Journal of Translational Medicine

REVIEW

Open Access

The potential role of reprogrammed glucose metabolism: an emerging actionable codependent target in thyroid cancer

Sai-li Duan[1], Min Wu[1], Zhe-Jia Zhang[1*] and Shi Chang[1,2,3,4*]

Abstract

Although the incidence of thyroid cancer is increasing year by year, most patients, especially those with differentiated thyroid cancer, can usually be cured with surgery, radioactive iodine, and thyroid-stimulating hormone suppression. However, treatment options for patients with poorly differentiated thyroid cancers or radioiodine-refractory thyroid cancer have historically been limited. Altered energy metabolism is one of the hallmarks of cancer and a well-documented feature in thyroid cancer. In a hypoxic environment with extreme nutrient deficiencies resulting from uncontrolled growth, thyroid cancer cells utilize "metabolic reprogramming" to satisfy their energy demand and support malignant behaviors such as metastasis. This review summarizes past and recent advances in our understanding of the reprogramming of glucose metabolism in thyroid cancer cells, which we expect will yield new therapeutic approaches for patients with special pathological types of thyroid cancer by targeting reprogrammed glucose metabolism.

Keywords Thyroid cancer, Glycolysis, Target therapy, Metabolism

Introduction

Thyroid cancer (TC) is an endocrine system tumor originating from follicular thyroid cells and parafollicular C cells, and its incidence rate is rising worldwide [1, 2]. Most thyroid malignancies (> 95%) are differentiated thyroid cancers (DTCs), which include papillary thyroid cancer (PTC) and follicular thyroid cancer (FTC) [3]. Lymph node metastasis is a common clinical feature of DTC, and a considerable portion of DTC is prone to early cervical lymph node metastases (approximately 20–70%), which is an important factor affecting the prognosis of DTC patients [4, 5]. Despite the widespread use of multimodality treatment (ie, surgery, chemotherapy, and radiotherapy), survival rates have not improved much over the past few decades, suggesting that new treatment options should be explored [6–8]. Therefore, we recommend seeking other effective treatments for TC. Probing the molecular mechanism of disease progress, and developing new targeted drugs remain the focus of TC research [9]. Initiation and progression of TC involves multiple genetic and epigenetic alterations, among which common mutations found in TC are point mutations in the BRAF and RAS genes as well as RET/PTC and PAX8/PPARγ chromosomal rearrangements [10, 11]. These alterations often lead to anomalies in the proliferation,

*Correspondence:
Zhe-Jia Zhang
zhangzhejia@csu.edu.cn
Shi Chang
xychangshi@163.com
[1] Department of General Surgery, Xiangya Hospital Central South University, Changsha 410008, Hunan, People's Republic of China
[2] Xiangya Hospital, National Clinical Research Center for Geriatric Disorders, Changsha 410008, Hunan, People's Republic of China
[3] Clinical Research Center for Thyroid Disease in Hunan Province, Changsha 410008, Hunan, People's Republic of China
[4] Hunan Provincial Engineering Research Center for Thyroid and Related Diseases Treatment Technology, Changsha 410008, Hunan, People's Republic of China

differentiation and metabolism patterns of thyroid follicular cells, acting synergistically to amplify their effects on thyroid tumor development. These mutations are crucial for the abnormal activation of the MAPK and PI3K-AKT signaling pathways, which primarily regulate cell proliferation and differentiation, but also directly regulate the activity of oxidative phosphorylation, cellular glucose uptake and aerobic glycolytic processes [12, 13]. Cancer cells frequently undergo a reorganization of metabolism to promote growth, survival, proliferation and long-term maintenance [14]. For some rapidly proliferating cells and tumors, cells use glycolysis to provide cancer cells with adenosine triphosphate (ATP), nucleotides, lipids, and amino acids needed for their growth, so that even under aerobic conditions, the glucose uptake rate is significantly increased and lactate is produced, a phenomenon known as the Warburg effect [15]. This metabolic change occurs in tumors, with marked differences in glucose use between cancer cells and normal cells [16]. However, the mechanism of the Warburg effect in TC has not yet been fully elucidated. Glucose metabolic reprogramming is a primary mode of energy production in TC and has been shown to be closely associated with tumorigenesis [15]. Importantly, these metabolic adaptations appear to be responsive not only to the genotype of the tumor, but also to the biochemical microenvironment [17]. Many studies have demonstrated that glycolysis is involved in the activation of oncogenes, such as phosphatidylinositol 3-kinase (PI3K) and hypoxia-inducible factor-1 alpha (HIF-1α) in the tumor microenvironment (TME), and acts as an energetic source for cancer cells [18]. The unique hypoxic and nutrient-deficient microenvironment further leads TC cells to utilize glucose in a hypoxic manner [15].

Here, our review mainly focuses on the interactions of glycolysis in the development of TC cells. As we understand the role of glycolysis in the growth, proliferation and metastasis of TC cells, we are able to put forward suggestions for better treatment of TC indications. At the same time, we describe the factors that affect the early detection of TC to find treatment methods that can achieve better clinical results. By understanding the process of glycolysis and its relationship with tumor cells, we can further consider the targeted treatment of TC based on the glycolysis pathway in combination with clinical treatment and whether TC can be diagnosed through the relevant factors of the glycolysis process, so as to gain insight for cancer treatment.

Insights from glycolysis in thyroid cancer

Cancer cells are well known for a series of patterns including constant proliferative signaling, growth suppressor's avoidance, resistance to cell death, replicative immortality, high angiogenesis, reprogrammed energy metabolism, immune-mediated destruction, invasion, and metastasis, by which they can surpass normal cells' capacity, occupy normal tissues, and even invade into surrounding or even distant area. These characteristics are largely supported by the reprogrammed energy metabolisms, which provide sufficient and instant material for cancer cells' energy consumption and superfluous anabolism [19]. In normal conditions, cells are dependent on glycolysis rather than oxygen-consuming mitochondrial metabolism for energy supply facing short of oxygen. However, cancer cells prefer glycolysis even when oxygen is on the scene, a phenomenon first observed by Otto Warburg [20]. Such preference is shown because even though glycolysis produce less ATP per molecule of glucose, it can yield energy at a much higher rate [21]. Hence, it satisfies the high demand of cancer cells and becomes the central pathway glucose metabolism. The cancer gene mutations together with altered glycolysis, as well, promote the branches of glucose metabolism such as pentose phosphate pathway (PPP) partly because of the upregulated flux of glucose entering the PPP branch. Besides the dysregulation of glucose metabolism, other metabolism pathways also undergone great change partly ascribe to the upstream glucose metabolism alteration and partly due to the requirements of biosynthesis of biomass, such as nucleotides, amino acids and lipids [22]. Aberrant lipid metabolism, amino acids metabolism, mitochondrial biogenesis, and other bioenergetic metabolism pathways have been gradually uncovered, showing the thorough reformation of metabolism in cancer cells [23, 24].

Differences in glycolysis between cancer and normal cells

There are three main differences in the glycolysis process in TC cells compared with normal cells (see Fig. 1), such as glucose transports, pyruvate kinases, and lactic acid metabolism. In terms of glucose transport, TC has a high demand for glucose, so it overexpresses glucose transporters to transport a large amount of glucose through the membrane. In this process, controlling the expression of pyruvate kinase (PK) will block the final step of glycolysis, leading to the accumulation of many early intermediate metabolites in tumor cells. Otherwise, enhanced glycolysis and reduced oxygen consumption in cancer cells would lead to the expansion of lactate.

Glucose transport

Excessive proliferation is one of the main differences between cancer and normal cells. Therefore, a common characteristic of metabolic changes in tumor cells is increased glucose uptake [25], which can also be observed when mitochondrial functions are complete

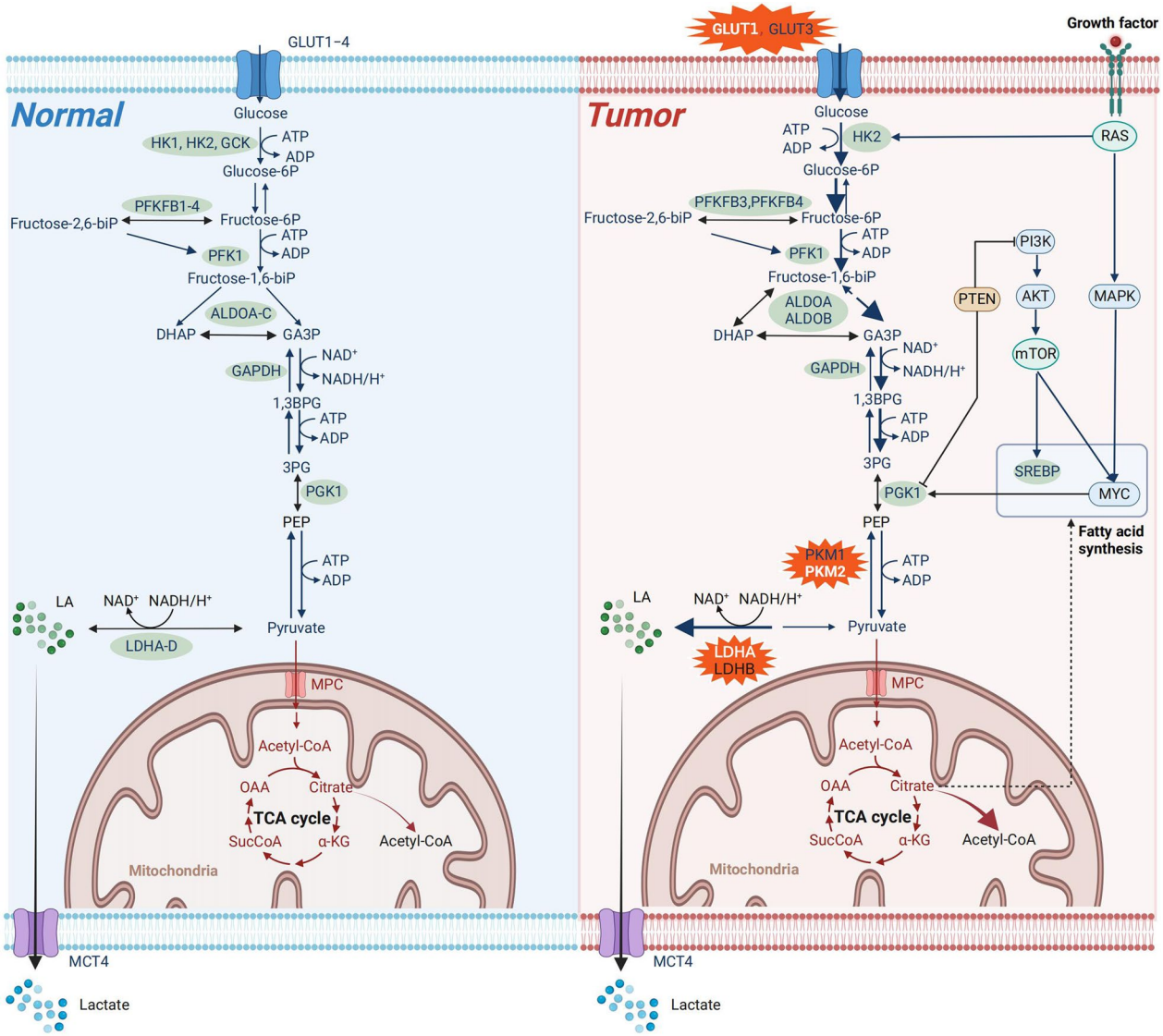

Fig. 1 Different glucose metabolic pathways between tumor cells and normal cells. Most nonproliferating normal cells transport glucose into cells through GLUTs by acquiring oxygen molecules, which are then decompose through glycolysis and the TCA cycle. In the last step of glycolysis, the existence of pyruvate kinase M1 isoforms ensures that the product pyruvate is transported to mitochondria, where it is then oxidized in the process of PDH to produce acetyl coenzyme A and enter the TCA cycle. In tumor cells, GLUT1 and 3 transport a large amount of glucose into the cytoplasm for glycolysis even in tumor cells with adequate oxygen supply. It relies on the pyruvate kinase M2 isoform to convert pyruvate into the substrate of LDHA, producing a large amount of lactic acid and secreting the extracellular matrix. Since only a small amount of glucose is transported to the mitochondria for decomposition, each glucose molecule is decomposed to fewer ATP molecules. GLUT, glucose transporter; HK, hexokinase; GCK, glucokinase; ATP, adenosine triphosphate; ADP, adenosine diphosphate; Glucose-6P, Glucose 6-phosphate; Fructose-6P, fructose-6-phosphate; PFKFB1-4, 6-phosphofructo-2-kinase/fructose 2,6-bisphosphatase; Fructose-1,6-biP, fructose-1,6-bisphosphate; Fructose-2,6-biP, fructose-2,6-bisphosphate; PFK1, phosphofructokinase 1; ALDO, aldolase; DHAP, dihydroxyacetone-phosphate; GA3P, glyceraldehyde 3-phosphate; GAPDH, glyceraldehyde- 3-phosphate dehydrogenase; GAPDH, Glyceraldehyde 3-phosphate dehydrogenase; 1,3BPG, 1,3-Bisphosphoglyceric acid; 3PG, 3-Phosphoglyceric acid; LDH, Lactate dehydrogenase; MPC, 2-methacryloyloxyethyl phosphorylcholine; OAA, oxaloacetate; Suc-CoA, Succinyl-CoA; α-KG, α-ketoglutarate; Acetyl-CoA, acetyl coenzyme A; MCT4, MCT, monocarboxylate transporter 4; TCA, tricarboxylic acid

[26–28]. To meet the large nutritional demands in the course of cell proliferation, tumor cells adopt a very uneconomic way of glucose metabolism to ensure that a large amount of glucose enters the cells for decomposition [29]. TC cells usually exhibit a state of hypoxia, which prevents the cells from performing sufficient glycolysis and providing sufficient ATP [30]. However, tumor cells are well adapted to this hypoxic environment [31] due to

glycolysis. This behavior has been observed in all sorts of tumors [32]. A defining feature of TC cells is their ability to absorb large amounts of glucose compared to normal thyroid tissues. The upregulation of glucose transporters (GLUTs) has been reported to be an indicator of aggressiveness and loss of tumor differentiation in TC [33]. In most cases, TC cells tend to exhibit GLUTs overexpression, particularly the hypoxic-reactive GLUT1 and GLUT3 proteins [34]. The primary cellular function of the GLUT is to facilitate the entry of glucose molecules into cells [35]. Among GLUTs, GLUT1 is the most frequent isoform in many cancers, such as lung cancer, colorectal cancer, prostate cancer, and hepatocellular carcinoma [36–39]. In several cancers, overexpression of GLUT1 is related to invasion and poor survival [40, 41], while increased GLUT1 expression improves glycolysis [42]. Previous studies have demonstrated that the translocation of GLUT1 to the cancer cell membrane is a factor limiting the rate of cellular energy generation [42]. The high expression of GLUT1 in TC is positively correlated with the proliferation index, which is equivalent to malignant characteristics [43]. In particular, overexpression of GLUT1 on cell membranes correlates perfectly with the rate of cell de-differentiation and greater biological aggressiveness of TC [44]. Greater GLUT1 expression can often be detected by immunostaining in TC, but not in benign nodules or normal thyroids [45]. This suggests that GLUT1, as a rate-limiting step in glucose metabolism in cancer cells and a modulator of glucose uptake pathways, is a promising target for the development of anti-cancer strategies.

Pyruvate kinase and pyruvate carboxylase

TC cells consume more glucose compared to normal cells [46], limiting the final step of the glycolysis pathway through their negative feedback mechanism and thus, leading to the accumulation of many early intermediate metabolites in tumor cells [47]. Even in a tumor microenvironment with normal oxygen levels, TC increases glucose absorption, metabolizes glucose to acrylic acid, and then converts the product to lactic acid (LA) rather than allowing it's to enter the TCA cycle [48]. Pyruvate kinase (PK) facilitates the last step of glycolysis, the exchange of phosphoenolpyruvate (PEP) with pyruvate and is involved in the TCA cycle. The intersection between anabolic and catabolic pathways is primarily conducted by PK [49], mainly PKM1 and PKM2. PKM1 regulates the transport of pyruvate from the cytoplasm to mitochondria, while PKM2 regulates the decomposition of pyruvate to LA in the cytoplasm of tumor cells [50]. Compared with PKM1, the PKM2 isoform has a low catalytic enzyme efficiency, leading to the accumulation of glycolytic intermediates, and is involved in other biochemical synthesis pathways [51–53]. During PKM1 activation, anabolic synthesis (or branching pathways in glycolysis) is promoted [54, 55], while phosphoenolpyruvate (PEP) is converted to pyruvate due to PKM2 activation, to produce ATP molecules [49, 56]. The activity of the PKM2 tetramer promotes the complete oxidative decomposition of glucose into ATP through oxidative phosphorylation, while the activity of its dimer promotes the glycolysis [57]. Some studies have suggested that PKM2 is related to the poor prognosis and has been identified as a prognostic marker in many cancers [58, 59]. One study has stated that PKM2 is involved in the progression of TC [60]. PKM2 is significantly overexpressed in PTC, especially in cases harboring BRAF mutations, and its overexpression is closely related to advanced tumor stage and lymph node metastasis [60]; meanwhile, PKM2 knockdown significantly inhibits PTC cell growth, lactic acid and ATP production, and glucose consumption [61]. Additionally, the activation or up-regulation of PKM2 could activate multiple cancer-related pathways such as ERK signaling and STAT3 signaling [62, 63]. Therefore, inhibition of PKM2 may be potential to inhibit glycolysis and thus the proliferation of tumor cells. Moreover, pyruvate carboxylase (PC), a key enzyme at the intersection of glycolysis and the TCA cycle in TC cells, plays an important role in replenishment [64]. It is reported that PC is strongly involved in the tumor aggressiveness of TC via its stimulation of fatty acid synthesis [65]. Hence, PC restraint can significantly reduce TC cell proliferation [65], suggesting that it may be possible to detect the expression of PC in living tissues to reflect the invasive behavior of tumors and provide valuable information for clinical diagnosis and treatment of TC.

Lactic acid metabolism

As a key energetic source, a glucose precursor, and a signal molecule, LA plays a vital role in shuttling between cells in vivo [66]. Previous studies have shown that glycolysis plays a role in cell signal transduction [67, 68], promoting proliferation, invasion, and drug resistance in cancer cells [69]. Aberrant glycolysis in TC involves increased LA production and accumulation, which further promotes pH conditions conducive to growth and invasion [70]. Lactate dehydrogenase (LDH), which includes two isoforms (LDHA and LDHB), plays a decisive role in LA production. LDHA is responsible for converting PA into LA and NAD, whereas LDHB converts LA into PA and promotes oxidative metabolism [66]. The increase of LDH activity leads to tumor immune evasion via inhibiting the function of immune cells [71]. For instance, LDHA-associated LA accumulation in melanoma has been shown to inhibit tumor monitoring by T and NK cells [71]. LDHA can increase acetylation and

transcription of interferon-γ (IFNG) to promote T cell effector functions, thereby highlighting the key role of LDH in inflammation [72]. Changes in LDHB expression are often associated with early metabolic adaptation [73]. LDHB-mediated LA use supports autophagy to maintain metabolic health and cancer cells growth [74], indicating that the production and use of LA may be involved in the metabolic adaptation of cancer cells to support the development of metastasis. For example, overexpression of LDHB significantly inhibits the inhibitory effects of HYOU1 silencing on aerobic glycolysis, proliferation, migration, and invasion of PTC cells [75]. In glycolytic tumors, LA levels in cancer cells are increased more than 40-fold and are highly correlated with cancer invasion and low survival rate [76, 77]. Inhibition of the mitochondrial biogenesis pathway will decrease tumor survival and reduce tumor progression [78]. LA inhibits the differentiation of monocyte into dendritic cells [79], suggesting that high LA levels in the TME may hinder the formation and accumulation of dendritic cell. Meanwhile, high LA levels in the TME also inhibit LA efflux from T cells, resulting in decreased cytokine production and cytotoxic activity [80]. Inhibition of LA shuttle has been reported to significantly reduce the proliferation and glycolytic capacity of ATC cells in a low-glucose environment [81]. TC cells rely on glucose to activate the PI3K pathway, which influences many cellular processes, such as metabolism, cancer progression, and metastasis [82]. PI3K signaling can regulate GLUT1 expression through Akt, enhance glucose intake and facilitate phosphofructokinase (PFK) activity [83] to further promote the increase in LA. Thyroid oncogene mutations, such as c-Myc, can also increase GLUT1 expression in cancer cells, affecting glucose metabolism, and driving cell malignant transformation [84]. Therefore, glycolysis can help cancer cells survive, grow, and metastasize and further help cells resist apoptosis and avoid immune system destruction [85]. The expression of LA and LDH can support the metabolic adaptation and tumorigenesis of cancer cells [81]. Therefore, targeted suppression of glycolytic and lactate processing pathways may represent an effective treatment strategy for TC.

The role of glycolysis in thyroid cancer

Abnormal glycolysis in TC can acidify the tumor microenvironment, further leading to the abnormal growth of cancer cells. Acidification leads to changes in biological factors in the environment, which can promote or inhibit further development of TC. The fatal element of TC is metastasis, which is also affected by alterations in the tumor microenvironment also affects tumor metastasis [86].

Thyroid cell carcinogenesis and tumor formation

A necessary condition for cell growth is energy supply, and glycolysis is a crucial method to provide power for cell growth. Compared with normal cells, tumor cells have inefficient energy production, which implies that their growth and reproduction require more glucose to provide power [87]. Tumor cells can exhibit a specific metabolic pattern, which can quickly transport and consume glucose to produce ATP and boost drug excretion [88]. Meanwhile, increased levels of reactive oxygen species (ROS) are also an essential feature of TC cells, and high ROS production may lead to cell damage and cell death [89]. ROS have been demonstrated to play a significant role in cell proliferation, metabolism, angiogenesis, cell growth, and survival in several advanced malignant tumors [90, 91]. In TC, cancer cells preferentially undergo glycolysis even under aerobic conditions [92]. Many genes are upregulated or downregulated to change glycolysis, thereby promoting or inhibiting tumor growth (shown in Table 1).

$BRAF^{V600E}$ mutations are common in TCs [93, 94]. The $BRAF^{V600E}$ mutation can alter the HIF1-Myc-PGC1 axis, leading to inhibition of mitochondrial respiration and enhancement of aerobic glycolysis [95]. Meanwhile, glycolytic enzymes (such as LDHA and PKM2) are regulated by HIF1 and Myc to promote glycolysis, and $BRAF^{V600E}$ can regulate phosphate MEK1/2, thereby reducing mitochondrial metabolism [95]. The role of $BRAF^{V600E}$ signaling in the regulation of tumor metabolism suggests that BRAF can generate biodynamic adaptation by inhibiting oxidative phosphorylation [96]. Other studies have shown that glucose restriction in the cellular environment can restrain the proliferation of ATC cells [97, 98], while programmed cell death protein 1 (PD-1) can promote the proliferation and viability of TC cells [99]. HIF1 inhibits mitochondrial respiration and Myc activity in TC by inhibiting the expression of peroxisome proliferator-activated receptor γ coactivator-1 (PGC-1), indicating that the metabolic reprogramming may be a key step in thyroid carcinogenesis [100].

Mutations in the RAS-MAPK-ERK and PI3K-Akt-mTOR pathways usually exist in highly differentiated tumor components, and most ATCs are developed from these tumor components [101, 102]. In ATC, genetic alterations in the p53 gene are the most common (55%) changes [103]. Approximately 40% of PTC and 22% of FTC have p53 gene changes [104]. Studies have found that pAKT is highly expressed with pERK and low in PTEN in ATC patients, which indicates that the two pathways of RAS-MAPK-ERK and PI3K-AKT-mTOR play a synergistic role in the development of ATC [99]. In addition, the mutation of p53 was negatively correlated with the expression of pAKT, and there was a

Table 1 Regulators of glycolysis associated with thyroid cancer cells growth

Regulators		Effects in glycolysis	Effects in TC growth	Downstream molecules	Participation pathway	Mechanism
Negative regulators	PTEN	Negative	Negative	HIF-1, VEGF, PCNA	PI3K/PTEN/AKT, PI3K-AKT-mTOR	Inhibit GLUT1 expression and glucose uptake in TC, downregulate PI3K-AKT-mTOR pathway and affect glucose metabolism
	P53	Negative	Negative	AMPK, GLUT1,3,4, PGM, TSC2, RRAD	PI3K-AKT-mTOR, caspase pathway	Shorten glucose uptake and promote mitochondrial oxidation, so as to resist Warburg effect, which also leads to cell cycle arrest and apoptotic cell death
	Iodide	Negative	Negative	GLUT1	Oxidation pathway, rate-limiting glucose-facilitated transport system	Inhibit TSH induced stimulation of glucose transport, reduce the number of available carrier sites and inhibit cell growth
	$BRAF^{V600E}$	Negative	Negative	GLUT1	RAF/MEK/ERK	Initiate the glycolytic table associated with GLUT1 overexpression and inhibit mitochondrial respiration in thyroid cells
Positive regulators	HIF-1	Positive	Positive	GLUT1, PDK, PKM2, HKII	PI3K/AKT	Enhance glycolysis, increase GLUTs expression, and promote tumor growth
	PI3K/AKT	Positive	Positive	GLUT1, HKII, PDK1	PI3K/AKT	Promote cell carcinogenesis and increase glycolytic flux
	TSH	Positive	Positive	mTOR	PI3K.AKT, RAS/MAPK	Promote thymocyte proliferation and thyroid proliferation
	c-Myc	Positive	Positive	GLUT1, LDHA, PK, PKM2, MCTs	APC, miR-222-3p/HIPK2/ERK	Promote anaerobic glycolysis, tumor growth and cell proliferation
	AMPK	Positive	Negative	HIF-1α, mTOR	AMPK/AKT, AMPT/mTOR	Regulate glycolysis and control cell growth, apoptosis and survival
	LDHA	Positive	Positive	STAT3	JAK/STAT	Promote the conversion of pyruvate to lactic acid, so as to promote the glycolysis process and tumor growth
	PD-1	Positive	Positive	SHP2, RAS	SHP2/RAS/MAPK, RAS-MAPK-ERS	Promote the proliferation and vitality of thyroid cancer cells

significant positive correlation between PTEN and pERK [99]. Activation of the PI3K-AKT-mTOR signaling pathway inhibits ERK1/2 activation, which suggests that the RAS-MAPK-ERK or PI3K-AKT-mTOR pathway controls the carcinogenic effects of ATC [105]. mTOR mediator signals are combined with PKB/Akt, HIF1, and AMPK signaling pathways to manage cell proliferation and survival under conditions of nutrient and energy deprivation [106]. mTOR is a central activator of the Warburg effect [2]. mTOR upregulates PKM1 expression through mediated transcriptional activation of HIF1α and c-Myc heteroribonucleoprotein-dependent regulation of PKM2 gene splicing [107]. The destruction of PKM1 inhibits oncogenic mTOR mediated tumorigenesis [108]. Unlike

normal cells, mTOR hyperactive cells are more sensitive to the inhibition of mTOR or glycolysis. The dual inhibition of mTOR and glycolysis synergistically passivates the proliferation and tumor development of mTOR hyperactive cells [107]. PD-1 can activate Ras-MAPK signaling cascade in TC cells and enhance the expression of Ras in TC cells [109]. In addition, RET/PTC or BRAF mutations can also lead to active PI3K [110]. In TC cells, downregulation and activation of the Ras-MAPK and PI3K-Akt pathways mainly inhibit cell migration and proliferation [111]. However, inactivation of Ras-MAPK signaling has a positive effect on the mobility of ATC cells [112]. Compared to the inhibition of a single pathway, the dual Ras-MAPK and PI3K-Akt-mTOR pathways can inhibit cell growth and even lead to growth retardation in TC cells in a congenerous manner [113]. In addition to the influence of these factors and pathways, glycolysis leads to acidification of the tumor microenvironment, which also promotes TC progression.

Glycolysis and thyroid cancer microenvironmental acidosis

Glucose is converted to LA in tumor cells and flows extracellularly to form lactate and produce lactate accumulation (Fig. 2) [114]. Through continuous aerobic glycolysis, glucose alters some of the microenvironment, resulting in side effects [115]. LDHA of the glycolysis process promotes the conversion of pyruvate to LA, which is associated with the development of various cancers, including TC [116–118]. Proton-linked monocarboxylate transporters (MCTs) transport LA across the plasma membrane, which requires binding of CAIX to the CD147, a widely expressed membrane glycoprotein [119]. Studies have shown that MCT1 is required for CD147 protein expression, causing the MCT/CD147 subunits to assemble and target the plasma membrane [120]. In rat thyroid tissues, MCT4 can output LA through the plasma membrane with the assistance of CD147 [120]. Research has found that Acriflavine (ACF) can disrupt the binding of MCT4 to its essential cofactor basigin [121]. ACF can effectively inhibit the growth of ATC cells in vitro by inhibiting LA output and subsequently inhibiting upstream glycolysis [81]. High levels of acid production result in a sharp local drop in the extracellular pH value. In addition to lactate, carbon dioxide (CO_2) manufactured by catalytic pathways, such as the pentose phosphate pathway (PPP), is also conducive to acidifying the TME [122, 123]. In this case, microenvironmental acidification can promote tumor invasion by destroying adjacent normal cells, inducing extracellular matrix (ECM) degradation, and promoting angiogenesis [114]. Long-term exposure of normal cells to an acidic microenvironment leads to cell necrosis or apoptosis depending on p53 and caspase-3 mechanisms [124]. Nevertheless, tumor cells adjust their survival conditions to adapt to the acidic microenvironment [125]. The acidic microenvironment can inhibit the growth of normal cells, but acidosis is an indispensable criterion for cancer cell migration and invasion [124]. High levels of LA in TME will reduce the activity of immune cells, thereby promoting tumors and metastasis [126, 127]. Meanwhile, the accumulation of lactate and acidification of TME will accelerate the remodeling of basement membranes (BM) or boost the progression of epithelial-mesenchymal transition (EMT), contributing to tumor invasion [128]. Acidosis can affect tumor progression, aggression and metastasis, a phenotypic feature of TME markers [129]. The glucose uptake of tumor cells increases due to hypoxia, and glucose restriction in the TME also facilitates the activation of the M2-like phenotype in tumor-infiltrating macrophages, promoting the anti-inflammatory response and tumor growth [130]. In conclusion, aerobic glycolysis in tumor cells produces many lactic acid accumulations, which acidifies the TME, destroys adjacent normal tissues, degrades the extracellular matrix, and promotes angiogenesis, thus promoting tumor invasion and metastasis.

Glucometabolic reprogramming in metastatic thyroid cancer

Tumor metastasis to distant organs is caused by tumor cells with primary heterogeneous tumor diffusion, and the sequential growth and survival of tumor metastasis depend on different metabolic changes [131]. Malignant tumors proliferate indefinitely and have a tendency for distant metastasis. They require large amounts of energy and biosynthetic precursors to promote cell division, invasion, and migration [132, 133]. Secreted lactic acid can affect cell types in TME by activating multiple processes such as tumor cell survival and proliferation [134]. LA accumulation can induce various events in the TME, including the upregulation of hyaluronic acid, which is conducive to tumor migration [135, 136]. Lactate excretion by tumor cells allows acidic degradation of the matrix around healthy tissues, leading to invasive growth [137]. Tumor metastasis is a multistep cascade process, and more than 90% of cancer deaths are not caused by tumors alone, but by tumor metastasis [138]. At the beginning of metastasis, invasion is required. That is, diffuse malignant cells must converge the normal ambient tissues into a collective tissue structure or separate into small cell clusters [139, 140]. As tumor cells reduce cell-to-cell adhesion to relax tight structures, they promote further cell invasion, which is a feature of the EMT process [141, 142]. During the EMT process, the viscosity of tumor cells decreases and the activity of tumor cells increases. After converging normal ambient tissues and forming a new vascular network by secreting vascular

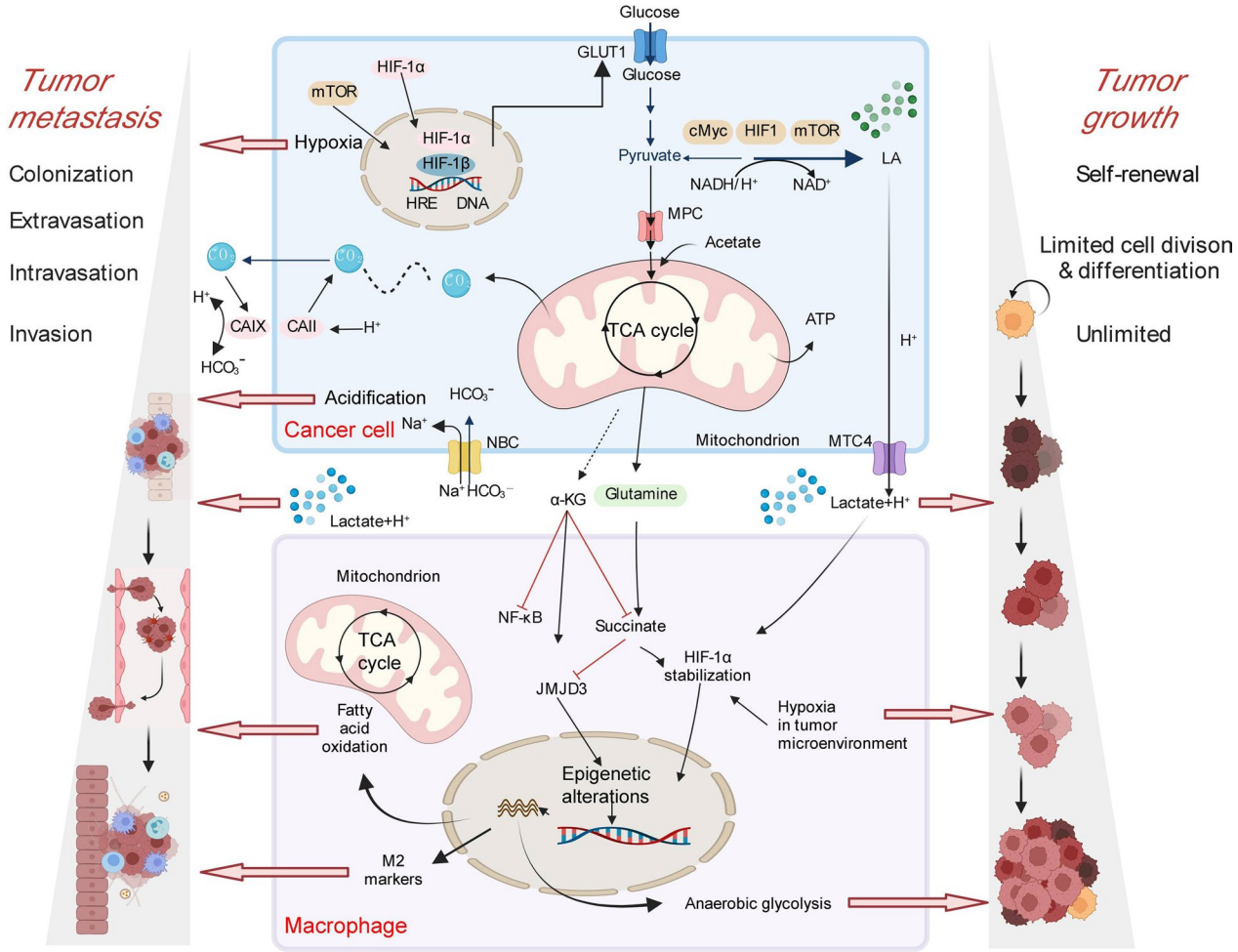

Fig. 2 Anaerobic glycolysis promotes the growth and metastasis of thyroid cancer cells. Anaerobic glycolysis of tumor cells produces a large accumulation of lactic acid, which acidifies the tumor microenvironment. Tumor growth mainly consists of three steps: self-renewal, limited cell division or differentiation, and an unlimited state. Tumor metastasis includes colonization, extravasation, intravasation, and invasion. A hypoxic environment, excessive lactic acid and anaerobic glycolysis can promote the rapid growth and metastasis of tumor cells. cMyc, HIF1α, and mTOR can promote the formation of lactic acid and the expression of GLUT1 to help tumor growth. The simultaneous hypoxia can promote tumor metastasis. The increased influx of sodium ions in tumor cells increases the level of HCO3-, further promoting tumor microenvironmental acidification and metastasis. Fatty acid oxidation in macrophages in the tumor microenvironment and M2 markers can also promote tumor cell migration. The glutamine produced by tumor cells can promote the production of succinate, thereby making HIF1α stabilization, which further promotes the hypoxia of the tumor microenvironment, so that tumor cells undergo anaerobic glycolysis, thereby assisting tumor cell growth and metastasis

factors, tumor cells will connect the small blood vessels, such as veins or capillaries, and lymph nodes and enter the circulation [143]. Interaction with neutrophils in circulation can promote further metastasis and diffusion. Neutrophils may also promote tumor cell extravasation by secreting matrix metalloproteinases (MMPs) [144]. Eventually, tumor cells can leave the blood circulation and invade secondary tissues.

Metastasis occurs in 10% of TC patients (Fig. 3), and approximately half of distant metastases occur in the lung, which may be associated with anti-nest loss apoptosis and pro-invasion signals mediated by LDHA phosphorylation [145, 146]. LDHA phosphorylation provides invasive signals in metastatic cancer cells by regulating redox status, and LDHA can also enhance tumor progression by possessing molecules related to EMT [147]. When LDHA is inhibited, more pyruvate will enter the tricarboxylic acid (TCA) cycle, resulting in an increased oxygen demand [147]. However, cancer cells are overdependent on aerobic glycolysis, which produces ATP rapidly and can use more precursors to

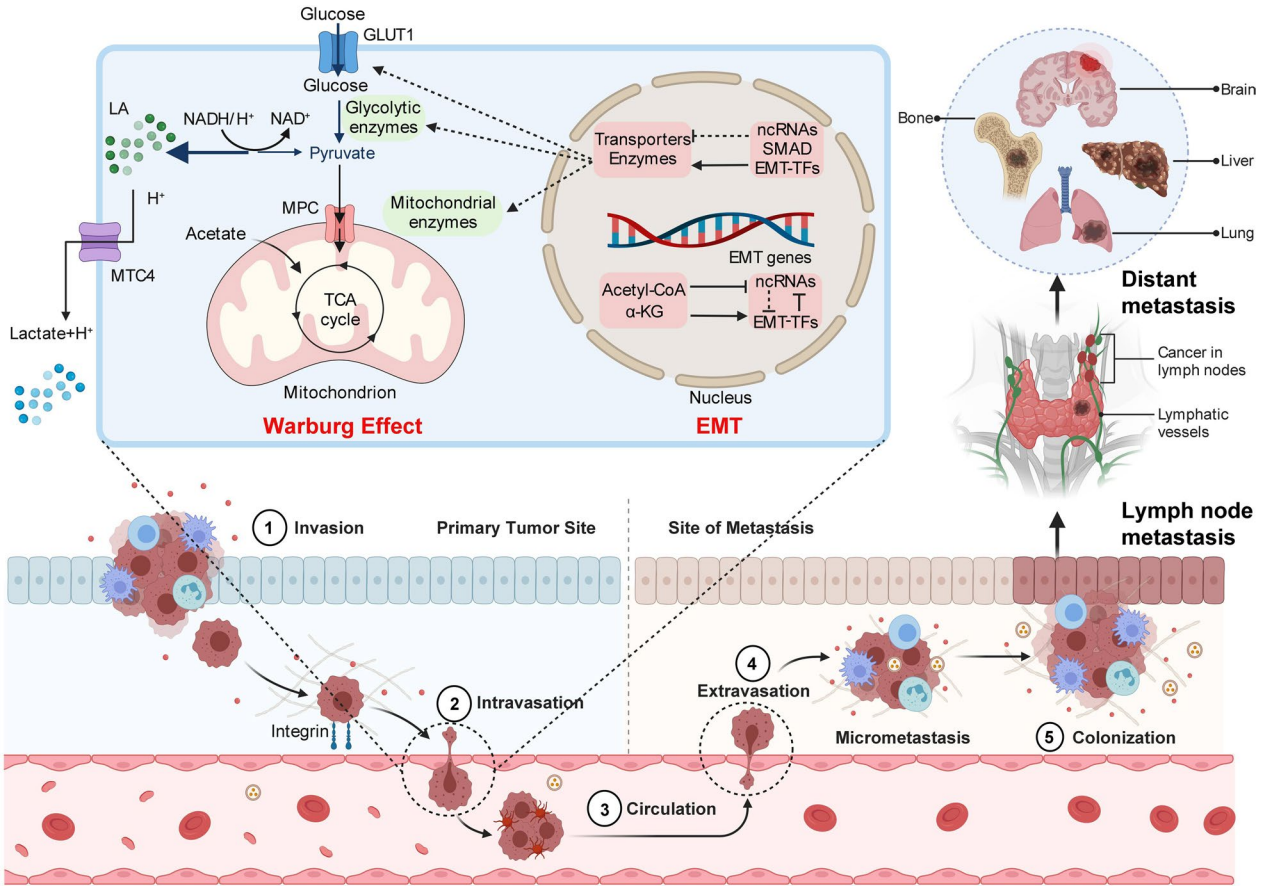

Fig. 3 Relationship between metastasis of thyroid cancer cells and glycolysis and EMT. Metastasis of thyroid cancer cell is a multistage process including invasion, intravasation, circulation, extravasation, and colonization. Intravasation and extravasation are closely related to glycolysis and the EMT process. One of the reasons for the extremely high risk of thyroid cancer is that it can metastasize remotely through lymph nodes, often to the lungs, bones, liver and brain

meet the metabolic requirements of rapid proliferation. Therefore, when LDHA is inhibited, it can affect the proliferation, invasion, and metastasis of TC cells and prevent TC cells from escaping immunity [100]. In conclusion, LDHA can cause EMT-like changes that promote migration and invasion of TC cells, and can therefore be considered as a target factor for the treatment of TC. Increased GLUT-1 expression is also related to the increased invasive behavior and metastasis characteristics [148, 149]. HIF1, a downstream target of GLUT1, is also involved in tumor metastasis and migration [150]. Under hypoxiaconditions, increased glucose uptake by cancer cells can upregulate the stability of HIF-1α, leading to a weakened antitumor immune response [18]. In addition, programmed death-ligand 1 (PD-L1) is a downstream target of HIF-1 that can bind to PD-1 on T cells. The PD-1/PD-L1 interaction can activate the dephosphorylation of PI3K and block the Akt/mTOR pathway [151, 152].

Potential clinical value of glycolysis in thyroid cancers

Tools for detecting thyroid glycolysis

At present, many methods are available to help diagnose TC, and each of these methods has its own advantages and disadvantages, such as ultrasonography, fine-needle aspiration biopsy (FNAB), computed tomography (CT), and magnetic resonance imaging (MRI) (See Table 2). Among them, the diagnostic method of fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) imaging is closely related to the glycolysis pathway. Taking advantage of exploiting the high activity of GLUT1 in tumor cells, FDG-PET imaging accumulates a significant amount of glucose in tumor cells and conducts in vivo detection in humans [153]. The diagnosis of malignant tumor metastasis relies heavily on this technology. In the thyroid gland, follicular epithelial cells exhibit fanatical iodine absorption mediated by the Na^+/I^- symporter (NIS) [154]. Glucose uptake is increased by GLUT1 overexpression during differentiation in TCs.

Table 2 Detection strategies in thyroid cancers

Method	Principle	Frequency	Advantages	Disadvantages
Ultrasonography	Use ultrasound to present the internal image of opaque objects	Always	Detection of residual thyroid cancer in cervical lymph nodes or soft tissue	Unclear imaging, difficult qualitative, inaccurate quantitative
FNAB	A sterile puncture needle was used to puncture the suspicious part of the nodule, and some nodule components were extracted for cytological and pathological examination	Always	Differential diagnosis between benign and malignant thyroid nodules and diffuse goiter	Too few materials to know whether the blood vessels and capsule are invaded at the same time
CT	The optical signal is changed into an electrical signal, then into a digital signal, and finally into a computer picture	Always	Preoperative staging, monitoring, re staging, location of metastatic disease and continuous monitoring of progression and treatment response of thyroid cancer	Difficult to find small lesions with little or no density change
MRI	Based on the low diffusion coefficient of water molecules in high cell tissues	Often	Helpful to detect lymph node involvement and lymph node metastasis before operation	Expensive equipment, long time to image and limited patients
Radioiodine imaging	TSH stimulates iodine uptake in residual normal and malignant thyroid tissues	Often	Identify, locate and monitor the progress or treatment response of iodine preference metastasis in differentiated thyroid cancer	Needed TSH to stimulate iodine uptake in residual normal and malignant thyroid tissues
$^{123}I/^{131}I/^{99m}Tc$ Thyroid Scintigraphy	Effective concentration of iodine based on thyroid follicular cells	Often	The only evidence of autonomic functional thyroid nodules	Uncertain to hyper-functional nodules
FDG-PET	Based on the mutual annihilation of positrons and electrons, two high-energy 511 keV photons are released in the opposite direction	Often	Evaluation of thyroid cancer recurrence and for systemic and focal dosimetry	Limitation for patients with newly discovered thyroid nodules or thyroid diseases were evaluated

The opposite relationship between iodine absorption and glucose utilization is known as the iodine/FDG 'turnover phenomenon', reflecting the cell differentiation state and heterogeneous pattern of NIS expression [155, 156]. FDG-PET imaging is not recommended for the evaluation of patients with newly identified thyroid nodules or thyroid diseases [156]. Nevertheless, skeletal muscle metastasis of thyroid microcarcinoma can be evaluated by 18F-FDG PET/CT [157]. 18F-fluoro-2-deoxy-D-glucose (18F-FDG) is the most commonly used radiotracer in oncology imaging for staging, re-documentation, and assessment of treatment response in several tumors [158]. In DTC patients, lesions with high 18F-FDG and low radioactive iodine uptake are more clinically invasive [159]. Studies have found that malignant cells have the lowest degree of differentiation and the highest ability to absorb 18F-FDG [160]. Quantitative 18F-FDG-PET/CT evaluation can exclude the malignancy of uncertain thyroid nodules [161]. 18F-FDG-PET/CT can also be used to evaluate response to treatment, detect lesions in metastatic patients, and predict the prognosis of high-risk patients [162]. Although the evaluation of node status has reasonable specificity (94%), 18F-FDG PET/CT imaging shows a low sensitivity (30%) [162, 163], and the current American Thyroid Association (ATA) criteria do not recommend 18F-FDG PET/CT as a routine preoperative test [164]. However, 18F-FDG PET/CT is strongly recommended for follow-up of high-risk patients with elevated serum thyroglobulin (Tg) and negative 131I imaging [164, 165]. FDG PET has been shown to be helpful in detecting persistent or recurrent DTC in patients with low Tg; however, when FDG PET-CT is negative, this does not exclude DTC and requires further investigation [166].

Diffusion-weighted imaging (DWI) provides quantitative and qualitative information based on the assessment of micro movement of water at the cell level, and can be used to distinguish benign and malignant diseases [167]. ATA states that cervical ultrasound is the best method to assess the status of lymph nodes prior to surgery [167]. MRI is a sensitive imaging modality that localizes sites of potential recurrence of DTC in the neck, mediastinum, bones, and liver, although the accuracy of detecting lung lesions is low [168]. MRI significantly reduced the total radiation dose of patients compared to PET/CT [169]. Meanwhile, PET/MRI is a promising tool with great potential to provide complementary data obtained under the same time and conditions. Diagnosis of thyroid nodules by conventional ultrasound relies on image quality, neck coverage, and ultrasound interpretation [170]. The current gold standard for confirming the diagnosis of TC is FNAB, but it remains highly likely to fail to describe micronodules of the thyroid gland [171]. Therefore, it is important to combine the available tools, such as ultrasound, CT and MRI, to establish a correct diagnosis of TC and evaluate the curative effect after treatment.

Therapeutic strategies targeting glycolysis dependence in thyroid cancers

Glycolysis brings many advantages to fast-growing tumor cells [172], and targeting metabolic pathways may be a promising method for tumor therapy [173]. Many targeted treatment methods are available for TCs, but the existing techniques are not systematically integrated. Among them, treatment strategies targeting glycolysis have received considerable attention. Below, we summarize some specific targeted treatment methods for TCs based on crucial factors of the glycolysis process (Fig. 4).

Tyrosine kinase inhibitors (TKIs)

Tyrosine kinase receptors are involved in cancer proliferation, angiogenesis and lymphangiogenesis [8, 174]. Angiogenesis plays a significant role in the occurrence and development of tumors, while lymphangiogenesis is critical for metastasis formation [175]. The expression of VEGF in TC cells can facilitate tumor angiogenesis [176]. Vascular endothelial growth factor receptor 2 (VEGFR2) is a TK receptor expressed by vascular endothelial cells from TME via immune cells, and its activation can initiate HIF1α in tumors and promote VEGF-α overexpression [177, 178]. VEGF-α is mainly expressed in ATC cells but not in normal thyroid tissues and upregulates the PI3K/Akt and MAPK pathways through growth factor signals [179]. In DTC, VEGF and VEGFR2 are overexpressed and can promote tumor progression and invasion. VEGF receptor is also overexpressed in MTC [180]. PI3K/Akt/mTOR and Raf/MEK/ERK are involved in ATC dedifferentiation and tumor growth [181]. TKIs targeting RET and VEGFR2 have shown promising results in phase II trials [182, 183]. Therefore, the study of TKIs in the treatment of TC plays a positive role in improving the current situation of TC patients.

ATA guidelines recommend that patients with stable or minimal progression should not be treated immediately and TKI treatment should be considered in "patients with metastatic, rapidly progressive, symptomatic, and/or imminently threatening disease [184, 185]. Several tyrosine kinase inhibitors have entered clinical trials: (1) sorafenib (BAY 43-9006) can inhibit RAF, VEGFR2, VEGFR3, and KIT kinase, which inhibits TC growth through anti-proliferation and anti-angiogenesis mechanisms [186, 187]; (2) Sunitinib (SU011248) preferentially inhibits VEGFR1-3, KIT, and PDGFR kinase [188]. Sunitinib inhibits the autophosphorylation of RET/PTC and the activation of STAT3, and blocks the transformation ability of RET/PTC [189]; (3) Vandetanib (ZD6474)

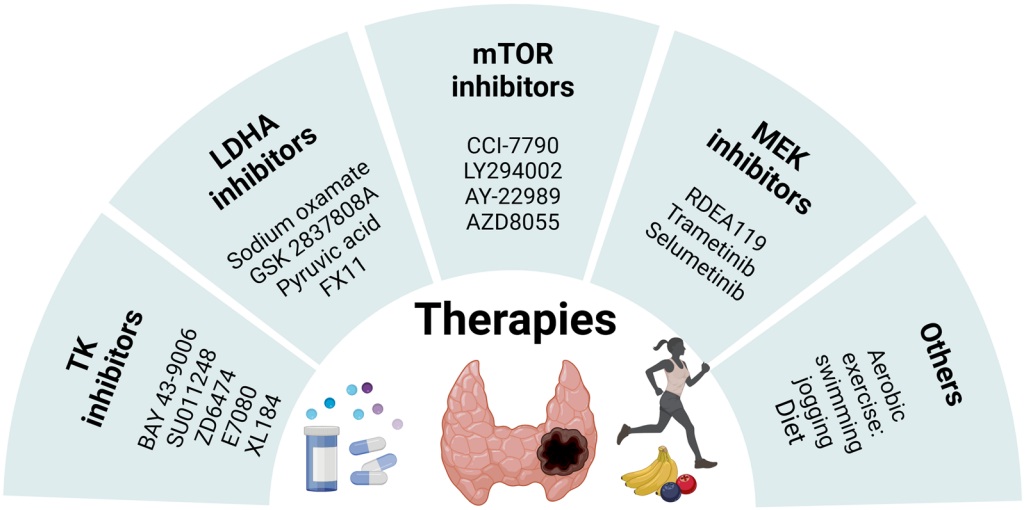

Fig. 4 Therapies targeting thyroid cancer based on crucial factor inhibitors of glycolysis. Four inhibitors associated with glycolysis can serve as prospective treatment methods for thyroid cancer: TK inhibitors, LDHA inhibitors, mTOR inhibitors, and MEK inhibitors. Additionally, aerobic exercise might be a new strategy to reduce the incidence of thyroid cancer

is an effective inhibitor of VEGFR2, VEGFR3, RET, and epidermal growth factor receptor kinase [190]; (4) Lenvatinib (E7080) inhibits FGFR1-4, PDGFRβ, Vegfr1-3, RET, and supporting element kinase [191]; and (5) Cabotanni (XL184) inhibits c-Met, VEGFR1, 2, and RET kinases [192]. ZD6474 and XL184 have been approved as targeted treatments for advanced MTC with symptoms or high tumor burden [8, 193]. Research has shown that long-term medication cessation in patients may not lead to rapid disease progression. However, it may result in long-term "TKI free" stable diseases in individual patients [194]. Analysis of calcitonin and CDT is necessary during discontinuation to reveal tumor progression. In the event of progress, the same TKI can be used to restart [195]. A large number of studies have demonstrated that TKIs represent a new targeted therapy for invasive, progressive, and refractory TCs [196]. However, there are toxic reactions to inhibiting VEGF treatment, such as hypertension, kidney injury, bleeding, cardiovascular toxicity, etc. [197]. Doctors should closely understand the toxicity, adopt appropriate treatment strategies, and decide on treatment interruption, dosage adjustment, and cessation as needed.

LDHA inhibitors

LDHA, one of the pivotal glycolytic enzymes, promotes the conversion of pyruvate to lactic acid by compensating for the reduction in oxidative mitochondrial function and sustains cell survival under hypoxia [117, 198]. The decrease in glucose uptake caused by LDHA inhibitors is not the cause of decreased cell density or reduced GLUT1 surface expression [199]. LDHA inhibitors inhibit the regeneration of nicotinamide adenine dinucleotide (NAD) and impair the activity of glyceraldehyde 3-phosphate dehydrogenase (GAPDH), which accumulates an intermediate volume of glucose in the initial step of glycolysis, increases the cellular level of unused glucose, and inhibits glucose uptake [200]. The overexpression of LDHA and increased phosphorylation are common findings in thyroid malignancies [201]. Patients with high LDHA expression have a poor prognosis, which is closely connected with metastasis, and high LDHA levels have been demonstrated to be related to lymph node metastasis [202]. STAT3 is a new upstream regulator of LDHA and a key transcription factor involved in many growth factors and cytokines, which can trigger various biological processes, including cell growth, differentiation, and survival [116]. The expression of STAT3 is positively associated with the expression of LDHA [203]. The expression levels of STAT3 and PSTAT3 are higher in the group with lymph node metastasis than in the group without lymph node metastasis [204]. LDHA can increase the proliferation, invasion, and metastasis of TC cells and help TC cells evade immunity [100]. Therefore, LDHA is considered as a promising target for the prevention and treatment of TC. Chemical inhibitors of LDHA are being developed, such as the LDHA inhibitors FX11, GSK 2837808A, sodium oxamate, and pyruvic acid, which significantly inhibit cell proliferation and induce apoptosis [205]. Phosphorylated AMPK levels increases when LDHA is knocked down or inhibited. As the primary downstream target of the AMPK signal, mTOR is involved in cell growth, cell proliferation, and cell survival [206]. LDHA knockdown or inhibition reduces the

phosphorylation level of mTOR, which also suggests that mTOR inhibitors can be used in the glycolysis process to inhibit the growth and metastasis of TC [202].

mTOR inhibitors

mTOR is involved in controlling the proliferation of normal and TC cells and regulating iodide absorption in normal thyroid cells; therefore, mTOR inhibition may efficiently reduce cell proliferation and stimulate iodide absorption in TC cells [207]. mTOR inhibition leads to severe impairment of proliferative signals via the PI3K/Akt pathway [208] and cell cycle arrest in the G1 stage, which can be activated by membrane receptors, including the insulin-like growth factor receptor (IGFR) and the thyroid-stimulating hormone (TSH) receptor in thyroid cells. Rapamycin analogs can directly inhibit mTOR signaling, such as LY294002, AY-22989, AZD8055, and temsirolimus (CCI-7790) [209], and reduce cell proliferation in TC cell lines [210]. Genes encoding TK receptors, mitochondrial activated protein kinase (MAPK) and PI3K/Akt pathway, are mutated in almost all ATC cases [102]. Two open-label phase II clinical trials have demonstrated the modest anti-tumor activity of everolimus and the stabilization of TC [211, 212]. However, neither trial demonstrated an association between tumor mutation status and drug response in patients with ATC. Therefore, targeting these two pathways at the same time may be particularly effective in the treatment of ATC. A PI3K inhibitor (LY294002) was found to inhibit mTOR, slow disease progression, eliminate lung metastasis and prolong the survival time in mice due to inhibition of cancer growth and proliferation, increased apoptosis, and decreased cell activity [213]. The growth inhibition of cancer cell lines treated with MAPK kinase (MEK) and mTOR inhibitor was greater than 60% [111]. Another study demonstrated the therapeutic potential of the novel MEK inhibitor RDEA119 in TC and its synergistic effect with the mTOR inhibitor temsirolimus [214].

MEK inhibitors

The MAPK-MEK signaling pathway is often overactivated in ATCs and correlated with the progression of ATCs [215]. MEK inhibitors can induce iodine uptake and retention in TCs, which exhibits G0/G1 arrest by downregulating MEK/ERK phosphorylation and inhibiting the viability of BRAF mutant cells [216, 217]. The MAPK pathway is an evolutionarily preserved signaling cascade that links extracellular and internal stimuli with the control of multiple cellular processes under physiological and pathological conditions, including cell proliferation, survival, invasion, migration, and differentiation [216]. Trametinib, an MEK1/2 inhibitor, has been demonstrated to independently improve survival in patients with metastatic melanoma [218]. Downstream MEK inhibition can not only prevent BRAF resistance in BRAF mutant cells but also block abnormal MAPK activation in BRAF wild-type cells [219]. Pretreatment with MAPK inhibitors improves the reactivity of RAI treatment [220]. MEK inhibitors (such as selumetinib) activate PI3K and MAPK pathways by stimulating HER3 gene expression, and the HER3 inhibitor lapatinib can prevent MAPK rebound and sensitize $BRAF^{v600E}$ positive TC cells to Raf or MAP/ERK inhibitors [221]. The most common adverse effects of selumetinib that were reported are fatigue, diarrhea, and rash [222]. A single-arm multicenter two-phase II clinical trial is currently underway in the UK to evaluate the efficacy of selumetinib in combination with RAI in patients with recurrent thyroid cancer [223]. HER inhibitors combined with BRAF/MEK inhibitors can improve the sensitivity of BRAFv600E positive PTC to BRAF/MEK inhibitors by preventing MAPK rebound and increasing NIS expression [224, 225]. MEK has many unique biochemical and biological characteristics, rendering it an attractive target from the perspective of anticancer drug development.

Other strategies

In addition to the above treatments targeting specific enzymes, some studies have found that aerobic exercise may also be a new treatment. Aerobic exercise, an anti-Warburg maneuver, such as swimming and jogging, can increase mitochondrial function and lactate clearance, which increases fat oxidation, decreases glycolysis and reduces dependence on glycogen and glucose [226]. In addition, exercise can reduce the harmful activity of c-Myc [227]. Hence, aerobic exercise helps counteract the metabolic conversion of cancer cells to glycolytic metabolism and produces epigenetic responses that help restore the oxidative phenotype [228]. Other studies have also proved that diets might affect the tumor growth and be a potential treatment [229]. Tailed diets are based on the nutritional vulnerabilities of tumor. Although lacking well-designed clinical trials, some preclinical studies have demonstrated that tailed diet such as low-carbohydrate diet and restring dietary serine and glycine can starve tumors and boots the effectiveness of cancer therapy [230]. Thus, alteration of cellular metabolism by low-carbohydrate ketogenic diets can be an important therapeutic strategy to selectively kill cancer cells that mainly survive on glycolysis [231]. Calorie-restricted diets enhance ameliorate metabolic pathogenesis and reduce the incidence of cancer [232, 233]. Also, caloric restriction promotes antineoplastic immune responses and suppresses tumor cell proliferation [234, 235]. Hence, metabolic interventions may have a great potential as co-adjuvant therapy in the management of TC.

Conclusions

The increasing incidence rate of TC has been a significant concern in the medical field. The unambiguous pathogenesis of TC is not yet fully understood because of its diversity. Glycolysis is a process that occurs in all cancer cells. Linking it with TC provides some insights for the treatment of TC. Warburg effect, that is, aerobic glycolysis in the presence of oxygen and mitochondria with normal function in principle, constitutes the main driving factor of cancer progression mechanism, resistance to traditional therapy and poor prognosis of patients. The molecular and functional processes associated with tumorigenesis may include: (a) significant acceleration of glycolytic flux; (b) generation of sufficient ATP to provide energy for cancer cells; (c) backup and transfer of glycolytic intermediates, promoting the biosynthesis of nucleotides, nonessential amino acids, lipids and hexosamine; (d) inhibition of pyruvate from entering mitochondria; (e) excessive formation and accumulation of lactate; (f) maintaining cell redox homeostasis and low ROS formation; and (h) HIF-1 overexpression, mutant p53 and mutant PTEN, which inhibit mitochondrial biogenesis and function. The Warburg effect can help cancer cells survive, grow and metastasize, further helping tumors resist apoptosis, and avoid destruction by the immune system. Glycolysis has a complete mechanism. By understanding the process of its occurrence and comparing differences in glycolysis processes between normal cells and cancer cells, we can target the glycolysis pathway to treat TC in follow-up research. The common treatment for TC is surgical resection, but recurrence or deterioration is still possible. For special types of TC, the current treatment cannot achieve a good therapeutic effect, and whether we can target glycolysis to achieve a therapeutic effect requires further exploration.

With improved understanding of "reprogramming of glucose metabolism" in TC, patients with poorly differentiated TC are no longer without effective therapies in terms of the development of new therapies. Novel diagnostic methods based on glycolysis mechanism, such as FDG-PET, as well as targeting drugs, such as FX11, trametinib, and AZD8055, and diets will be of great significance to further deepen our understanding of glycolysis regulation and reasonably design strategies for the diagnosis and treatment of TC, especially for patients with poorly differentiated TC or relapse status. Many inhibitors have entered the stage of clinical experimental research, but no extraordinary evidence shows that they have a good therapeutic effect. Research in this field still needs to be further strengthened. Moreover, how to affect the occurrence and development of TC requires further verification. Whether inhibitors affecting the glycolysis pathway have a definitive inhibitory effect on TC and their safety warrants our attention. Taken together, targeting the cancer metabolism holds great promise as a therapeutic modality in TC.

Abbreviations

TC	Thyroid cancer
DTC	Differentiated thyroid cancers
PTC	Papillary thyroid cancer
FTC	Follicular thyroid cancer
MTC	Medullary thyroid cancer
ATC	Anaplastic thyroid cancer
RAIR	Radioiodine refractory
ATP	Adenosine triphosphate
PI3K	Phosphatidylinositol 3-kinase
HIF-1α	Hypoxia-inducible factor-1 alpha
TME	Tumor microenvironment
PK	Pyruvate kinase
GLUT1	Glucose transporter 1
TCA cycle	Tricarboxylic acid cycle
LA	Lactic acid
PEP	Phosphoenolpyruvate
GLS	Glutaminase
GDH	Glucose dehydrogenase
PFK	Phosphofructokinase
ROS	Reactive oxygen species
LDHA	Lactate-dehydrogenase A
PD-1	Programmed cell death protein 1
PGC-1	Peroxisome proliferator-activated receptor γ coactivator-1
MAPK	Mitogen-activated protein kinase
MCTs	Proton-linked monocarboxylate transporters
ACF	Acriflavine
CO2	Carbon dioxide
PPP	Pentose phosphate pathway
ECM	Extracellular matrix
BM	Basement membrane
EMT	Epithelial-mesenchymal transition
MMP	Matrix metalloproteinases
PD-L1	Programmed death-ligand 1
FNAB	Fine-needle aspiration biopsy
CT	Computed tomography
MRI	Magnetic resonance imaging
FDG-PET	Fluoro-2-deoxy-D-glucose positron emission tomography
NIS	Na + /I- symporter
ATA	American Translators Association
Tg	Thyroglobulin
DWI	Diffusion-weighted imaging
TKIs	Tyrosine kinase inhibitors
VEGFR2	Vascular endothelial growth factor receptor 2
VEGF	Vascular endothelial growth factor
PDGFR	Platelet-derived growth factor receptors
STAT3	Signal transducer and activator of transcription 3
NAD	Nicotinamide adenine dinucleotide
GAPDH	Glyceraldehyde 3-phosphate dehydrogenase
IGFR	Insulin-like growth factor receptor
TSH	Thyroid stimulating hormone

Acknowledgements

We wish to thank all the authors who participated in this study.

Author contributions

SLD, ZJZ and SC conceived and planned the study design; SLD and MW collected formal resources and wrote the original draft; SLD and MW prepared the tables and figures; ZJZ and SC provided critical revisions and contributed to the editing of the paper. All authors read and approved the final manuscript.

Funding
This work was supported by the National Natural Science Foundation of China (Grant No.81902729, 81974423), the Special Funding for the Construction of Innovative Provinces in Hunan (Grant No.2019SK2031, Grant No.2020SK4003), the Natural Science Foundation of Hunan Province (Grant No.2020JJ5904), the China Postdoctoral Science Foundation (Grant No.2020M672517, 2021T140749), the Project Program of National Clinical Research Center for Geriatric Disorders (Xiangya Hospital, Grant No.2021KFJJ03).

Availability of data and materials
This article contains data to support the results of this study. The datasets generated and/or analyzed during the current study are not publicly available due to participant information privacy but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study was approved by the Ethics Review Committee of Xiangya Hospital, Central South University, and followed the Declaration of Helsinki (20211245). The informed consent was waived because of the retrospective and anonymous nature of the study.

Consent for publication
All authors gave consent for the publication of this study.

Competing interests
The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential competing interests.

Received: 7 August 2023 Accepted: 11 October 2023
Published online: 18 October 2023

References

1. Baloch ZW, Asa SL, Barletta JA, Ghossein RA, Juhlin CC, Jung CK, LiVolsi VA, Papotti MG, Sobrinho-Simoes M, Tallini GJ. Overview of the 2022 WHO classification of thyroid neoplasms. Endocr Pathol. 2022;33:27–63.
2. Shi YB, Chen SY, Liu RB. The new insights into autophagy in thyroid cancer progression. J Transl Med. 2023;21(1):1–3.
3. van Houten P, Netea-Maier RT, Smit JW. Differentiated thyroid carcinoma: an update. Best Pract Res Clin Endocrinol Metab. 2023;37(1):101687.
4. Cabanillas ME, McFadden DG, Durante C. Thyroid cancer. Lancet. 2016;388:2783–95.
5. Filetti S, Durante C, Hartl D, Leboulleux S, Locati LD, Newbold K, Papotti MG, Berruti A. Thyroid cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-updagger. Ann Oncol. 2019;30:1856–83.
6. Oh JM, Ahn BC. Molecular mechanisms of radioactive iodine refractoriness in differentiated thyroid cancer: Impaired sodium iodide symporter (NIS) expression owing to altered signaling pathway activity and intracellular localization of NIS. Theranostics. 2021;11:6251–77.
7. Gild ML, Tsang VHM, Clifton-Bligh RJ, Robinson BG. Multikinase inhibitors in thyroid cancer: timing of targeted therapy. Nat Rev Endocrinol. 2021;17:225–34.
8. Cabanillas ME, Ryder M, Jimenez C. Targeted therapy for advanced thyroid cancer: kinase inhibitors and beyond. Endocr Rev. 2019;40:1573–604.
9. Lin R. Thyroid cancer stem cells. Nat Rev Endocrinol. 2011;7:609–16.
10. Fallahi P, Ferrari SM, Galdiero MR, Varricchi G, Elia G, Ragusa F, Paparo SR, Benvenga S, Antonelli A. Molecular targets of tyrosine kinase inhibitors in thyroid cancer. Semin Cancer Biol. 2022;79:180–96.
11. Hu J, Yuan IJ, Mirshahidi S, Simental A, Lee SC. Thyroid carcinoma: phenotypic features, underlying biology and potential relevance for targeting therapy. Int J Mol Sci. 2021;22(4):1950.
12. Bryant KL, Stalnecker CA, Zeitouni D, Klomp JE, Peng S, Tikunov AP, Gunda V, Pierobon M, Waters AM, George SD, et al. Combination of ERK and autophagy inhibition as a treatment approach for pancreatic cancer. Nat Med. 2019;25:628–40.
13. Su WY, Tian LY, Guo LP, Huang LQ, Gao WY. PI3K signaling-regulated metabolic reprogramming: from mechanism to application. Biochim Biophys Acta. 2023;25:188952.
14. Liberti MV, Locasale JW. The Warburg effect: how does it benefit cancer cells? Trends Biochem Sci. 2016;41:211–8.
15. Coelho RG, Fortunato RS, Carvalho DP. Metabolic reprogramming in thyroid carcinoma. Front Oncol. 2018;8:82.
16. Heydarzadeh S, Moshtaghie AA, Daneshpour M, Hedayati M. Correction to: regulators of glucose uptake in thyroid cancer cell lines. Cell Commun Signal. 2022;20:11.
17. Somarribas Patterson LF, Vardhana SA. Metabolic regulation of the cancer-immunity cycle. Trends Immunol. 2021. https://doi.org/10.1016/j.it.2021.09.002.
18. Nagao A, Kobayashi M, Koyasu S, Chow CCT, Harada H. HIF-1-dependent reprogramming of glucose metabolic pathway of cancer cells and its therapeutic significance. Int J Mol Sci. 2019;20:238.
19. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011;144:646–74.
20. Warburg O. Origin of cancer cells. Oncol. 1956;9:75–83.
21. Lunt SY, Vander Heiden MG. Aerobic glycolysis: meeting the metabolic requirements of cell proliferation. Annu Rev Cell Dev Biol. 2011;27:441–64.
22. Khatami F, Payab M, Sarvari M, Gilany K, Larijani B, Arjmand B, Tavangar SM. Oncometabolites as biomarkers in thyroid cancer: a systematic review. Cancer Manag Res. 2019;11:1829–41.
23. Biswas SK. Metabolic reprogramming of immune cells in cancer progression. Immunity. 2015;43:435–49.
24. Mates JM, Campos-Sandoval JA, Santos-Jimenez JL, Marquez J. Dysregulation of glutaminase and glutamine synthetase in cancer. Cancer Lett. 2019;467:29–39.
25. Reya T, Morrison SJ, Clarke MF, Weissman IL. Stem cells, cancer, and cancer stem cells. Nature. 2001;414:105–11.
26. Warburg O. On the origin of cancer cells. Science. 1956;123:309–14.
27. Pascale RM, Calvisi DF, Simile MM, Feo CF, Feo F. The Warburg effect 97 years after its discovery. Cancers (Basel). 2020;12:2819.
28. Vaupel P, Multhoff G. Revisiting the Warburg effect: historical dogma versus current understanding. J Physiol. 2021;599:1745–57.
29. Moreno-Sánchez R, Rodríguez-Enríquez S, Marín-Hernández A, Saavedra E. Energy metabolism in tumor cells. FEBS J. 2007;274:1393–418.
30. Bose S, Le A. Glucose metabolism in cancer. Adv Exp Med Biol. 2018;1063:3–12.
31. Bose S, Zhang C, Le A. Glucose metabolism in cancer: the Warburg effect and beyond. Adv Exp Med Biol. 2021;1311:3–15.
32. Qin C, Yang G, Yang J, Ren B, Wang H, Chen G, Zhao F, You L, Wang W, Zhao Y. Metabolism of pancreatic cancer: paving the way to better anticancer strategies. Mol Cancer. 2020;19:50.
33. Heydarzadeh S, Moshtaghie AA, Daneshpoor M, Hedayati M. Regulators of glucose uptake in thyroid cancer cell lines. Cell Commun Signal. 2020;18:83.
34. Shi Y, Liu S, Ahmad S, Gao Q. Targeting key transporters in tumor glycolysis as a novel anticancer strategy. Curr Top Med Chem. 2018;18:454–66.
35. Adekola K, Rosen ST, Shanmugam M. Glucose transporters in cancer metabolism. Curr Opin Oncol. 2012;24:650–4.
36. Meziou S, Ringuette Goulet C, Hovington H, Lefebvre V, Lavallée É, Bergeron M, Brisson H, Champagne A, Neveu B, Lacombe D, et al. GLUT1 expression in high-risk prostate cancer: correlation with (18) F-FDG-PET/CT and clinical outcome. Prostate Cancer Prostatic Dis. 2020;23:441–8.
37. Cho H, Lee YS, Kim J, Chung JY, Kim JH. Overexpression of glucose transporter-1 (GLUT-1) predicts poor prognosis in epithelial ovarian cancer. Cancer Invest. 2013;31:607–15.
38. Whitaker RM, Wills LP, Stallons LJ, Schnellmann RG. cGMP-selective phosphodiesterase inhibitors stimulate mitochondrial biogenesis and promote recovery from acute kidney injury. J Pharmacol Exp Ther. 2013;347:626–34.

39. Gonzalez-Menendez P, Hevia D, Alonso-Arias R, Alvarez-Artime A, Rodriguez-Garcia A, Kinet S, Gonzalez-Pola I, Taylor N, Mayo JC, Sainz RM. GLUT1 protects prostate cancer cells from glucose deprivation-induced oxidative stress. Redox Biol. 2018;17:112–27.
40. Kunkel M, Reichert TE, Benz P, Lehr HA, Jeong JH, Wieand S, Bartenstein P, Wagner W, Whiteside TL. Overexpression of Glut-1 and increased glucose metabolism in tumors are associated with a poor prognosis in patients with oral squamous cell carcinoma. Cancer. 2003;97:1015–24.
41. Kawamura T, Kusakabe T, Sugino T, Watanabe K, Fukuda T, Nashimoto A, Honma K, Suzuki T. Expression of glucose transporter-1 in human gastric carcinoma: association with tumor aggressiveness, metastasis, and patient survival. Cancer. 2001;92:634–41.
42. Chen JQ, Russo J. Dysregulation of glucose transport, glycolysis, TCA cycle and glutaminolysis by oncogenes and tumor suppressors in cancer cells. Biochim Biophys Acta. 2012;1826:370–84.
43. Bongiovanni M, Paone G, Ceriani L, Pusztaszeri MJC, Imaging T. Cellular and molecular basis for thyroid cancer imaging in nuclear medicine. Clin Transl Imaging. 2013;1:149–61.
44. Grabellus F, Nagarajah J, Bockisch A, Schmid KW, Sheu SY. Glucose transporter 1 expression, tumor proliferation, and iodine/glucose uptake in thyroid cancer with emphasis on poorly differentiated thyroid carcinoma. Clin Nucl Med. 2012;37:121–7.
45. Haber RS, Weiser KR, Pritsker A, Reder I, Burstein DE. GLUT1 glucose transporter expression in benign and malignant thyroid nodules. Thyroid. 1997;7:363–7.
46. Liu L, Qi L, Knifley T, Piecoro DW, Rychahou P, Liu J, Mitov MI, Martin J, Wang C, Wu J, et al. S100A4 alters metabolism and promotes invasion of lung cancer cells by up-regulating mitochondrial complex I protein NDUFS2. J Biol Chem. 2019;294:7516–27.
47. Sokolov SS, Balakireva AV, Markova OV, Severin FF. Negative feedback of glycolysis and oxidative phosphorylation: mechanisms of and reasons for it. Biochemistry (Mosc). 2015;80:559–64.
48. Warburg O, Wind F, Negelein E. The metabolism of tumors in the body. J Gen Physiol. 1927;8:519–30.
49. Mazurek S. Pyruvate kinase M2: a key enzyme of the tumor metabolome and its medical relevance. Br J Nutr. 2012;23:133–41.
50. Luo W, Semenza GL. Pyruvate kinase M2 regulates glucose metabolism by functioning as a coactivator for hypoxia-inducible factor 1 in cancer cells. Oncotarget. 2011;2:551–6.
51. Zahra K, Dey T, Mishra SP, Pandey U. Pyruvate Kinase M2 and cancer: the role of PKM2 in promoting tumorigenesis. Front Oncol. 2020;10:159.
52. Amin S, Yang P, Li Z. Pyruvate kinase M2: a multifarious enzyme in non-canonical localization to promote cancer progression. Biochim Biophys Acta Rev Cancer. 2019;1871:331–41.
53. Wang C, Zhang S, Liu J, Tian Y, Ma B, Xu S, Fu Y, Luo Y. Secreted pyruvate kinase M2 promotes lung cancer metastasis through activating the integrin beta1/FAK signaling pathway. Cell Rep. 2020;30:1780-1797.e1786.
54. Ye J, Mancuso A, Tong X, Ward PS, Fan J, Rabinowitz JD, Thompson CB. Pyruvate kinase M2 promotes de novo serine synthesis to sustain mTORC1 activity and cell proliferation. Proc Natl Acad Sci USA. 2012;109:6904–9.
55. Yang M, Vousden KH. Serine and one-carbon metabolism in cancer. Nat Rev Cancer. 2016;16:650–62.
56. Shulman RG, Rothman DL. The glycogen shunt maintains glycolytic homeostasis and the Warburg effect in cancer. Trends Cancer. 2017;3:761–7.
57. Dayton TL, Jacks T, Vander Heiden MG. PKM2, cancer metabolism, and the road ahead. EMBO Rep. 2016;17:1721–30.
58. Hsu MC, Hung WC. Pyruvate kinase M2 fuels multiple aspects of cancer cells: from cellular metabolism, transcriptional regulation to extracellular signaling. Mol Cancer. 2018;17:35.
59. Zhu S, Guo Y, Zhang X, Liu H, Yin M, Chen X, Peng C. Pyruvate kinase M2 (PKM2) in cancer and cancer therapeutics. Cancer Lett. 2021;503:240–8.
60. Feng C, Gao Y, Wang C, Yu X, Zhang W, Guan H, Shan Z, Teng W. Aberrant overexpression of pyruvate kinase M2 is associated with aggressive tumor features and the BRAF mutation in papillary thyroid cancer. J Clin Endocrinol Metab. 2013;98:E1524-1533.
61. Liu B, Song M, Qin H, Zhang B, Liu Y, Sun Y, Ma Y, Shi T. Phosphoribosyl pyrophosphate amidotransferase promotes the progression of thyroid cancer via regulating pyruvate kinase M2. Onco Targets Ther. 2020;13:7629–39.
62. Zheng B, Geng L, Zeng L, Liu F, Huang Q. AKT2 contributes to increase ovarian cancer cell migration and invasion through the AKT2-PKM2-STAT3/NF-κB axis. Cell Signal. 2018;45:122–31.
63. Wang B, Liu S, Fan B, Xu X, Chen Y, Lu R, Xu Z, Liu X. PKM2 is involved in neuropathic pain by regulating ERK and STAT3 activation in rat spinal cord. J Headache Pain. 2018;19:7.
64. Strickaert A, Corbet C, Spinette SA, Craciun L, Dom G, Andry G, Larsimont D, Wattiez R, Dumont JE, Feron O, Maenhaut C. Reprogramming of energy metabolism: increased expression and roles of pyruvate carboxylase in papillary thyroid cancer. Thyroid. 2019;29:845–57.
65. Liu C, Zhou X, Pan Y, Liu Y, Zhang Y. Pyruvate carboxylase promotes thyroid cancer aggressiveness through fatty acid synthesis. BMC Cancer. 2021;21:722.
66. Certo M, Tsai CH, Pucino V, Ho PC, Mauro C. Lactate modulation of immune responses in inflammatory versus tumour microenvironments. Nat Rev Immunol. 2021;21:151–61.
67. Wellen KE, Thompson CB. A two-way street: reciprocal regulation of metabolism and signalling. Nat Rev Mol Cell Biol. 2012;13:270–6.
68. Kishton RJ, Sukumar M, Restifo NP. Metabolic regulation of T cell longevity and function in tumor immunotherapy. Cell Metab. 2017;26:94–109.
69. Lee LJ, Papadopoli D, Jewer M, Del Rincon S, Topisirovic I, Lawrence MG, Postovit LM. Cancer plasticity: the role of mRNA translation. Trends Cancer. 2021;7:134–45.
70. Icard P, Shulman S, Farhat D, Steyaert JM, Alifano M, Lincet H. How the Warburg effect supports aggressiveness and drug resistance of cancer cells? Drug Resist Updat. 2018;38:1–11.
71. Brand A, Singer K, Koehl GE, Kolitzus M, Schoenhammer G, Thiel A, Matos C, Bruss C, Klobuch S, Peter K, et al. LDHA-associated lactic acid production blunts tumor immunosurveillance by T and NK cells. Cell Metab. 2016;24:657–71.
72. Peng M, Yin N, Chhangawala S, Xu K, Leslie CS, Li MO. Aerobic glycolysis promotes T helper 1 cell differentiation through an epigenetic mechanism. Science. 2016;354:481–4.
73. Kurpińska A, Suraj J, Bonar E, Zakrzewska A, Stojak M, Sternak M, Jasztal A, Walczak M. Proteomic characterization of early lung response to breast cancer metastasis in mice. Exp Mol Pathol. 2019;107:129–40.
74. Mishra D, Banerjee DJC. Lactate dehydrogenases as metabolic links between tumor and stroma in the tumor microenvironment. Cancers (Basel). 2019;11:750.
75. Wang JM, Jiang JY, Zhang DL, Du X, Wu T, Du ZX. HYOU1 facilitates proliferation, invasion and glycolysis of papillary thyroid cancer via stabilizing LDHB mRNA. J Cell Mol Med. 2021;25:4814–25.
76. San-Millán I, Brooks GA. Reexamining cancer metabolism: lactate production for carcinogenesis could be the purpose and explanation of the Warburg effect. Carcinogenesis. 2017;38:119–33.
77. Lis P, Dyląg M, Niedźwiecka K, Ko YH, Pedersen PL, Goffeau A, Ułaszewski S. The HK2 dependent "Warburg effect" and mitochondrial oxidative phosphorylation in cancer: targets for effective therapy with 3-bromopyruvate. Molecules. 2016;21:1730.
78. Lebelo MT, Joubert AM, Visagie MH. Warburg effect and its role in tumourigenesis. Arch Pharm Res. 2019;42:833–47.
79. Gottfried E, Kunz-Schughart LA, Ebner S, Mueller-Klieser W, Hoves S, Andreesen R, Mackensen A, Kreutz M. Tumor-derived lactic acid modulates dendritic cell activation and antigen expression. Blood. 2006;107:2013–21.
80. Xia H, Wang W, Crespo J, Kryczek I, Li W, Wei S, Bian Z, Maj T, He M, Liu RJ, et al. Suppression of FIP200 and autophagy by tumor-derived lactate promotes naïve T cell apoptosis and affects tumor immunity. Sci Immunol. 2017;2:eaan4631.
81. Zhao B, Aggarwal A, Im SY, Viswanathan K, Landa I, Nehs MA. Effect of lactate export inhibition on anaplastic thyroid cancer growth and metabolism. J Am Coll Surg. 2022;234:1044–50.
82. Hoxhaj G, Manning BD. The PI3K-AKT network at the interface of oncogenic signalling and cancer metabolism. Nat Rev Cancer. 2020;20:74–88.
83. DeBerardinis RJ, Lum JJ, Hatzivassiliou G, Thompson CB. The biology of cancer: metabolic reprogramming fuels cell growth and proliferation. Cell Metab. 2008;7:11–20.

84. Osthus RC, Shim H, Kim S, Li Q, Reddy R, Mukherjee M, Xu Y, Wonsey D, Lee LA, Dang CV. Deregulation of glucose transporter 1 and glycolytic gene expression by c-Myc. J Biol Chem. 2000;275:21797–800.
85. Abbaszadeh Z, Çeşmeli S, Biray Avcı Ç. Crucial players in glycolysis: cancer progress. Gene. 2020;726: 144158.
86. Boedtkjer E, Pedersen SF. The acidic tumor microenvironment as a driver of cancer. Annu Rev Physiol. 2020;82:103–26.
87. Epstein T, Gatenby RA, Brown JS. The Warburg effect as an adaptation of cancer cells to rapid fluctuations in energy demand. PLoS ONE. 2017;12(9): e0185085.
88. Zhang X, Ai Z, Chen J, Yi J, Liu Z, Zhao H, Wei H. Glycometabolic adaptation mediates the insensitivity of drug-resistant K562/ADM leukaemia cells to adriamycin via the AKT-mTOR/c-Myc signalling pathway. Mol Med Rep. 2017;15:1869–76.
89. Ferro F, Servais S, Besson P, Roger S, Dumas JF, Brisson L. Autophagy and mitophagy in cancer metabolic remodelling. Semin Cell Dev Biol. 2020;98:129–38.
90. Du J, Liu J, Smith BJ, Tsao MS, Cullen JJ. Role of Rac1-dependent NADPH oxidase in the growth of pancreatic cancer. Cancer Gene Ther. 2011;18:135–43.
91. Bisevac JP, Djukic M, Stanojevic I, Stevanovic I, Mijuskovic Z, Djuric A, Gobeljic B, Banovic T, Vojvodic D. Association between oxidative stress and melanoma progression. J Med Biochem. 2018;37:12–20.
92. Zhao B, Aggarwal A, Marshall JA, Barletta JA, Kijewski MF, Lorch JH, Nehs MA. Glycolytic inhibition with 3-bromopyruvate suppresses tumor growth and improves survival in a murine model of anaplastic thyroid cancer. Surgery. 2021. https://doi.org/10.1016/j.surg.2021.05.055.
93. Nagarajah J, Le M, Knauf JA, Ferrandino G, Montero-Conde C, Pillarsetty N, Bolaender A, Irwin C, Krishnamoorthy GP, Saqcena M, et al. Sustained ERK inhibition maximizes responses of BrafV600E thyroid cancers to radioiodine. J Clin Invest. 2016;126:4119–24.
94. Younis E. Oncogenesis of thyroid cancer. Asian Pac J Cancer Prev. 2017;18(5):1191.
95. Kumar SM, Yu H, Edwards R, Chen L, Kazianis S, Brafford P, Acs G, Herlyn M, Xu X. Mutant V600E BRAF increases hypoxia inducible factor-1alpha expression in melanoma. Cancer Res. 2007;67:3177–84.
96. Haq R, Fisher DE, Widlund HR. Molecular pathways: BRAF induces bioenergetic adaptation by attenuating oxidative phosphorylation. Clin Cancer Res. 2014;20:2257–63.
97. Sandulache VC, Skinner HD, Wang Y, Chen Y, Dodge CT, Ow TJ, Bankson JA, Myers JN, Lai SY. Glycolytic inhibition alters anaplastic thyroid carcinoma tumor metabolism and improves response to conventional chemotherapy and radiation. Mol Cancer Ther. 2012;11:1373–80.
98. Li Y, Qin J, He Z, Cui G, Zhang K, Wu B. Knockdown of circPUM1 impedes cell growth, metastasis and glycolysis of papillary thyroid cancer via enhancing MAPK1 expression by serving as the sponge of miR-21-5p. Genes Genomics. 2021;43:141–50.
99. Milosevic Z, Pesic M, Stankovic T, Dinic J, Milovanovic Z, Stojsic J, Dzodic R, Tanic N, Bankovic J. Targeting RAS-MAPK-ERK and PI3K-AKT-mTOR signal transduction pathways to chemosensitize anaplastic thyroid carcinoma. Transl Res. 2014;164:411–23.
100. Gao Y, Yang F, Yang XA, Zhang L, Yu H, Cheng X, Xu S, Pan J, Wang K, Li P. Mitochondrial metabolism is inhibited by the HIF1α-MYC-PGC-1β axis in BRAF V600E thyroid cancer. FEBS j. 2019;286:1420–36.
101. Wang HM, Huang YW, Huang JS, Wang CH, Kok VC, Hung CM, Chen HM, Tzen CY. Anaplastic carcinoma of the thyroid arising more often from follicular carcinoma than papillary carcinoma. Ann Surg Oncol. 2007;14:3011–8.
102. Liu Z, Hou P, Ji M, Guan H, Studeman K, Jensen K, Vasko V, El-Naggar AK, Xing M. Highly prevalent genetic alterations in receptor tyrosine kinases and phosphatidylinositol 3-kinase/akt and mitogen-activated protein kinase pathways in anaplastic and follicular thyroid cancers. J Clin Endocrinol Metab. 2008;93:3106–16.
103. Smallridge RC, Copland JA. Anaplastic thyroid carcinoma: pathogenesis and emerging therapies. Clin Oncol (R Coll Radiol). 2010;22:486–97.
104. Agrawal N, Akbani R, Aksoy BA, Ally A, Arachchi H, Asa SL, Auman JT, Balasundaram M, Balu S, Baylin SB. Integrated genomic characterization of papillary thyroid carcinoma. Cell. 2014;159:676–90.
105. Liu R, Chen Y, Liu G, Li C, Song Y, Cao Z, Li W, Hu J, Lu C, Liu Y. PI3K/AKT pathway as a key link modulates the multidrug resistance of cancers. Cell Death Dis. 2020;11:797.
106. Jiang W, Zhu Z, Thompson HJ. Effects of limiting energy availability via diet and physical activity on mammalian target of rapamycin-related signaling in rat mammary carcinomas. Carcinogenesis. 2013;34:378–87.
107. 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. 2011;108:4129–34.
108. Fan H, Wu Y, Yu S, Li X, Wang A, Wang S, Chen W, Lu Y. Critical role of mTOR in regulating aerobic glycolysis in carcinogenesis. Int J Oncol. 2021;58:9–19.
109. Liotti F, Kumar N, Prevete N, Marotta M, Sorriento D, Ieranò C, Ronchi A, Marino FZ, Moretti S, Colella R, et al. PD-1 blockade delays tumor growth by inhibiting an intrinsic SHP2/Ras/MAPK signalling in thyroid cancer cells. J Exp Clin Cancer Res. 2021;40:22.
110. Saji M, Ringel MD. The PI3K-Akt-mTOR pathway in initiation and progression of thyroid tumors. Mol Cell Endocrinol. 2010;321:20–8.
111. Jin N, Jiang T, Rosen DM, Nelkin BD, Ball DW. Dual inhibition of mitogen-activated protein kinase kinase and mammalian target of rapamycin in differentiated and anaplastic thyroid cancer. J Clin Endocrinol Metab. 2009;94:4107–12.
112. Liu D, Xing M. Potent inhibition of thyroid cancer cells by the MEK inhibitor PD0325901 and its potentiation by suppression of the PI3K and NF-kappaB pathways. Thyroid. 2008;18:853–64.
113. Glassmann A, Winter J, Kraus D, Veit N, Probstmeier R. Pharmacological suppression of the Ras/MAPK pathway in thyroid carcinoma cells can provoke opposite effects on cell migration and proliferation: the appearance of yin-yang effects and the need of combinatorial treatments. Int J Oncol. 2014;45:2587–95.
114. Lyssiotis CA, Kimmelman AC. Metabolic interactions in the tumor microenvironment. Trends Cell Biol. 2017;27:863–75.
115. Gatenby RA, Gillies RJ. Why do cancers have high aerobic glycolysis? Nat Rev Cancer. 2004;4:891–9.
116. Huo N, Cong R, Sun ZJ, Li WC, Zhu X, Xue CY, Chen Z, Ma LY, Chu Z, Han YC, et al. STAT3/LINC00671 axis regulates papillary thyroid tumor growth and metastasis via LDHA-mediated glycolysis. Cell Death Dis. 2021;12:799.
117. Cai H, Li J, Zhang Y, Liao Y, Zhu Y, Wang C, Hou J. LDHA promotes oral squamous cell carcinoma progression through facilitating glycolysis and epithelial-mesenchymal transition. Front Oncol. 2019;9:1446.
118. Ban EJ, Kim D, Kim JK, Kang SW, Lee J, Jeong JJ, Nam KH, Chung WY, Kim K. Lactate dehydrogenase A as a potential new biomarker for thyroid cancer. Endocrinol Metab (Seoul). 2021;36:96–105.
119. Cardone RA, Alfarouk KO, Elliott RL, Alqahtani SS, Ahmed SB, Aljarbou AN, Greco MR, Cannone S, Reshkin SJ. The role of sodium hydrogen exchanger 1 in dysregulation of proton dynamics and reprogramming of cancer metabolism as a sequela. Int J Mol Sci. 2019;20:3694.
120. Fanelli A, Grollman EF, Wang D, Philp NJ. MCT1 and its accessory protein CD147 are differentially regulated by TSH in rat thyroid cells. Am J Physiol Endocrinol Metab. 2003;285:E1223-1229.
121. Singh M, Afonso J, Sharma D, Gupta R, Kumar V, Rani R, Baltazar F, Kumar V. Targeting monocarboxylate transporters (MCTs) in cancer: how close are we to the clinics? Semin Cancer Biol. 2023. https://doi.org/10.1016/j.semcancer.2023.01.007.
122. Cassim S, Pouyssegur J. Tumor microenvironment: a metabolic player that shapes the immune response. Int J Mol Sci. 2019;21:157.
123. Xia A, Wu Y. Joint interactions of carbon and nitrogen metabolism dominated by bicarbonate and nitrogen in *Orychophragmus violaceus* and *Brassica napus* under simulated karst habitats. BMC Plant Biol. 2022;22:264.
124. Park HJ, Lyons JC, Ohtsubo T, Song CW. Acidic environment causes apoptosis by increasing caspase activity. Br J Cancer. 1999;80:1892–7.
125. Maiuri MC, Tasdemir E, Criollo A, Morselli E, Vicencio JM, Carnuccio R, Kroemer G. Control of autophagy by oncogenes and tumor suppressor genes. Cell Death Differ. 2009;16:87–93.
126. Kierans SJ, Taylor CT. Regulation of glycolysis by the hypoxia-inducible factor (HIF): implications for cellular physiology. J Physiol. 2021;599:23–37.
127. Zheng T, Jäättelä M, Liu B. pH gradient reversal fuels cancer progression. Int J Biochem Cell Biol. 2020;125: 105796.
128. Niu D, Luo T, Wang H, Xia Y, Xie Z. Lactic acid in tumor invasion. Clin Chim Acta. 2021;522:61–9.

129. Kato Y, Ozawa S, Miyamoto C, Maehata Y, Suzuki A, Maeda T, Baba Y. Acidic extracellular microenvironment and cancer. Cancer Cell Int. 2013;13:89.
130. Chang CH, Qiu J, O'Sullivan D, Buck MD, Noguchi T, Curtis JD, Chen Q, Gindin M, Gubin MM, van der Windt GJ, et al. Metabolic competition in the tumor microenvironment is a driver of cancer progression. Cell. 2015;162:1229–41.
131. El Hassouni B, Granchi C, Vallés-Martí A, Supadmanaba IGP, Bononi G, Tuccinardi T, Funel N, Jimenez CR, Peters GJ, Giovannetti E, Minutolo F. The dichotomous role of the glycolytic metabolism pathway in cancer metastasis: interplay with the complex tumor microenvironment and novel therapeutic strategies. Semin Cancer Biol. 2020;60:238–48.
132. Bettum IJ, Gorad SS, Barkovskaya A, Pettersen S, Moestue SA, Vasiliauskaite K, Tenstad E, Øyjord T, Risa Ø, Nygaard V, et al. Metabolic reprogramming supports the invasive phenotype in malignant melanoma. Cancer Lett. 2015;366:71–83.
133. Yang J, Ren B, Yang G, Wang H, Chen G, You L, Zhang T, Zhao Y. The enhancement of glycolysis regulates pancreatic cancer metastasis. Cell Mol Life Sci. 2020;77:305–21.
134. Clambey ET, McNamee EN, Westrich JA, Glover LE, Campbell EL, Jedlicka P, de Zoeten EF, Cambier JC, Stenmark KR, Colgan SP, Eltzschig HK. Hypoxia-inducible factor-1 alpha-dependent induction of FoxP3 drives regulatory T-cell abundance and function during inflammatory hypoxia of the mucosa. Proc Natl Acad Sci USA. 2012;109:E2784-2793.
135. Fong GH, Takeda K. Role and regulation of prolyl hydroxylase domain proteins. Cell Death Differ. 2008;15:635–41.
136. Sasidharan Nair V, Saleh R, Toor SM, Cyprian FS, Elkord E. Metabolic reprogramming of T regulatory cells in the hypoxic tumor microenvironment. Cancer Immunol Immunother. 2021;70:2103–21.
137. Beckert S, Farrahi F, Aslam RS, Scheuenstuhl H, Königsrainer A, Hussain MZ, Hunt TK. Lactate stimulates endothelial cell migration. Wound Repair Regen. 2006;14:321–4.
138. Valastyan S, Weinberg RA. Tumor metastasis: molecular insights and evolving paradigms. Cell. 2011;147:275–92.
139. Lambert AW, Pattabiraman DR, Weinberg RA. Emerging biological principles of metastasis. Cell. 2017;168:670–91.
140. van Zijl F, Krupitza G, Mikulits W. Initial steps of metastasis: cell invasion and endothelial transmigration. Mutat Res. 2011;728:23–34.
141. Ye X, Weinberg RA. Epithelial-mesenchymal plasticity: a central regulator of cancer progression. Trends Cell Biol. 2015;25:675–86.
142. Lamouille S, Xu J, Derynck R. Molecular mechanisms of epithelial-mesenchymal transition. Nat Rev Mol Cell Biol. 2014;15:178–96.
143. Thews O, Riemann A. Tumor pH and metastasis: a malignant process beyond hypoxia. Cancer Metastasis Rev. 2019;38:113–29.
144. Spiegel A, Brooks MW, Houshyar S, Reinhardt F, Ardolino M, Fessler E, Chen MB, Krall JA, DeCock J, Zervantonakis IK, et al. Neutrophils suppress intraluminal NK cell-mediated tumor cell clearance and enhance extravasation of disseminated carcinoma cells. Cancer Discov. 2016;6:630–49.
145. Schmid KW. Lymph node and distant metastases of thyroid gland cancer. Metastases in the thyroid glands. Pathologe. 2015;36(Suppl 2):171–5.
146. Hirsch D, Levy S, Tsvetov G, Gorshtein A, Slutzky-Shraga I, Akirov A, Robenshtok E, Shimon I, Benbassat CA. Long-term outcomes and prognostic factors in patients with differentiated thyroid cancer and distant metastases. Endocr Pract. 2017;23:1193–200.
147. Hou XM, Yuan SQ, Zhao D, Liu XJ, Wu XA. LDH-A promotes malignant behavior via activation of epithelial-to-mesenchymal transition in lung adenocarcinoma. Biosci Rep. 2019;39:BSR20181476.
148. Wang J, Ye C, Chen C, Xiong H, Xie B, Zhou J, Chen Y, Zheng S, Wang L. Glucose transporter GLUT1 expression and clinical outcome in solid tumors: a systematic review and meta-analysis. Oncotarget. 2017;8:16875–86.
149. Zhang B, Xie Z, Li B. The clinicopathologic impacts and prognostic significance of GLUT1 expression in patients with lung cancer: a meta-analysis. Gene. 2019;689:76–83.
150. Zhang JZ, Behrooz A, Ismail-Beigi F. Regulation of glucose transport by hypoxia. Am J Kidney Dis. 1999;34:189–202.
151. Chen J, Jiang CC, Jin L, Zhang XD. Regulation of PD-L1: a novel role of pro-survival signalling in cancer. Ann Oncol. 2016;27:409–16.
152. Ruf M, Moch H, Schraml P. PD-L1 expression is regulated by hypoxia inducible factor in clear cell renal cell carcinoma. Int J Cancer. 2016;139:396–403.
153. Mihailovic J, Killeen RP, Duignan JA. PET/CT variants and pitfalls in head and neck cancers including thyroid cancer. Semin Nucl Med. 2021;51:419–40.
154. Dohán O, Carrasco N. Advances in Na(+)/I(−) symporter (NIS) research in the thyroid and beyond. Mol Cell Endocrinol. 2003;213:59–70.
155. Garcia D, Singh V. Nuclear medicine PET/CT thyroid cancer assessment, protocols, and interpretation. In: StatPearls. Treasure Island (FL): StatPearls Publishing Copyright © 2021, StatPearls Publishing LLC.; 2021.
156. Duarte PS, Marin JFG, de Carvalho JWA, Sapienza MT, Buchpiguel CA. Iodine/FDG "flip-flop" phenomenon inside a large metastatic thyroid cancer lesion better characterized on SPECT/CT and PET/CT studies. Clin Nucl Med. 2018;43:436–8.
157. Hitu L, Cainap C, Apostu D, Gabora K, Bonci EA, Badan M, Mester A, Piciu A. Skeletal muscle metastasis in papillary thyroid microcarcinoma evaluated by F18-FDG PET/CT. Diagnostics (Basel). 2020;10:100.
158. Wartski M, Sauvanet A. 18F-FDG PET/CT in pancreatic adenocarcinoma: a role at initial imaging staging? Diagn Interv Imaging. 2019;100:735–41.
159. Kukulska A, Krajewska J, Kołosza Z, Paliczka-Cies Lik E, Puch Z, Gubała E, Król A, Kalemba M, Kropin Ska A, Jarząb B. The role of FDG-PET in localization of recurrent lesions of differentiated thyroid cancer (DTC) in patients with asymptomatic hyperthyroglobulinemia in a real clinical practice. Eur J Endocrinol. 2016;175:379–85.
160. Zhang Y, Zhao H, Liu Y, Zeng M, Zhang J, Hao D. Diagnostic performance of dynamic contrast-enhanced MRI and (18)F-FDG PET/CT for evaluation of soft tissue tumors and correlation with pathology parameters. Acad Radiol. 2022;29:1842–51.
161. de Koster EJ, Noortman WA, Mostert JM, Booij J, Brouwer CB, de Keizer B, de Klerk JMH, Oyen WJG, van Velden FHP, de Geus-Oei LF, Vriens D. Quantitative classification and radiomics of [(18)F]FDG-PET/CT in indeterminate thyroid nodules. Eur J Nucl Med Mol Imaging. 2022;49:2174–88.
162. Zampella E, Klain M, Pace L, Cuocolo A. PET/CT in the management of differentiated thyroid cancer. Diagn Interv Imaging. 2021;102:515–23.
163. Kim DH, Kim SJ. Diagnostic role of F-18 FDG PET/CT for preoperative lymph node staging in thyroid cancer patients; a systematic review and meta analysis. Clin Imaging. 2020;65:100–7.
164. Luster M, Aktolun C, Amendoeira I, Barczyński M, Bible KC, Duntas LH, Elisei R, Handkiewicz-Junak D, Hoffmann M, Jarząb B, et al. European perspective on 2015 American thyroid association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: an interactive international symposium. Thyroid. 2019;29:7–26.
165. Mu X, Huang X, Jiang Z, Li M, Jia L, Lv Z, Fu W, Mao J. [(18)F]FAPI-42 PET/CT in differentiated thyroid cancer: diagnostic performance, uptake values, and comparison with 2-[(18)F]FDG PET/CT. Eur J Nucl Med Mol Imaging. 2023;50:1205–15.
166. Lebbink CA, de Vries LH, Borel Rinkes IHM, Braat A, van Leeuwaarde RS, Lodewijk L, van Treijen MJC, Vriens MR, Valk GD, van Santen HM, de Keizer B. FDG PET/CT in differentiated thyroid cancer patients with low thyroglobulin levels. Eur J Endocrinol. 2022;187:101–10.
167. Stecco A, Trisoglio A, Soligo E, Berardo S, Sukhovei L, Carriero A. Whole-body MRI with diffusion-weighted imaging in bone metastases: a narrative review. Diagnostics (Basel). 2018;8:45.
168. Klain M, Nappi C, Nicolai E, Romeo V, Piscopo L, Giordano A, Gaudieri V, Zampella E, Pace L, Carlo C, et al. Comparison of simultaneous (18)F-2-[18F] FDG PET/MR and PET/CT in the follow-up of patients with differentiated thyroid cancer. Eur J Nucl Med Mol Imaging. 2020;47:3066–73.
169. Alavi A, Saboury B, Nardo L, Zhang V, Wang M, Li H, Raynor WY, Werner TJ, Høilund-Carlsen PF, Revheim ME. Potential and most relevant applications of total body PET/CT imaging. Clin Nucl Med. 2022;47:43–55.
170. Shao C, Li Z, Zhang C, Zhang W, He R, Xu J, Cai Y. Optical diagnostic imaging and therapy for thyroid cancer. Mater Today Bio. 2022;17:100441.
171. Alzahrani AS. Metabolism: Clinical use of molecular data in thyroid nodules and cancer. J Clin Endocrinol Metab. 2023. https://doi.org/10.1210/clinem/dgad282.
172. Pfeiffer T, Schuster S, Bonhoeffer S. Cooperation and competition in the evolution of ATP-producing pathways. Science. 2001;292:504–7.

173. Macheda ML, Rogers S, Best JD. Molecular and cellular regulation of glucose transporter (GLUT) proteins in cancer. J Cell Physiol. 2005;202:654–62.
174. Sammarco G, Varricchi G, Ferraro V, Ammendola M, De Fazio M, Altomare DF, Luposella M, Maltese L, Currò G, Marone G, et al. Mast cells, angiogenesis and lymphangiogenesis in human gastric cancer. Int J Mol Sci. 2019;20:2106.
175. Karaman S, Detmar M. Mechanisms of lymphatic metastasis. J Clin Invest. 2014;124:922–8.
176. Gulubova M, Ivanova K, Ananiev J, Gerenova J, Zdraveski A, Stoyanov H, Vlaykova T. VEGF expression, microvessel density and dendritic cell decrease in thyroid cancer. Biotechnol Biotechnol Equip. 2014;28:508–17.
177. Varricchi G, Granata F, Loffredo S, Genovese A, Marone G. Angiogenesis and lymphangiogenesis in inflammatory skin disorders. J Am Acad Dermatol. 2015;73:144–53.
178. Loffredo S, Borriello F, Iannone R, Ferrara AL, Galdiero MR, Gigantino V, Esposito P, Varricchi G, Lambeau G, Cassatella MA, et al. Group V secreted phospholipase A(2) induces the release of proangiogenic and antiangiogenic factors by human neutrophils. Front Immunol. 2017;8:443.
179. Valerio L, Pieruzzi L, Giani C, Agate L, Bottici V, Lorusso L, Cappagli V, Puleo L, Matrone A, Viola D, et al. Targeted therapy in thyroid cancer: state of the art. Clin Oncol (R Coll Radiol). 2017;29:316–24.
180. Capp C, Wajner SM, Siqueira DR, Brasil BA, Meurer L, Maia AL. Increased expression of vascular endothelial growth factor and its receptors, VEGFR-1 and VEGFR-2, in medullary thyroid carcinoma. Thyroid. 2010;20:863–71.
181. Samimi H, Fallah P, Naderi Sohi A, Tavakoli R, Naderi M, Soleimani M, Larijani B, Haghpanah V. Precision medicine approach to anaplastic thyroid cancer: advances in targeted drug therapy based on specific signaling pathways. Acta Med Iran. 2017;55:200–8.
182. Schlumberger MJ, Elisei R, Bastholt L, Wirth LJ, Martins RG, Locati LD, Jarzab B, Pacini F, Daumerie C, Droz JP, et al. Phase II study of safety and efficacy of motesanib in patients with progressive or symptomatic, advanced or metastatic medullary thyroid cancer. J Clin Oncol. 2009;27:3794–801.
183. Wells SA Jr, Gosnell JE, Gagel RF, Moley J, Pfister D, Sosa JA, Skinner M, Krebs A, Vasselli J, Schlumberger M. Vandetanib for the treatment of patients with locally advanced or metastatic hereditary medullary thyroid cancer. J Clin Oncol. 2010;28:767–72.
184. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, Pacini F, Randolph GW, Sawka AM, Schlumberger M, et al. 2015 American thyroid association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American thyroid association guidelines task force on thyroid nodules and differentiated thyroid cancer. Thyroid. 2016;26:1–133.
185. Motzer RJ, Jonasch E, Boyle S, Carlo MI, Manley B, Agarwal N, Alva A, Beckermann K, Choueiri TK, Costello BA, et al. NCCN guidelines insights: kidney cancer, version 1.2021. J Natl Compr Canc Netw. 2020;18:1160–70.
186. Fallahi P, Ferrari SM, Santini F, Corrado A, Materazzi G, Ulisse S, Miccoli P, Antonelli A. Sorafenib and thyroid cancer. BioDrugs. 2013;27:615–28.
187. Worden F, Fassnacht M, Shi Y, Hadjieva T, Bonichon F, Gao M, Fugazzola L, Ando Y, Hasegawa Y, Park DJ, et al. Safety and tolerability of sorafenib in patients with radioiodine-refractory thyroid cancer. Endocr Relat Cancer. 2015;22:877–87.
188. Ferrari SM, Centanni M, Virili C, Miccoli M, Ferrari P, Ruffilli I, Ragusa F, Antonelli A, Fallahi P. Sunitinib in the treatment of thyroid cancer. Curr Med Chem. 2019;26:963–72.
189. Kim DW, Jo YS, Jung HS, Chung HK, Song JH, Park KC, Park SH, Hwang JH, Rha SY, Kweon GR, et al. An orally administered multitarget tyrosine kinase inhibitor, SU11248, is a novel potent inhibitor of thyroid oncogenic RET/papillary thyroid cancer kinases. J Clin Endocrinol Metab. 2006;91:4070–6.
190. Carlomagno F, Vitagliano D, Guida T, Ciardiello F, Tortora G, Vecchio G, Ryan AJ, Fontanini G, Fusco A, Santoro M. ZD6474, an orally available inhibitor of KDR tyrosine kinase activity, efficiently blocks oncogenic RET kinases. Cancer Res. 2002;62:7284–90.
191. Nair A, Lemery SJ, Yang J, Marathe A, Zhao L, Zhao H, Jiang X, He K, Ladouceur G, Mitra AK, et al. FDA approval summary: lenvatinib for progressive, radio-iodine-refractory differentiated thyroid cancer. Clin Cancer Res. 2015;21:5205–8.
192. Fallahi P, Ferrari SM, Di Bari F, Materazzi G, Benvenga S, Miccoli P, Antonelli A. Cabozantinib in thyroid cancer. Recent Pat Anticancer Drug Discov. 2015;10:259–69.
193. Chau NG, Haddad RI. Vandetanib for the treatment of medullary thyroid cancer. Clin Cancer Res. 2023;19(3):524–9.
194. Brandenburg T, Tiedje V, Muchalla P, Theurer S, Weber F, Schmid KW, Dralle H, Führer D. Continued discontinuation of TKI treatment in medullary thyroid carcinoma—lessons from individual cases with long-term follow-up. Front Endocrinol (Lausanne). 2021;12: 718418.
195. Nylén C, Mechera R, Maréchal-Ross I, Tsang V, Chou A, Gill AJ, Clifton-Bligh RJ, Robinson BG, Sywak MS, Sidhu SB, Glover AR. Molecular markers guiding thyroid cancer management. Cancers (Basel). 2020;12:2164.
196. Ferrari SM, Ruffilli I, Centanni M, Virili C, Materazzi G, Alexopoulou M, Miccoli M, Antonelli A, Fallahi P. Lenvatinib in the therapy of aggressive thyroid cancer: state of the art and new perspectives with patents recently applied. Recent Pat Anticancer Drug Discov. 2018;13:201–8.
197. Enokida T, Tahara M. Management of VEGFR-targeted TKI for thyroid cancer. Cancers (Basel). 2021;13:5536.
198. Wang C, Li Y, Yan S, Wang H, Shao X, Xiao M, Yang B, Qin G, Kong R, Chen R, Zhang N. Interactome analysis reveals that lncRNA HULC promotes aerobic glycolysis through LDHA and PKM2. Nat Commun. 2020;11:3162.
199. Boudreau A, Purkey HE, Hitz A, Robarge K, Peterson D, Labadie S, Kwong M, Hong R, Gao M, Del Nagro C, et al. Metabolic plasticity underpins innate and acquired resistance to LDHA inhibition. Nat Chem Biol. 2016;12:779–86.
200. Pathria G, Scott DA, Feng Y, Sang Lee J, Fujita Y, Zhang G, Sahu AD, Ruppin E, Herlyn M, Osterman AL, Ronai ZA. Targeting the Warburg effect via LDHA inhibition engages ATF4 signaling for cancer cell survival. Embo J. 2018;37: e99735.
201. Kachel P, Trojanowicz B, Sekulla C, Prenzel H, Dralle H, Hoang-Vu C. Phosphorylation of pyruvate kinase M2 and lactate dehydrogenase A by fibroblast growth factor receptor 1 in benign and malignant thyroid tissue. BMC Cancer. 2015;15:140.
202. Hou X, Shi X, Zhang W, Li D, Hu L, Yang J, Zhao J, Wei S, Wei X, Ruan X, et al. LDHA induces EMT gene transcription and regulates autophagy to promote the metastasis and tumorigenesis of papillary thyroid carcinoma. Cell Death Dis. 2021;12:347.
203. Levy DE, Inghirami G. STAT3: a multifaceted oncogene. Proc Natl Acad Sci USA. 2006;103:10151–2.
204. Zhang J, Gill A, Atmore B, Johns A, Delbridge L, Lai R, McMullen T. Upregulation of the signal transducers and activators of transcription 3 (STAT3) pathway in lymphatic metastases of papillary thyroid cancer. Int J Clin Exp Pathol. 2011;4:356–62.
205. Jafary F, Ganjalikhany MR, Moradi A, Hemati M, Jafari S. Novel peptide inhibitors for lactate dehydrogenase A (LDHA): a survey to inhibit LDHA activity via disruption of protein-protein interaction. Sci Rep. 2019;9:4686.
206. Wang Z, Wang N, Liu P, Xie X. AMPK and cancer. Exp Suppl. 2016;107:203–26.
207. Souza EC, Ferreira AC, Carvalho DP. The mTOR protein as a target in thyroid cancer. Expert Opin Ther Targets. 2011;15:1099–112.
208. Mita MM, Mita A, Rowinsky EK. Mammalian target of rapamycin: a new molecular target for breast cancer. Clin Breast Cancer. 2003;4:126–37.
209. Elit L. CCI-779 Wyeth. Curr Opin Investig Drugs. 2002;3:1249–53.
210. Liu D, Hou P, Liu Z, Wu G, Xing M. Genetic alterations in the phosphoinositide 3-kinase/Akt signaling pathway confer sensitivity of thyroid cancer cells to therapeutic targeting of Akt and mammalian target of rapamycin. Cancer Res. 2009;69:7311–9.
211. Hanna GJ, Busaidy NL, Chau NG, Wirth LJ, Barletta JA, Calles A, Haddad RI, Kraft S, Cabanillas ME, Rabinowits GJ. Genomic correlates of response to everolimus in aggressive radioiodine-refractory thyroid cancer: a phase II study. Clin Cancer Res. 2018;24:1546–53.
212. Schneider TC, de Wit D, Links TP, van Erp NP, van der Hoeven JJM, Gelderblom H, Roozen ICFM, Bos M, Corver WE, van Wezel T, et al. Everolimus in patients with advanced follicular-derived thyroid cancer: results of a phase II clinical trial. J Clin Endocrinol Metab. 2016;102:698–707.

213. Furuya F, Lu C, Willingham MC, Cheng SY. Inhibition of phosphatidylinositol 3-kinase delays tumor progression and blocks metastatic spread in a mouse model of thyroid cancer. Carcinogenesis. 2007;28:2451–8.
214. Liu D, Xing J, Trink B, Xing M. BRAF mutation-selective inhibition of thyroid cancer cells by the novel MEK inhibitor RDEA119 and genetic-potentiated synergism with the mTOR inhibitor temsirolimus. Int J Cancer. 2010;127:2965–73.
215. Zhu X, Park S, Lee WK, Cheng SY. Potentiated anti-tumor effects of BETi by MEKi in anaplastic thyroid cancer. Endocr Relat Cancer. 2019;26:739–50.
216. Zaballos MA, Acuña-Ruiz A, Morante M, Crespo P, Santisteban P. Regulators of the RAS-ERK pathway as therapeutic targets in thyroid cancer. Endocr Relat Cancer. 2019;26:R319-r344.
217. Kurata K, Onoda N, Noda S, Kashiwagi S, Asano Y, Hirakawa K, Ohira M. Growth arrest by activated BRAF and MEK inhibition in human anaplastic thyroid cancer cells. Int J Oncol. 2016;49:2303–8.
218. Flaherty KT, Robert C, Hersey P, Nathan P, Garbe C, Milhem M, Demidov LV, Hassel JC, Rutkowski P, Mohr P, et al. Improved survival with MEK inhibition in BRAF-mutated melanoma. N Engl J Med. 2012;367:107–14.
219. Subbiah V, Baik C, Kirkwood JM. Clinical development of BRAF plus MEK inhibitor combinations. Trends Cancer. 2020;6:797–810.
220. Sabra MM, Dominguez JM, Grewal RK, Larson SM, Ghossein RA, Tuttle RM, Fagin JA. Clinical outcomes and molecular profile of differentiated thyroid cancers with radioiodine-avid distant metastases. J Clin Endocrinol Metab. 2013;98:E829-836.
221. Montero-Conde C, Ruiz-Llorente S, Dominguez JM, Knauf JA, Viale A, Sherman EJ, Ryder M, Ghossein RA, Rosen N, Fagin JA. Relief of feedback inhibition of HER3 transcription by RAF and MEK inhibitors attenuates their antitumor effects in BRAF-mutant thyroid carcinomas. Cancer Discov. 2013;3:520–33.
222. Laha D, Nilubol N, Boufraqech M. New therapies for advanced thyroid cancer. Front Endocrinol (Lausanne). 2020;11:82.
223. Brown SR, Hall A, Buckley HL, Flanagan L, Gonzalez de Castro D, Farnell K, Moss L, Gregory R, Newbold K, Du YJ. Investigating the potential clinical benefit of Selumetinib in resensitising advanced iodine refractory differentiated thyroid cancer to radioiodine therapy (SEL-I-METRY): protocol for a multicentre UK single arm phase II trial. BMC Cancer. 2019;19:1–10.
224. Aashiq M, Silverman DA, Na'ara S, Takahashi H, Amit M. Radioiodine-refractory thyroid cancer: molecular basis of redifferentiation therapies, management, and novel therapies. Cancers (Basel). 2019;11:1382.
225. Cheng L, Jin Y, Liu M, Ruan M, Chen L. HER inhibitor promotes BRAF/MEK inhibitor-induced redifferentiation in papillary thyroid cancer harboring BRAFV600E. Oncotarget. 2017;8:19843–54.
226. Turcotte LP, Richter EA, Kiens B. Increased plasma FFA uptake and oxidation during prolonged exercise in trained vs. untrained humans. Am J Physiol. 1992;262:E791-799.
227. Gohil K, Brooks GA. Exercise tames the wild side of the Myc network: a hypothesis. Am J Physiol Endocrinol Metab. 2012;303:E18-30.
228. Friedenreich CM, Orenstein MR. Physical activity and cancer prevention: etiologic evidence and biological mechanisms. J Nutr. 2002;132:3456s–64s.
229. Bellastella G, Scappaticcio L, Caiazzo F, Tomasuolo M, Carotenuto R, Caputo M, Arena S, Caruso P, Maiorino MI, Esposito K. Mediterranean diet and thyroid: an interesting alliance. Nutrients. 2022;14:4130.
230. Aggarwal A, Yuan Z, Barletta JA, Lorch JH, Nehs MA. Ketogenic diet combined with antioxidant N-acetylcysteine inhibits tumor growth in a mouse model of anaplastic thyroid cancer. Surgery. 2020;167:87–93.
231. Tella SH, Kommalapati A, Esquivel MA, Correa R. Potential role of metabolic intervention in the management of advanced differentiated thyroid cancer. Front Oncol. 2017;7:160.
232. Sowah SA, Milanese A, Schübel R, Wirbel J, Kartal E, Johnson TS, Hirche F, Grafetstätter M, Nonnenmacher T, Kirsten R, et al. Calorie restriction improves metabolic state independently of gut microbiome composition: a randomized dietary intervention trial. Genome Med. 2022;14:30.
233. Madeo F, Carmona-Gutierrez D, Hofer SJ, Kroemer G. Caloric restriction mimetics against age-associated disease: targets, mechanisms, and therapeutic potential. Cell Metab. 2019;29:592–610.
234. Ferrere G, Tidjani Alou M, Liu P, Goubet AG, Fidelle M, Kepp O, Durand S, Iebba V, Fluckiger A, Daillère R, et al. Ketogenic diet and ketone bodies enhance the anticancer effects of PD-1 blockade. JCI Insight. 2021;6:e145207.
235. Vernieri C, Fucà G, Ligorio F, Huber V, Vingiani A, Iannelli F, Raimondi A, Rinchai D, Frigè G, Belfiore A, et al. Fasting-mimicking diet is safe and reshapes metabolism and antitumor immunity in patients with cancer. Cancer Discov. 2022;12:90–107.

Publisher's Note