pyruvate kinase M2 (PKM2) is upregulated in cancer cells. Allosteric and covalent inhibition of PKM2 channels glycolytic intermediates upstream of pyruvate into biosynthetic pathways [11]. Although metabolic reprogramming has long been observed as a feature of neoplasia and tumor growth, the mechanism triggering and modulating this process remains largely unclear. In this review, we mainly focus on the mechanism underlying the regulation of glycolytic switch in tumors. In addition to signal molecules and transcription factors HIF-1α, c-Myc, Akt, and mTOR, the main regulators which have been well documented, several other regulators including oncogene K-Ras, tumor suppressor p53, energy sensor adenosine monophosphate activated protein kinase (AMPK), non-coding RNAs, and sirtuin family proteins and deacetylation will also be discussed.

**Master regulator HIF-1α**

Hypoxia-inducible factor-1 (HIF1) consists of two subunits, HIF-1α and HIF-1β, also known as ARNT. Under physiological oxygen levels, the HIF-1α subunit is sensitive to oxygen concentration and is hydroxylated by prolyl-hydroxylases (PHD) and targeted for proteasomal degradation. Increase of reactive oxygen species (ROS) under hypoxia inhibits PHD and stabilizes the HIF-1α subunit. HIF-1α is a master regulator of glycolysis and plays an important role as an activator of aerobic glycolysis and lactate

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**Figure 1.** Main steps in glycolysis and possible key enzymes regulated in the Warburg effect. The three reactions catalyzed by hexokinase (HK), phosphofructokinase-1 (PFK1), and pyruvate kinase (PK) in this process are rate-limiting steps. During glycolysis, four molecules of ATP are produced per molecule of oxidized glucose via substrate-level phosphorylation, and the net yield is two molecules of ATP after deduction of two ATPs consumed in phosphorylation. The fate of pyruvate depends largely on the availability of oxygen for the cells. Pyruvate is reduced to lactate under hypoxia via an anaerobic glycolysis pathway or, under aerobic conditions, oxidized to yield acetyl-coenzyme A, which is then oxidized completely to CO2 via the citric acid cycle, resulting in the production of large amounts of ATP. G-6-P, glucose-6-phosphate; G6PD, glucose-6-phosphate dehydrogenase; GLUT, glucose transporter; Fru-2,6-P2, fructose-2,6-bisphosphate; LDH, lactate dehydrogenase; MCT, monocarboxylate transporter; TPI, triose phosphate isomerase.
production. It potentiates the transcription of glucose transporters (GLUT) and glycolytic enzymes including GLUT1, hexokinase II (HKII), pyruvate dehydrogenase kinase (PDK), and PKM2 [14–16]. The upregulation of HIF-1α-mediated HKII results in a high glycolytic rate in hypoxic solid tumor [17]. Phosphorylation of pyruvate dehydrogenase leads to its inactivation and inhibits conversion of pyruvate into acetyl-CoA for the tricarboxylic acid (TCA) cycle [18, 19]. PKM2 is less catalytically active than is PKM1. A higher level of PKM2 in tumor cells, leading to accumulation of carbohydrate intermediates, facilitates the biosynthesis of macromolecules and tumor cell proliferation. HIF-1α drives expression of many glycolytic enzymes, and hypoxic glycolysis is, in turn, necessary for maintaining HIF-1α activity. This constitutes a novel feed-forward mechanism of glycolysis-HIF-1α signaling (Fig 2) [20].

HIF-1α activity is tightly regulated by oncogenes and other factors. For example, the WW domain-containing oxidoreductase (WWOX), lacking in many cancer types, interacts with HIF-1α and modulates its levels and transactivation function. WWOX absence is associated with enhanced glycolysis, and WWOX-deficient cells are more tumorigenic [21]. Enhancer of zeste 2 polycomb repressive complex 2 (EZH2), a multifaceted oncogenic protein, promotes glioblastoma tumorigenesis and malignant progression through activation of HIF-1α and the Warburg effect. HIF-1α activation is necessary for EZH2-mediated metabolic adaption [22]. Ribosomal protein S7 (RPS7) inhibits glycolysis in colorectal cancer by suppressing the expression of HIF-1α as well as of GLUT4 and lactate dehydrogenase B (LDHB) [23]. Vascular endothelial growth factor (VEGF) enhances glycolysis in pancreatic cancer via upregulation of HIF-1α [24]. Histone demethylase JMJD1A facilitates glycolysis via coactivation of HIF-1α and promotes cancer progression [25].

HIF-1α activity can be regulated by modifying its stabilization. Transkelolase-like 1 (TKTL1) contributes to carcinogenesis through increased HIF-1α stabilization and the upregulation of downstream glycolytic enzymes and aerobic glycolysis [26]. The von Hippel-Lindau (VHL) gene is a tumor suppressor involved in the regulation of HIF-1α stability. VHL protein serves as an E3 ligase that ubiquitinates HIF-1α and results in its degradation by the proteasome. HIF-1α becomes constitutively activated in the absence of VHL [27]. The gene associated with retinoid-interferon-induced mortality-19 (GRIM-19), a potential tumor suppressor, promotes VHL-mediated HIF-1α ubiquitination and degradation in glioblastoma cells [28]. Lysine specific demethylase 1 (LSD1), a histone demethylase, prevents HIF-1α from subsequent acetylation-dependent degradation and maintains the HIF1α-dependent glycolytic process [29].

**Akt and mTOR signaling**

Akt is a serine/threonine kinase that promotes cancer growth and has been called ‘Warburg kinase,’ because it facilitates a glycolytic switch in tumor cells under normoxic conditions [30, 31]. Akt activation promotes the expression and activity of glucose transporters and glycolytic enzymes. The transcription of GLUT1, a widely expressed glucose transporter, is enhanced upon the activation of Akt [32, 33]. Lack of S-phase kinase-associated protein 2 (Skp2), an E3 ligase, impairs Akt activation, GLUT1 expression, glycolysis, and cancer progression [34]. Akt signaling induces the expression of HKII, a rate-controlling enzyme of glycolysis [33, 35]. Akt phosphorylates and activates PFK2 to produce fructose-2,6-bisphosphate, an allosteric activator of PFK1 [36]. Active Akt accumulates in the mitochondria during hypoxia and phosphorylates pyruvate dehydrogenase kinase 1 (PDK1) to inactivate the pyruvate dehydrogenase complex, switching tumor metabolism toward glycolysis [37]. Importantly, Akt-mediated aerobic glycolysis does not affect the rate of OXPHOS. Increased glycolytic

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**Figure 2.** HIF-1α is a master regulator of the Warburg effect and plays a critical role as an activator of aerobic glycolysis. Hypoxia increases the production of ROS, which stabilizes HIF-1α. HIF-1α induces expression of glucose transporters and glycolytic enzymes, facilitating glycolysis that is, in turn, essential for maintaining HIF-1α activity. Many oncogenes and tumor suppressors are involved in the regulation of HIF-1α. EZH2, enhancer of zeste 2 polycomb repressive complex 2; GRIM-19, gene associated with retinoid-interferon-induced mortality-19; LSD1, lysine specific demethylase 1; ROS, reactive oxygen species; RPS7, ribosomal protein S7; TKTL1, transkelolase-like 1; VEGF, vascular endothelial growth factor; VHL, von Hippel-Lindau; WWOX, WW domain-containing oxidoreductase.
flux is required for rapidly proliferating tumor cells to obtain essential metabolic intermediates. Akt-mediated enhanced aerobic glycolysis results in acquired radioresistance of tumor cells [38]. Constitutively active Akt leads to cell death in low-glucose conditions [31].

The mammalian target of rapamycin (mTOR) is also a serine/threonine kinase downstream of Akt and consists of two complexes, mTORC1 and mTORC2. mTOR acts as a central activator of the Warburg effect by inducing expression of glycolytic enzymes under normoxic conditions. mTORC1-mediated upregulation of PKM2, a rate-limiting glycolytic enzyme expressed exclusively in tumor cells, is critical to aerobic glycolysis and tumor growth [39]. Tuberous sclerosis protein 1 and 2 complex (TSC1/TSC2) negatively regulates the expression of GLUT3 through the inactivation of mTORC1 signaling [40]. The transmembrane mucin MUC16 increases glycolysis through activation of mTOR. The mTOR-mediated expression of glycolytic proteins involves activation of HIF-1α, NFκB, and c-Myc [39-42]. Upon stimulation, the receptor tyrosine kinases (RTKs) activate membrane PI3K, which recruits and activates Akt. Thus, RTKs-PI3K-Akt-mTOR signaling plays a critical role in the regulation of aerobic glycolysis and tumor growth (Fig 3) [43-45].

**Oncogenes and tumor suppressors**

Oncogenic K-Ras promotes metabolic reprogramming in tumors [46, 47]. Mutated K-Ras has been found to upregulate the expression of the GLUT1 and facilitate cell survival in low-glucose culture conditions via increased glucose uptake and glycolysis [48]. Thus, K-Ras mutated tumor cells are highly vulnerable to the glycolytic inhibitor [48]. The small guanosine triphosphatase (GTPase) ADP-ribosylation factor 6 (ARF6) is a target of mutated K-Ras and promotes the Warburg effect and pancreatic cancer growth [49]. The K-Ras G12D mutation stimulates glucose uptake and drives glycolytic intermediates into the nonoxidative PPP [50]. K-Ras (G12V) activation leads to mitochondrial dysfunction, promoting a metabolic switch from OXPHOS to glycolysis and enhancing the tumorigenicity of the transformed cells [51]. The K-Ras G13D mutation is associated with increased expression of glycolytic proteins in colorectal cancer [52].

Tumor suppressor p53 negatively regulates cellular glycolysis, contributing to tumor metabolic reprogramming via promotion of mitochondrial OXPHOS and suppression of glycolysis via several routes [53, 54]. It downregulates the expression of glucose transporters GLUT1, GLUT3, and GLUT4 [55, 56] and promotes the ubiquitination-mediated degradation of phosphoglycerate mutase (PGM) [57]. p53 also directly inhibits glucose-6-phosphate dehydrogenase (G6PD), the first and rate-limiting enzyme in the PPP [58]. Inactivation of p53 and the resultant enhanced PPP glucose flux may increase glucose consumption and channel glucose to biosynthesis in tumor cells. In addition, p53 may
inhibit glycolysis through its target genes [59-61]. For example, p53 induces Ras-related associated with diabetes (RRAD), which in turn inhibits the translocation of GLUT1 and glycolysis in lung cancer cells [59]. p53 downregulates glycolysis by transcribing TP53-induced glycolysis and apoptosis regulator (TIGAR) [60, 62]. TIGAR degrades fructose-2,6-bisphosphate (Fru-2,6-P2) to fructose-6-phosphate and causes a significant reduction in cellular Fru-2,6-P2 levels. Fru-2,6-P2 serves as an allosteric activator of PFK1 and promotes the production of fructose-1,6-bisphosphate in glycolysis. p53 also negatively regulates the PI3K-Akt-mTOR pathway through its target genes. p53 activates adenosine monophosphate activated protein kinase (AMPK), a major upstream negative regulator of mTOR, and induces Pten and TSC2 to negatively regulate PI3K-Akt signaling and mTOR activity [63, 64]. HKII-mediated aerobic glycolysis is required for Pten-/p53-deficiency-driven tumor growth in xenograft mouse models of prostate cancer [65]. Pten deletion promotes HKII mRNA translation via the activation of the Akt-mTORC1-4EBP1 axis [65]. Absence of p53 enhances HKII mRNA stability through the inhibition of miR143 biogenesis [65].

Given the high mutation rate of p53 in human tumors, the loss of p53 function could be an important factor contributing to the Warburg effect. It has been determined that tumor-associated mutant p53 (mutp53) drives the Warburg effect under normoxia, and inhibition of glycolysis impairs mutp53-promoting tumorigenesis [66]. Mutant R175H and R273H p53 proteins trigger PKM2 phosphorylation via mTOR signaling [67]. CD147 promotes reprogramming of glucose metabolism by inhibiting the p53-dependent signaling pathway [68]. Uprogulation of glucokinase, PK, and PFK2 levels was observed in the liver of c-Myc transgenic mice about two decades ago, suggesting that transcription factor c-Myc is a regulator of glycolytic enzymes [69]. c-Myc promotes glucose uptake via the upregulation of GLUT1 [14, 70] and potentiates transcription of glycolytic enzymes HKII, PFK [14], and lactate dehydrogenase A (LDHA) [14, 71, 72]. c-Myc upregulates the expression of monocarboxylate transporter (MCT) through direct transcriptional activation or by suppressing transcription of miR-29a and miR-29c [73]. c-Myc promotes transcription of polypyrimidine tract binding protein (PTB), which binds to PKM pre-mRNA and switches PKM splicing to favor the PKM2 variant, ensuring a high PKM2/PKM1 ratio [74, 75]. Inhibition of c-Myc in tumor cells blunts hypoxia-dependent glycolytic reprogramming and is a potential strategy for tumor therapy [76, 77].

Some molecules promote glycolysis via regulation of c-Myc activity. Proto-oncogene human pituitary tumor-transforming gene (PTTG) regulates GLUT1 and several glycolytic enzymes via the c-Myc pathway [78]. N-Myc downstream-regulated gene (NDRG) family members can manipulate Myc-mediated tumor metabolic pathways and ultimately modify the Warburg effect [79]. NDRG2, a tumor suppressor, acts as a critical regulator of glycolysis via repression of c-Myc through downregulation of c-Myc transcriptional activator β-catenin, consequently suppressing the expression of GLUT1, HKII, PKM2, and LDHA in colorectal cancer cells [80]. Inhibitor of differentiation 1 (Id1), a transcription factor, promotes a metabolic shift to aerobic glycolysis in hepatocellular carcinoma cells by regulating the expression levels of c-Myc [81]. IncRNA-MIF, a c-Myc-activated long non-coding RNA, inhibits aerobic glycolysis by promoting c-Myc degradation. IncRNA-MIF acts as a molecular sponge for miR-586, competing with Fbxw7 mRNA for miR-586. Fbxw7 serves as an E3 ligase for c-Myc that promotes c-Myc degradation [82].

Energy sensor

Cellular energy metabolism is strictly regulated. Adenosine monophosphate activated protein kinase (AMPK) is a metabolic sensor that helps maintain cellular energy homeostasis [83]. Increases in AMP:ATP and ADP:ATP ratios activate AMPK, potentiating the metabolic process from an anabolic condition to a catabolic state by switching off the synthesis of lipids, carbohydrates, ribosomal RNA, and proteins [84, 85]. This leads to downregulation of glycolytic enzymes and glucose transporters. Thus, AMPK negatively regulates aerobic glycolysis in tumor cells and suppresses tumor growth in vivo [86]. Inactivation of AMPK promotes a metabolic shift to aerobic glycolysis, which requires normoxic stabilization of HIF-1α [86].

AMPK is involved in the regulation of glycolysis in many tumors, but its underlying mechanism remains unclear. The role of AMPK in glycolytic shift is also controversial. Several studies report a glycolysis-promoting effect of AMPK. For example, AMPK supports the growth of aggressive experimental tumors in part through positive regulation of glycolysis [87]. Manganese superoxide dismutase (MnSOD/SOD2) upregulation in cancer cells increases mitochondrial ROS that sustains AMPK activation and the metabolic shift to glycolysis [88]. Astrocyte elevated gene-1 (AEG-1) mediates glycolysis and tumorigenesis in colorectal carcinoma cells via AMPK signaling [89]. Prostate cancer cell growth mediated by androgen receptor signaling is
involved in an AMPK-mediated metabolic switch to glycolysis [90]. miR-101-3p targets AMPK in triple negative breast cancer to regulate glycolysis [91]. AMPK is also essential to balance glycolysis and mitochondrial metabolism in acute T cell lymphoblastic leukemia [92].

Non-coding RNAs

microRNAs (miRNAs) are involved in the genesis of various cancers and may inhibit aerobic glycolysis via regulation of glucose uptake and glycolytic enzymes (Fig 4) [93]. miR-22, miR-144, and miR-1291 directly target glucose transporter GLUT1 in breast [94], ovarian [95], and renal cancer cells [96], respectively, while miR-195-5p targets GLUT3 in bladder cancer cells [97]. Thus, downregulation of these miRNAs in tumors stimulates aerobic glycolysis. HKII, a key mediator of glycolysis, is another main target of miRNAs. miR-143 directly inhibits the expression of HKII and regulates cancer glycolysis [98-102]. The miR-143 level inversely correlates with HKII protein expression in several cancers, including head and neck squamous cell carcinoma (HNSCC) [100], breast cancer [102], glioma [99], and lung cancer [98]. The absence of miR-143-mediated repression of HKII may contribute to the shift toward aerobic glycolysis in tumors [101] and enhance stemness of glioblastoma stem-like cells [99]. miR-143 can be downregulated by mTOR activation [98] or by miR-155 [102], which also stimulates HKII transcription via activating the signal transducer and activator of transcription 3 (STAT3). In addition to miR-143, miR-98 and miR-199a-5p directly targets HKII [103, 104], and miR-29b downregulates HKII/PKM2 through directly targeting Akt [105]. Expression of these miRNAs is downregulated in several cancers. miR-378* induces glycolytic shift in breast cancer cells via the PGC-1β/ERRγ transcription pathway [106].

In addition to HKII, other glycolytic enzymes and signal molecules are miRNA targets. miR-320a regulates PFK1 expression and, consequently, its lactate production [107]. miR-26b and miR-206 downregulate PFK2-driven glycolysis [108, 109]. A set of miRNAs targets LDHA and regulates glycolysis in colorectal cancer [110]. miR-129-5p blocks glycolysis to retard hepatocarcinogenesis via targeting mitochondrial pyruvate dehydrogenase kinase 4 (PDK4) [111]. miR-448 promotes glycolytic metabolism in gastric cancer by downregulating KDM2b, a reader for methylated CpGs [112]. miR-21 acts as a molecular switch to regulate aerobic glycolysis in bladder cancer cells [113].

![Figure 4. Non-coding RNAs target glucose transporters and glycolytic enzymes. The downregulation of several miRNAs in some tumors facilitates aerobic glycolysis and promotes the development and progression of the tumors. HIF-1α is a primary target of non-coding RNAs. miRNA absence, or IncRNA-mediated HIF-1α stabilization, enhances HIF-1α activity, contributing to the Warburg effect. PDH, pyruvate dehydrogenase; PDK, pyruvate dehydrogenase kinase.](http://www.jcancer.org)
Along with targeting glucose transporters and glycolytic enzymes, many miRNAs exert their functions by targeting HIF-1α, a master regulator of glycolysis (Fig 4). It has been reported that miR-18b [114], miR-186 [115], miR-199a [116, 117], and miR-592 [118] inhibit aerobic glycolysis through directly targeting HIF-1α in several cancer types. Low expression of these miRNAs facilitates aerobic glycolysis and promotes the development and progression of the tumors. The upregulation of HIF-1α under hypoxic conditions, in turn, suppresses miRNA expression and promotes glycolysis [103, 117]. miR-150 targets VHL, a specific E3 ligase for HIF-1α, and promotes the Warburg effect in glioma [119].

Long non-coding RNA (lncRNA) is also an important player in the regulation of the Warburg effect [120, 121]. LncRNA-p21 is hypoxia-responsive and is essential for hypoxia-enhanced glycolysis. It binds to HIF-1α and VHL, disrupting VHL-HIF-1α interaction and VHL-mediated HIF-1α ubiquitination, resulting in HIF-1α accumulation [120]. Long intergenic non-coding RNA for kinase activation (LINK-A), a cytoplasmic lncRNA, mediates BRK-dependent HIF-1α phosphorylation, leading to HIF-1α stabilization under normoxic conditions [121]. LINK-A-dependent normoxic HIF-1α signaling promotes breast cancer glycolysis reprogramming and tumorigenesis [121].

**Sirtuin family proteins and deacetylation**

Sirtuins are a highly conserved family of nicotinamide adenine dinucleotide (NAD⁺)-dependent protein deacetylases that regulate a large number of cellular processes [122]. Growing evidence demonstrates that sirtuins are involved in the regulation of cancer metabolism [123, 124]. Of the seven mammalian sirtuins (SIRT1-7), SIRT1, SIRT3, and SIRT6 have been implicated in the regulation of glucose utilization [125, 126].

The histone deacetylase SIRT6 has been identified as a tumor suppressor that regulates aerobic glycolysis in cancer cells. Deficiency of SIRT6 in mice results in severe hypoglycemia [127]. SIRT6 acts as a histone H3K9 deacetylase to function as a co-repressor of HIF-1α and Myc and control the expression of multiple glycolytic genes [128, 129]. HIF-1α activity and glycolysis are increased in SIRT6-deficient cells [128, 129]. Lack of SIRT6 can lead to tumor formation even without activation of known oncogenes [129].

SIRT3 is the major deacetylase within the mitochondrial matrix and works as a tumor suppressor by inhibiting the Warburg effect [130, 131]. SIRT3 regulates the stability of HIF-1α via lowering cellular ROS levels [130, 131]. Absence of SIRT3 increases cellular ROS, leading to stabilization of HIF-1α and metabolic reprogramming [131, 132]. In contrast, SIRT3 overexpression represses glycolysis and proliferation in breast cancer cells [131]. The SIRT3-mediated alterations in ROS are attributed to deacetylation and activation of isocitrate dehydrogenase 2 (IDH2) and superoxide dismutase 2 (SOD2) [133]. In addition, SIRT3 deacetylates glutamate oxaloacetate transaminase 2 (GOT2) to inhibit its binding to malate dehydrogenase 2 (MDH2), consequently preventing the malate-aspartate shuttle in the mitochondrial intermembrane space [134]. The malate shuttle is able to restore cytosolic NAD⁺, which is essential for a high rate of glycolysis. SIRT3 also deacetylates and activates pyruvate dehydrogenase A1 (PDHA1) and PDH phosphatase 1 (PDP1) of the PDH complex (PDC), promoting the conversion of pyruvate to acetyl-CoA for OXPHOS [135, 136].

It has been reported that SIRT1 stimulates the expression of glycolysis genes and the tumor cell proliferation in pancreatic neoplastic lesions [137]. A SIRT1-mTOR/HIF-1α glycolytic pathway is required for differentiation of myeloid-derived suppressor cells into the M1 phenotype [138].

**Other regulators**

Although the roles of the several mentioned master controllers are critical to the Warburg effect, other regulators are also involved in the glycolytic shift in cancer cells. Wnt signaling-mediated PDK1 expression promotes glycolysis and tumor growth [139]. CUE domain-containing protein 2 (CUEDC2) facilitates aerobic glycolysis and tumorigenesis via upregulating the GLUT3 and LDHA [140]. Pro-inflammatory cytokine interleukin-22 facilitates aerobic glycolysis in colon cancer cells via c-Myc and STAT3-mediated up-regulation of HKII [141]. Carboxyl terminus of Hsc70-interacting protein (CHIP), an E3 ligase, inhibits aerobic glycolysis progression of ovarian carcinomas through CHIP-mediated PKM2 degradation [142]. iNOS/NO promotes glycolysis via inducing PKM2 nuclear translocation [143]. Mitochondrial calcium uptake 1 (MICU1) increases aerobic glycolysis and chemoresistance in ovarian cancer [144]. Epidermal growth factor (EGF) promotes aerobic glycolysis, inducing epithelial-mesenchymal transition (EMT) and cancer stem-like cell properties in human oral carcinoma cells [145]. Toll-like receptor 3 signaling [146] and serotonin signaling [147] also trigger metabolic reprogramming of cancer cells. Molecular chaperone TNF receptor-associated protein 1 (TRAP1) [148], focal adhesion kinase (FAK) [149], plasma
membrane-associated protein Caveolin 1 [150-152], α/β-hydrolase domain-containing 5 (Abhd5) [153], Krüppel-like factor 4 (KLF4) [154, 155], Ecdysoneless [156], and Jumonji C domain-containing dioxygenase (JMJD5) [157] are associated with the glycolytic switch in tumors. Some viruses or virus-encoded proteins can induce aerobic glycolysis in tumors [158-160].

Conclusions

The triggering of the Warburg effect is a complex process with the involvement of multiple regulators (Table 1) [161]. HIF-1α is a master activator. In tumorigenesis, overproduced or mutated growth factors activate transcription factors HIF-1α, NFκB, and c-Myc via the RTKs-PI3K-Akt-mTOR pathway, leading to the expression of glucose transporters and glycolytic enzymes. Oncogene activation and tumor suppressor inactivation during carcinogenesis modify the key signal molecules of the PI3K-Akt-mTOR pathway and downstream HIF-1α activity, promoting glycolytic flux and tumor development. Oncoproteins may also activate sirtuins, a protein deacetylase family, directly suppressing the transcription of glycolytic enzymes or inhibiting HIF-1α and c-Myc expression. Hypoxia and the ROS accumulation and energy depletion resulting from rapid tumor growth further stimulate HIF-1α activity or regulate the production of glycolytic enzymes and glucose transporter through energy sensor AMPK. Absence of miRNAs or lncRNA dysfunction during carcinogenesis promotes aerobic glycolysis via targeting glycolytic enzymes or regulating HIF-1α. A crucial question is whether the Warburg effect is the cause or the effect of cancer. There is no doubt that aerobic glycolysis is a hallmark of tumor metabolism, and is essential to tumor survival and growth. An important focus of study is the stage in tumorigenesis at which reprogramming of glucose metabolism is initiated. Research has revealed that the expression of glycolytic enzymes is modified in the precancerous stage of some tumors [162, 163]. The imaging data also indicated that elevated glycolysis may occur at early-stages of neoplasia and critically contribute to cancer initiation [164, 165]. It has been reported that 14-3-3ζ-mediated upregulation of LDHA in early stage precancerous breast epithelial cells promotes glycolysis, contributing to breast cancer initiation [166]. We have found enhanced expression of several enzymes involved in glycolysis in high grade cervical intraepithelial neoplasia, a typical precancerous lesion of the cervix (Yu et al., unpublished data). This implies that the reprogramming of glucose metabolism occurs at an early stage of carcinogenesis. Additional studies are needed to shed light on this topic.

Increased glycolysis in tumor cells provides a potential target for tumor therapy. Actually, disrupting glycolysis does interfere with tumor growth [167, 168]. Glucose transporters, monocarboxylate transporters, and critical glycolytic enzymes such as HK II, LDHA, PFK, and PKM2 have been proposed as potential targets. Several small molecules including lonidamine, 2-deoxyglucose (2-DG), dichloroacetate, and 3-bromopyruvate (3-BP) have been clinically tested, but many candidates are still under experimental studies [161].

Table 1. The major players in the glycolytic switch and their main features

| Regulators | Downstream molecules | Effects | References |
|------------|----------------------|---------|------------|
| Akt        | GLUT1, HK II, PDK1, PFK2 | +       | [32, 33, 35-37] |
| AMPK       | HIF-1α               | +       | [86] |
| c-Myc      | Glucokinase, GLUT1, HKII, LDHA, MCTs, PFK, PK, PKM2 | +       | [14, 69-75] |
| HIF-1α     | GLUT1, HK II, PDK, PKM2 | +       | [14-17] |
| K-Ras      | GLUT1                | +       | [48] |
| IncRNA     | HIF-1α, VHL          | +       | [120, 121] |
| miRNAs     | Akt, GLUT1, GLUT3, HIF-1α, HKII, LDHA, PDK4, PFK, PFKFB3, PKM2 | +, - | [94-105, 107-111] |
| mTOR       | GLUT3, HIF-1α, c-Myc, NFκB, PKM2 | +       | [39-42] |
| p53        | AMPK, GLUT1, GLUT3, GLUT4, G6PD, miR143, PGM, Pten, RRAD, TIGAR, TSC2 | +       | [55-60, 62-65] |
| SIRT1, SIRT3, SIRT6 | HIF-1α, Myc, PDHA1, PDPI | +, - | [126-132, 135-137] |

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Competing Interests

The authors have declared that no competing interest exists.

References

1. Nolop KB, Rhodes CG, Brudin LH, Beaney RF, Krausz T, Jones T, et al. Glucose utilization in vivo by human pulmonary neoplasms. Cancer. 1987; 60: 2682-9.
2. Gottschalk S, Anderson N, Hainz C, Eckhardt SG, Serkova NJ. Imatinib (ST671)-mediated changes in glucose metabolism in human leukemia BCR-ABL-positive cells. Clin Cancer Res. 2004; 10: 6661-8.

3. Cunphy M, Liu Y, Xu J, Yu S, Ellis C. Contribution by different fuels and metabolic pathways to the total ATP turnover of proliferating MCF-7 breast cancer cells. Biochem J. 2002; 364: 309-15.

4. Martin M, Beauvoit B, Voisin P, Guerin B, Rigoulet M. Energetic and morphological plasticity of C6 glioma cells grown on a 3-D support: Effect of transient glutamine deprivation. J Bioenerg Biomembr. 1998; 30: 565-78.

5. Pasoldis P, Devaud E, Voisin P, Bouchaud V, Rigoulet M, Beauvoit B. Contribution of the phosphorylatable complex I in the growth phase-dependent reorganization of C6 glioma cells. Biochem Biophys Res Commun. 2003; 349: 50-9.

6. Moreno-Sanchez R, Rodriguez-Enriquez S, Martin-Hernandez A, Saaedra E. Energy metabolism in tumor cells. FEBS J. 2007; 274: 1393-48.

7. Bonnet S, Archer SL, Allalunis-Turner J, Haromy A, Beaulieu C, Thompson R, et al. TFIIIC subunit K3 channel axis is suppressed in cancer and its normalization promotes apoptosis and inhibits cancer growth. Cancer Cell. 2017; 11: 37-51.

8. de Souza AC, Justo GZ, de Araujo DR, Cavadas AG. Defining the molecular basis of tumor metabolism: a continuing challenge since Warburg's discovery.

9. Cell Physiol Biochem. 2011; 28: 771-92.

10. Gannapathy-Kanniappan S, Geschwind JF. Tumor glycolysis as a target for cancer therapy: progress and prospects. Mol Cancer. 2013; 12: 152.

11. Locarnale JW, Cantley LC. Altered metabolism in cancer. BMC Biol. 2010; 8: 88.

12. Fan J, Tanaka RB, Chen S. Targeting glucose metabolism for cancer therapy. J Exp Med. 2012; 209: 211-3.

13. Lunt SY, Vander Heiden MG. Aerobic glycolysis: meeting the metabolic requirements of cell proliferation. Annu Rev Cell Dev Biol. 2011; 27: 441-64.

14. DeBerardinis RJ, Dwyer NJ, Dittsworth D, Thompson CB. Brick by brick: metabolism and tumor cell growth. Curr Opin Genet Dev. 2008; 18: 54-61.

15. Denko NC. Hypoxia, HIF1 and glucose metabolism in the solid tumour. Nat Rev Cancer. 2008; 9: 1-16.

16. Dang CV, Kim JW, Tchernyshyov I, Semenza GL, Dang CV. HIF-1-mediated expression of tumor glycolysis. Cancer Res. 2016;76:4259-69.

17. Hamanaka RB, Chandel NS. Targeting glucose metabolism for cancer therapy. Proc Natl Acad Sci U S A. 2011; 108: 18311-2.

18. Kluza J, Corazao-Rozas P, Touil Y, Jendoubi M, Maire C, Guerreschi P, et al. Role of E2F1 signaling in JMYD1A promotes urinary bladder cancer progression by enhancing EAF2-HIF1alpha signaling. Oncotarget. 2016; 7: 45134-43.

19. Lee JH, Lee HJ, Wu Y, Yang P, Zhang T, Xie Y, et al. EGFR phosphorylates FAM129B to promote Ras activation. Cell Cycle. 2013; 12: 1831-43.

20. Makishima H, Takita M, Haridas D, Iwashita M, Souchek J, et al. MUC16-mediated activation of mTOR and c-Myc programs pancreatic cancer metabolism. Oncotarget. 2015; 6: 1918-31.

21. Masui K, Tanaka K, Akutsu H, Imai G, Bariu M, Matsutani T, et al. mTOR complex 2 controls glycolytic metabolism in glioblastoma through FoxO acetylation and up-regulation of c-Myc. Cell Metab. 2018; 18: 726-39.

22. Martin M, Beauvoit B, Voisin PJ, Canioni P, Guerin B, Rigoulet M. Energetic and morphological plasticity of C6 glioma cells grown on a 3-D support: Effect of transient glutamine deprivation. J Bioenerg Biomembr. 1998; 30: 565-78.

23. Yoon J, Rago C, Cheong I, Pagliarini R, Angenendt P, Rajagopalan H, et al. The interplay between MYC and HIF in cancer. Nat Rev Cancer. 2012; 12: 113-30.

24. Shi S, Xu J, Zhang B, Ji S, Xu W, Liu J, et al. Regulation of PKM2 function through Akt phosphorylation. Cell Cycle. 2015; 14: 1599-67.

25. Yang H, Li, H, Liu Z, FAM129B activates Ras to promote malignant transformation in cancer cells. J Exp Med. 2012; 209: 211-5.
60. Bensaad K, Tsuruta A, Selak MA, Vidal MN, Nakano K, Bartrons R, et al. TIGAR, a p53-inducible regulator of glycolysis and apoptosis. Cell. 2006; 126: 107-20.

61. Liu S, Tan B, Liu W, Chen L, Xiao D, Xi S, et al. As a novel p53 direct target, bidirectional gene HepR2/alpha crystallin regulates the ROS level and Warburg effect. Biochem Biophys Acta. 2014; 1839: 592-603.

62. Madan E, Gogna R, Bhattacharjee S, Shukla S, Mahdi AA. Regulation of glucose metabolism by p53: emerging new roles for the tumor suppressor. Oncotarget. 2011; 2: 948-57.

63. Feng Z, Hu W, de Staechina E, Teresky AK, Jin S, Lowe S, et al. The regulation of AMPK beta, TSC2, and PTEN expression by p53: stress, cell type specificity, and the role of these gene products in modulating the IGF-1-AKT-mTOR pathways. Cancer Res. 2007; 67: 3043-51.

64. Budanov AV, Karin M. p53 target genes sestrin1 and sestrin2 connect genotoxic stress and mTOR signaling. Cell. 2008; 134: 451-60.

65. Wang L, Xie Y, Wu F, Zhang Y, Wang J, Zhao X, et al. Hexokinase 2-mediated Warburg effect is required for PTEN- and p53-deficiency-driven prostate cancer growth. Cell Rep. 2014; 8: 1461-74.

66. Zhang C, Liu J, Liang Y, Wu R, Zhao Y, Hong X, et al. Tumour-associated p53 drives the Warburg effect. Nat Commun. 2013; 4: 2093.

67. Dando I, Cordani M, Donadell M. Mutant p53 and mTOR/PKM2 regulation in cancer cells. JUBMB Life. 2016; 68: 722-6.

68. Huang Q, Li J, Xing J, Li W, Li H, Ke X, et al. CD147 promotes reprogramming of glucose metabolism and cell proliferation in HCC cells by inhibiting the p38 MAPK signaling pathway. J Hepatol. 2014; 60: 859-66.

69. Valera A, Pujoel A, Gregory P, Riu E, Visa J, Bosch F. Evidence from transgenic mice that myc regulates hepatic glycolysis. FASEB J. 1995; 9: 1067-78.

70. Osthus RC, Shim H, Kim S, Li Q, Reddy R, Mukherjee M, et al. Deregression of glucose transporter 1 and glycolytic gene expression by c-Myc. J Biol Chem. 2000; 275: 21797-800.

71. Shim H, Dolce C, Lewis BC, Wu CS, Dang C, Jungmann RA, et al. c-myc transactivation of LDHA: implications for tumor metabolism and growth. Proc Natl Acad Sci U S A. 1997; 94: 6569-74.

72. He TL, Zhang YJ, Jiang H, Li XH, Zhu H, Zheng KL. The c-Myc-LDHA axis maintains energy homeostasis. Nat Rev Mol Cell Biol. 2012; 13: 251-62.

73. Dando I, Cordani M, Donadell M. Mutant p53 and mTOR/PKM2 regulation in cancer cells. JUBMB Life. 2016; 68: 722-6.

74. David CJ, Chen M, Assanah M, Canoll P, Manley JL. HnRNP proteins negatively associate with the c-Myc-LDHA transcriptional complex to promote glucose uptake and proliferation of breast cancer cells. Oncogene. 2014; 33: 5521-31.

75. Luan W, Wang Y, Chen X, Shi Y, Wang J, Zhang J, et al. PKM2 promotes metabolic shift in ovarian cancer cells via directly targeting hexokinase 2 gene. J Biol Chem. 2012; 287: 23227-35.

76. Yamazaki T, Seki N, Yoshihito H, Itsako T, Yamada Y, Tatarano S, et al. Tumor-suppressive microRNA-1291 directly regulates glucose transporter 1 in endothelial cells. Cancer Sci. 2013; 104: 1411-9.

77. Fei X, Qi M, Wu B, Song Y, Wang Y, Li T. MicroRNA-195-5p suppresses glucose uptake and proliferation of human bladder cancer T24 cells by regulating GLUT1 expression. FEBS Lett. 2012; 586: 392-7.

78. Fang R, Xiao T, Fang Z, Sun Y, Li F, Gao Y, et al. MicroRNA-143 (miR-143) regulates glycolysis via targeting hexokinase 2 gene. J Biol Chem. 2014; 289: 19055-63.

79. Zhao S, Liu H, Liu Y, Wu J, Wang C, Hou X, et al. miR-143 inhibits glycolysis and depletes stemness of glioblastoma stem-like cells. Cancer Lett. 2013; 333: 253-60.

80. Peschiaroli A, Giacobbe A, Formosa A, Markert EK, Bongiorno-Borbone L, Levine AJ, et al. miR-143 regulates hexokinase 2 expression in cancer cells. Oncogene. 2012; 32: 797-802.

81. Gregersen LH, Jacobsen L, Frankel LB, Wen J, Krogh A, Lund AH. MicroRNA-143 down-regulates hexokinase 2 in colon cancer cells. BMC Cancer. 2012; 12: 252.

82. Jiang S, Zhang LF, Zhang HW, Hu S, Lu MH, Liang S, et al. A novel miR-135-miR-143 cascade controls glycolysis by regulating hexokinase 2 in breast cancer cells. EMBO J. 2012; 31: 1985-98.

83. Guo W, Qiu Z, Wang Z, Wang Q, Tan N, Chen T, et al. MiR-199a-5p is negatively associated with malignancies and regulates glycolysis and lactate production by targeting hexokinase 2 in liver cancer. Hepatology. 2015; 62: 1132-44.

84. Zhu W, Huang Y, Pan Q, Xiang P, Xie N, Yu H. MicroRNA-98 Suppress Warburg Effect by Targeting HK2 in Colon Cancer Cells. Dig Dis Sci. 2017; 62: 4661-76.

85. Teng Y, Zhang Y, Qu K, Yang X, Fu J, Chen W, et al. MicroRNA-29B (mir-29b) regulates the Warburg effect in ovarian cancer by targeting AKT2 and AKT3. Oncotarget. 2015; 6: 36106-16.

86. Song HT, Qiu Y, Xie Y, Xu Z, Zhang X, Cai Y, et al. miR-199a-5p and HIF-1alpha Modulates the Warburg Effect in Hepatocellular Carcinoma Cells. Cell Metab. 2016; 23: 649-62.

87. Madan E, Gogna R, Bhattacharjee S, Shukla S, Mahdi AA. Regulation of glucose metabolism by p53: emerging new roles for the tumor suppressor. Oncotarget. 2011; 2: 948-57.

88. Fuchs K, Yang W, Zhu Y, Shi Y, Wang J, Zhang J, et al. PKM2 promotes glucose metabolism and cell growth in gliomas through a mechanism involving a let-7a-c-Myc/hnRNP A1 feedback loop. Oncotarget. 2015; 6: 13006-18.

89. Mongiardi MP, Savino F, Falchetti ML, Illii B, Bozzo F, Valle C, et al. c-MYC inhibition impairs hypoxia response in glioblastoma multiforme. Oncotarget. 2016; 7: 33257-71.

90. Tateshi K, Iafrette AJ, Ho Q, Curry WT, Batchelor TT, Flaherty KT, et al. TIGAR, a p53-inducible regulator of glycolysis and apoptosis. Cell. 2006; 126: 107-20.

91. Liu S, Tan B, Liu W, Chen L, Xiao D, Xi S, et al. As a novel p53 direct target, bidirectional gene HepR2/alpha crystallin regulates the ROS level and Warburg effect. Biochem Biophys Acta. 2014; 1839: 592-603.

92. Madan E, Gogna R, Bhattacharjee S, Shukla S, Mahdi AA. Regulation of glucose metabolism by p53: emerging new roles for the tumor suppressor. Oncotarget. 2011; 2: 948-57.

93. Feng Z, Hu W, de Staechina E, Teresky AK, Jin S, Lowe S, et al. The regulation of AMPK beta, TSC2, and PTEN expression by p53: stress, cell type specificity, and the role of these gene products in modulating the IGF-1-AKT-mTOR pathways. Cancer Res. 2007; 67: 3043-51.

94. Budanov AV, Karin M. p53 target genes sestrin1 and sestrin2 connect genotoxic stress and mTOR signaling. Cell. 2008; 134: 451-60.

95. Wang L, Xie Y, Wu F, Zhang Y, Wang J, Zhao X, et al. Hexokinase 2-mediated Warburg effect is required for PTEN- and p53-deficiency-driven prostate cancer growth. Cell Rep. 2014; 8: 1461-74.

96. Zhang C, Liu J, Liang Y, Wu R, Zhao Y, Hong X, et al. Tumour-associated p53 drives the Warburg effect. Nat Commun. 2013; 4: 2093.
118. Jia YY, Zhao JY, Li BL, Gao K, Song Y, Liu MY, et al. miR-592/WSF1/HIF-1α axis inhibits glycolytic metabolism to decrease hepatocellular carcinoma growth. Oncotarget. 2016; 7: 35275-69.

119. Liu S, Liu HL, Tan J, Li XY, Wang XY. MicroRNA-150 regulates glycolysis by targeting von Hippel-Lindau in glioma cells. Am J Transl Res. 2017; 9: 1058-66.

120. Yang F, Zhang H, Mei Y, Wu M. Reciprocal regulation of HIF-1α and linkrpn-p21 modulates the Warburg effect. Mol Cell. 2014; 53: 88-100.

121. Lin A, Li C, Liu HL, Tan J, Li XY, Wang XY. MicroRNA-150 regulates glycolysis by targeting von Hippel-Lindau in glioma cells. Am J Transl Res. 2017; 9: 1058-66.

122. Finkel T, Deng CX, Mostoslavsky R. Recent progress in the biology and physiology of sirtuins. Nature. 2009: 462-66.

123. Jeong SM, Haigis MC. Sirtuins in Cancer: A Balancing Act between Genome Stability and Metabolism. Mol Cells. 2015; 38: 750-8.

124. Chakladaki A, Guarnera L. The multifaceted functions of sirtuins in cancer. Nat Rev Cancer. 2015; 15: 606-24.

125. Martinez-Pastor B, Mostoslavsky R. Sirtuins, metabolism, and cancer. Front Pharmacol. 2012; 3: 22.

126. Zhou L, Mostoslavsky R. Fine tuning our cellular factories: sirtuins in domain-containing protein 2. Cell Metab. 2011; 13: 621-6.

127. Mostoslavsky R, Chuai KF, Lombard DB, Lee J, Souza A, Egia A, Zhang J, et al. SIRT3 opposes mitochondrial respiration and aerobic glycolysis. Cell Rep. 2014; 9: 1798-811.

128. Shi M, Cui J, Du J, Wei D, Jia Z, Jiang J, et al. Novel KLF4/LDH1A signaling module stimulates aerobic glycolysis in prostate cancer. Cancer Res. 2013; 73: 1900-11.

129. Yu W, Denu RA, Krautkramer KA, Grindle KM, Yang DT, Asimakopoulos F, et al. Tyr phosphorylation of mammalian Sirtuin1 stimulates the proliferation and the expression of glycolysis genes in cancer cells. Free Radic Biol Med. 2014; 76: 163-72.

130. Haigis MC, Deng CX, Finley LW, Kim HS, Gius D. SIRT3 is a mitochondrial deacetylase. Cell. 2010; 140: 280-93.

131. Finley LW, Carracedo A, Lee J, Souza A, Egia A, Zhang J, et al. SIRT3 opposes reprogramming of cancer cell metabolism through HIF1α destabilization. Cancer Cell. 2011; 19: 416-28.

132. Tang SL, Li XJ, Wang XY. MicroRNA-150 regulates glycolysis by targeting von Hippel-Lindau in glioma cells. Am J Transl Res. 2017; 9: 1058-66.

133. Yu L, Chen X, Wang L, Chen S. The sweet trap in tumors: aerobic glycolysis and fate of myeloid-derived suppressor cells in tumors by orchestrating Wnt signaling. Autophagy. 2012; 8: 3340.

134. Liu Y, Xiang F, Huang Y, Shi L, Hu C, Yang Y, et al. Interleukin-22 promotes HIF-1α-dependent tumor progression. Mol Carcinog. 2017; 56: 1214-26.

135. Fan J, Shan C, Kang HB, Elf S, Xie J, Tucker M, et al. Tyr phosphorylation of cell death domain-containing protein 2 promotes the Warburg effect and tumorigenesis. Oncotarget. 2016; 7: 38908-26.

136. Riibbås S, Ciglano A, Kroeger N, Pilo MG, Terracciano I, Burchard M, et al. PI3K/AKT/mTOR pathway plays a major pathogenic role in glycogen accumulation and tumor development in renal distal tubules of rats and men. Oncotarget. 2015; 6: 13021-30.

137. Riibbås S, Calvisi DF, Ciglano A, Sailer Y, Peters M, Rausch J, et al. Molecular and metabolic changes in human liver clear cell foci resemble the alterations occurring in rat hepatocarcinogenesis. J Hepatol. 2013; 57: 747-57.

138. Zhang R, Su J, Xue SL, Yang H, Ji Y, et al. HPV E6/p53 mediated up-regulation of miR-34a inhibits Warburg effect through targeting LDHA in cervical cancer. Am J Cancer Res. 2016; 6: 312-20.

139. Yu L, Chen X, Wang L, Chen S. The sweet trap in tumors: aerobic glycolysis and potential targets for therapy. Oncotarget. 2016; 7: 38908-26.

140. Christofk HR, Vander Heiden MG, Harris MH, Ramanathan A, Gerszten RE, et al. Endogenous two-photon fluorescence imaging elucidates metabolic changes occurring in rat hepatocarcinogenesis. J Hepatol. 2013; 57: 1147-56.

141. Dey P, Raghagni S, Chakraborty S, Singh PK, Zhao X, Gurnemuth CB, et al. Overexpression of ecdysone in pancreatic cancer and its role in oncogenesis by regulating glycolysis. Clin Cancer Res. 2014; 20: 6188-97.

142. Zhang J, Gao Q, Zhou Y, Dier U, Hempel N, Hochwald SN. Focal adhesion kinase-promoted mitochondrial metabolism is associated with a shift of mitochondrial respiration to glycolysis. Oncogene. 2016; 35: 1926-42.

143. Ha TK, Chi SG. CAV1/ caveolin 1 enhances aerobic glycolysis in colon cancer cells via activation of SLC2A3/GLUT3 transcription. Autophagy. 2012; 8: 473-85.

144. Chakraborty PK, Mustafi SB, Xiong X, Dwivedi SKD, Nesin V, Saha S, et al. Molecular chaperone TRAP1 regulates a metabolic switch between mitochondrial respiration and aerobic glycolysis. Proc Natl Acad Sci U S A. 2013; 110: E1604-12.

145. Zhang J, Gao Q, Zhou Y, Dier U, Hempel N, Hochwald SN. Focal adhesion kinase-promoted mitochondrial metabolism is associated with a shift of mitochondrial respiration to glycolysis. Oncogene. 2016; 35: 1926-42.

146. Yoshida S, Tsutsumi S, Muihlebach G, Sourrier C, Lee MJ, Lee S, et al. Molecular chaperone TRAP1 regulates a metabolic switch between mitochondrial respiration and aerobic glycolysis. Proc Natl Acad Sci U S A. 2013; 110: E1604-12.

147. Jiang SH, Li J, Dong FY, Yang JY, Liu DJ, Yang XM, et al. Increased Serotonin Signaling Contributes to the Warburg Effect in Pancreatic Tumor Cells Under Metabolic Stress and Promotes Growth of Pancreatic Tumors in Mice. Gastroenterology. 2017; 153: 277-91.