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Metabolic Reprogramming of Thyroid Cancer Cells and Crosstalk in Their Microenvironment

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Metabolism differs significantly between tumor and normal cells. Metabolic reprogramming in cancer cells and metabolic interplay in the tumor microenvironment (TME) are important for tumor formation and progression. Tumor cells show changes in both catabolism and anabolism. Altered aerobic glycolysis, known as the Warburg effect, is a well-recognized characteristic of tumor cell energy metabolism. Compared with normal cells, tumor cells consume more glucose and glutamine. The enhanced anabolism in tumor cells includes *de novo* lipid synthesis as well as protein and nucleic acid synthesis. Although these forms of energy supply are uneconomical, they are required for the functioning of cancer cells, including those in thyroid cancer (TC). Increasing attention has recently focused on alterations of the TME. Understanding the metabolic changes governing the intricate relationship between TC cells and the TME may provide novel ideas for the treatment of TC.

Keywords: metabolic reprogramming, thyroid cancer, microenvironment, metabolic interplay, Warburg effect

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INTRODUCTION

Thyroid cancer (TC) remains the most frequently diagnosed endocrine malignancy; with a sharp increase in incidence worldwide, this disease is projected to become the fourth leading type of cancer globally (1). Based on its histological features, TC is grouped into four types: papillary thyroid carcinoma (PTC), follicular thyroid carcinoma (FTC), medullary thyroid cancer (MTC), and anaplastic thyroid carcinoma (ATC). Approximately 90% of all TCs are differentiated, including PTC, which is the most common histological type of differentiated thyroid cancer, followed by FTC (2). Notably, different TC subtypes exhibit distinct tumor aggressiveness and progression and show heterogeneous responses to different treatments (3). Although well-differentiated TCs have good prognoses, approximately 10% of patients do not respond to radioactive iodine therapy and are more likely to relapse. While the incidence of poorly differentiated TCs such as ATC and MTC is very low, they are characterized by high invasiveness, early metastasis, and poor prognosis (4, 5). Conventional therapy consists of surgery, radiotherapy, and endocrine suppression treatment (6, 7). However, these treatments have various limitations and side effects (8, 9).

The large differences in metabolism between tumor cells and normal human somatic cells are mainly reflected in catabolic and biosynthesis metabolism (10). The metabolic changes in tumor cells are often considered to be closely related to tumor formation and progression (11). Thus, the unique metabolism of tumor cells is both an opportunity and a challenge. Here, we review the catabolic and anabolic metabolism changes in TC cells. We also describe the mutual relationship between metabolic reprogramming and the tumor microenvironment (TME) in TC, which provides the theoretical basis for new therapeutic targets and prognostic indicators.

METABOLIC CHANGES IN TUMOR CELLS

Cancer cells always acquire energy and material basis for rapid tumor growth by enhanced anabolism, including rapid aerobic glycolysis, glutaminolysis, *de novo* lipid synthesis and nucleotide synthesis (12, 13). Thyroid cancer cells generate energy primarily by increasing glycolysis and glutaminolysis. In addition, the production of glycolysis can also provide materials for nucleic acid synthesis through pentose phosphate pathway (PPP). Nucleic acid synthesis, protein synthesis, and *de novo* lipid synthesis are enhanced to support thyroid cancer cell proliferation. During metastasis, tumor cells rely on catabolism to survive from metabolic stress, mainly through aerobic glycolysis, OXPHOS, glutamine metabolism and autophagy to produce ATP (14). Thyroid tumors acquired aggressive phenotype and epithelial-mesenchymal transformation(EMT) *via* sirtuin 6 (SIRT6)-Autophagy-Warburg Effect Axis (15). AMPK signal is also essential for activating adaptive changes in cell metabolism such as inhibiting anabolism and promoting catabolism, which is the basis for cell survival under metabolic stress. In TC, AMPK activation inhibits TC cell proliferation and promotes cell migration (16). Moreover, carnitine palmitoyltransferase 1C which is regulated by AMPK, transfers long-chain fatty acids into mitochondria to further oxidation and promotes TC cells survival under metabolic stress conditions (17).

Changes in Catabolism

Glucose Metabolism

Cells produce ATP for energy in two main ways: glycolysis and oxidative phosphorylation (OXPHOS). To satisfy the need of energy for proliferation, thyroid tumor cells increased the level of glycolysis. Although aerobic glycolysis is inefficient compared to OXPHOS, it can provide energy for tumor cell proliferation and invasion and a constant supply of material for biosynthesis (18). The Warburg effect suggests that tumor cells require more glucose than normal cells and derive their energy mainly from glycolysis even when oxygenated adequately (19). However, the energy sources of different tumors also show heterogeneity, and even different areas of the same tumor have different energy sources (20–22). It is noteworthy that glycolysis plays a more important role in sustaining the balance of the PPP in thyroid cells, which is more critical for thyroid hormone synthesis than ATP production even in TC (23) (**Figure 1**).

Hypoxia-inducible factor (HIF) is a transcription factor that is widespread in mammals and humans under hypoxic conditions. HIF plays roles in glycolysis, promote angiogenesis, cell survival or apoptosis. As the basic regulator of glycolysis, HIF can upregulate the activity of 90% of glycolytic reactivity enzymes and inhibit the

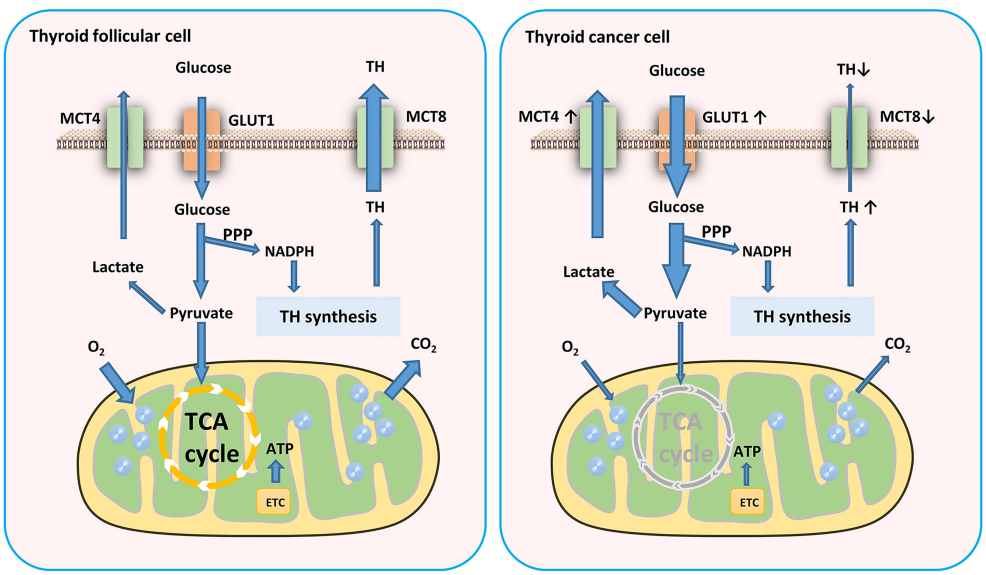

FIGURE 1 | Glucose metabolism in TC cells. TC cells require more glucose than normal cells and derive their energy mainly from glycolysis. This aerobic glycolytic phenotype generates more lactates which transported by MCT4. MCT8 downregulation in TC cells results in TH accumulation in TC tissues. GLUT, glucose transporter; TH, thyroid hormones; ETC, electron transport chain; MCT, monocarboxylate transporter.

use of pyruvate by mitochondria (24). In TC cells, aerobic glycolysis can be enhanced through the alteration of the HIF1α-MYC-PGC-1β axis (25). Zhou et al. showed that hypoxia promoted FTC progression by upregulating HIF1α and programmed death-ligand 1 (PD-L1) (26). In PTC, SIRT6 promotes the EMT of cancer cells through HIF-1α (27). Klaus et al. demonstrated the critical role of HIF-1α in the desmoplastic stroma reaction and metastatic processes in FTC (28). HIF can stimulate the expression of MYC, a transcription factor that is highly expressed in tumors and has a variety of biological functions, including cell metabolism. *MYC* can promote glycolysis and glucose transporter (GLUT) expression, thus transforming tumor energy metabolism into the Warburg effect (29–31). Myc overexpression can also lead to abnormally increased synthesis of lactate dehydrogenase A (LDHA), which catalyzes pyruvate to lactate. Compared to normal thyroid tissues, LDHA expression is higher in PTC. Hou et al. reported that LDHA not only promoted PTC tumorigenesis but also migration and invasion by regulating autophagy and inducing EMT gene transcription. Moreover, they also found that the metabolic products catalyzed by LDHA increased the acetylation of the related *H3K27* and induced EMT (32). LDHA is phosphorylated by HER2 and SRC39, resulting in the increased invasive and metastatic potential of head and neck cancer (33).

GLUT is a transporter that helps cells to take up glucose and is the first rate-limiting step in glucose metabolism. Many studies have demonstrated the upregulation of GLUT subtypes during carcinogenesis (34–36). Samih et al. reported that the phosphoinositide 3-kinase (PI3K)/Akt pathway is the key to GLUT1 transfer from the cytoplasm to the plasma membrane (37). GLUT1 overexpression is also associated with cancer cell aggressiveness and dedifferentiation. Mediated by the transcription factor HIF, GLUT3 is upregulated in response to hypoxia. The overexpression of GLUT1 and GLUT3 is generally recognized as one of the characteristics of tumors (38). Jóźwiak et al. reported that most PTC samples showed higher GLUT1 and GLUT3 expression than the expression in FTC and non-neoplastic thyroid lesions (39). Chai et al. analyzed the expression of GLUT family genes and concluded that the upregulation of the genes encoding GLUT1, GLUT3, GLUT14 was associated with decreased overall survival in patients with PTC (40).The function and tissue distribution of GLUT14 are uncharacterized, although there is some disease association, specifically in inflammatory bowel disease. GLUT14 is a GLUT3 variant that has also been found in the genome as a duplicon of GLUT3. Moreover, the upregulation of GLUT14 was associated with the maintenance of glucose uptake in hypoxia (41). The localization of GLUT1 is heterogeneous among TCs. For example, it exhibits a focal circumferential form in plasma membrane of PTC cells, shows a non-symmetric distribution in the basilar membrane of tumor cells adjacent to the capillary blood supply and stroma, and focal distribution in the center of metastatic tumors or ATC (42). Previous studies indicated that GLUT1 and GLUT3 expression levels may be associated with increased invasion and a worse prognosis of TC. Glucose transported by GLUT involved in glycolysis, the products of which eventually enter the mitochondria to generate ATP for cell energy through OXPHOS. The mitochondrial pyruvate carrier 1 (MPC1) is a critical channel that connects glycolysis to OXPHOS by regulating the transport of pyruvate into the mitochondrial inner membrane. MPC1 deficiency may cause metabolic reprogramming and is associated with a poor prognosis. MPC1 expression is strongly negatively correlated with tumor purity and immune cell infiltration in TC (43).

Many enzymes are involved in the aerobic glycolysis of tumor cells, including pyruvate kinase M2 (PKM2), hexokinase (HK), phosphofructokinase 1 (PKF1). The PI3K/Akt pathway can enhance the Warburg effect of tumors by increasing the activity of these factors (44). HK is the first rate-limiting enzyme in glycolysis and catalyzes the phosphorylation of glucose into glucose 6-phosphate. HK2 is also highly expressed in TC (45, 46). Huang et al. demonstrated the promotion of thyroid carcinoma cell proliferation and migration through the activation of AKT/mTOR/HK2-mediated glycolysis (47). Feng et al. reported that PKM2 overexpression in PTC was related to poor clinicopathological features such as advanced tumor stages and lymph node metastasis (48). In their proteomic analysis of five PTC specimens, Aurélie Strickaert et al. investigated the cellular distribution of several upregulated metabolic proteins in the cancerous and stromal cells of these tumors. They discovered the upregulation of many metabolism-related proteins including pyruvate carboxylase (PC) (49). Verhagen et al. compared PK in human thyroid carcinomas, follicular adenomas, and normal thyroid tissue and reported a positive correlation between the specific activities of PK and tumor proliferation (50). The results of these studies demonstrated that PK overexpression plays an important role in TC.

Amino Acid Metabolism

Glutamine is a nonessential amino acid in normal cells and can be converted from glucose. However, tumor cells cannot grow in a culture medium without glutamine; thus, glutamine is an essential amino acid in these cells (51). Ample evidence supports the essential role of glutamine in tumors. Tumor cells consume large amounts of glutamine as an alternative energy supply pathway to glycolysis (52–54). However, the requirements for glutamine in cancer vary in different tissues and situations (55) (**Table 1**) . Several studies demonstrated the changes in glutamine metabolism of thyroid tumors. Inhibition of glutamine metabolism in TC cells results in insufficient energy supply, which inhibits cell proliferation, migration, and invasion (56). Kim et al. performed tissue microarrays of 557 TC cases and immunohistochemical staining of glutaminolysis-related proteins. They reported that glutaminase 1 (GLS1) and glutamate dehydrogenase (GDH) showed the highest expression in ATC compared to other subtypes. Tumoral amino acid transporter-2 expression was higher in MTC but lower in FTC. In PTC, the expression levels of tumoral GLS1 and GDH were higher in the conventional type than those in the follicular variant, and in the $BRAF^{V600E}$ mutation than those in cases without the $BRAF^{V600E}$ mutation (57). The expression levels of glutaminolysis-related proteins including GLS1, GDH, and GLUD were higher in Hürthle cell neoplasm of the thyroid than in those of follicular neoplasm. The expression of SLC1A5 was highest in Hürthle cell adenomas, followed by FC and FA (58). When glutamine enters the

TABLE 1 | The metabolic differences and similarities in cancers.

Metabolic pathways	Tumor types	Difference	Similarity
Glycolysis metabolism	Thyroid cancer	Produce NAPDH through the PPP pathway for thyroid hormone synthesis, ATP production (17)	Enhancement of glycolysis and lactate production
	Other cancers	Mainly used for ATP production (13)	
Energy source	Primary thyroid cancer	Glucose and glutamine metabolism(186)	Increased energy demand
	Metastatic thyroid cancer	Unknown	
	Primary breast cancer	Glucose and glutamine metabolism (15)	
	Metastatic breast cancer	Pyruvate (lung metastases) to sustain the TCA cycle (15) Serine and acetate (brain metastases) to sustain the TCA cycle (16)	
	Non-small cell lung cancer	Carbon source: glucose (areas with low perfusion); glucose and other sources (highly perfused areas) (14)	
Lipid metabolism	Thyroid cancer	Low correlation between MUFAs and MUPCs or monosaturated and polyunsaturated lipids (85) ACC2 downregulation (83)	Enhancement of de novo lipid synthesis
	Breast, lung, colorectal, esophageal and gastric cancer	Highly positive correlation between MUFAs and MUPCs negative correlation between monosaturated and polyunsaturated lipids (85)	
	liver, breast and prostate	ACC upregulation (82)	

cell, it is hydrolyzed to glutamic acid and ammonia by glutaminase. Glutamate can be converted into α-KG to enter the tricarboxylic acid (TCA) cycle, providing intermediate metabolites and energy for cell metabolism. This is particularly evident in the truncated TCA cycle, which can be used as feedstock for the passive TCA cycle due to the lack of citrate (44). This phenomenon, termed anapleurosis, suggests that the use of glutamine affects glucose absorption. Therefore, reducing the use of glutamine can also reduce that of glucose (59). In general, glucose and glutamine metabolism influence each other. Other changes in protein metabolism are present besides glutamine. Sun et al. analyzed 557 different types of TC and found a higher expression level of serine/glycine metabolism-related proteins in PDC and PTC compared to that in MTC. In PTC, the rate of expression was higher in cases with $BRAF^{V600E}$ mutation than in those with a follicular variant (60).

Changes in Biosynthesis Metabolism

Enhancement of *De Novo* Lipid Synthesis

Compared to normal tissue, tumor cells synthesize lipids more rapidly and from different sources. Accumulating evidence has demonstrated the important role of lipid metabolism reprogramming in tumor cell development and metastasis (61–67). Liao et al. reported that lysine methyltransferase 5A (KMT5A), a regulator of lipid metabolism in PTC, was significantly associated with extrathyroidal extension and lymph node metastasis in PTC (68). Instead of nutrient uptake, the raw materials of lipid synthesis in tumor cells mainly come from glucose metabolism. Approximately 93% of the fatty acids in tumor cells are synthesized *de novo* (69, 70). The enzymes involved in the fatty acid synthesis, such as ATP citrate lyase (ACLY), Acetyl-CoA carboxylase (ACC), and fatty acid synthase (FASN) are changed in tumor cells (71–83). Citrate, the intermediate product of glucose metabolism, forms Ac-CoA under the catalysis of ACLY, and Ac-CoA forms malonyl CoA (Mal-CoA) under the catalysis of ACC. Ac-CoA and MAL-CoA synthesize palmitic acid catalyzed by FASN, and palmitic acid forms lipid components required by cells catalyzed by other specific enzymes.

Several studies on thyroid carcinoma also demonstrated lipid metabolism reprogramming. In their transcriptome analysis of lipid metabolism-related genes in PTC, Xu et al. described the use of these genes for PTC classification (84). Recent cases reported by Leng et al. suggested abnormality in the metabolism of fatty acid synthases and lipids. They detected 18 types of FFAs with increased levels in carcinoma tissue compared to the normal tissue of the thyroid (85). Several studies have reported abnormal changes in lipogenic enzymes in TC. FASN is upregulated in various TC subtypes, including PTC, ATC, and FTC (86–88). Under hypoxic conditions, ACC is upregulated in most types of cancer such as liver, breast, and prostate cancer (89) and is downregulated in PTC. The downregulation of ACC2 *via* $BRAF^{V600E}$ plays a critical role in PTC and establishes favorable conditions for TC cell proliferation (90). Of the lipogenic enzymes upregulated in ATC, stearoyl-CoA desaturase-1 (SCD1) that can mediate the desaturation of endogenously synthesized saturated fatty acids into monounsaturated fatty acids (MUFAs) and promote the proliferation of various cancer cell types showed the most significant differential expression when compared with that in normal thyroid tissues (91). A highly positive correlation between MUFAs and monounsaturated phosphatidylcholines (MUPCs) and negative correlations between monosaturated and polyunsaturated lipids have been observed in many types of cancers including breast, lung, colorectal, esophageal, and gastric cancer; thus, similar lipogenic mechanisms may exist to generate the lipids. However, it should be noted that a lower correlation than that mentioned above in TC was observed (92) (**Table 1**). These findings suggest the presence of different lipid metabolism in TC while it is not clear at this stage. Overall, these cases support the view that TC cells are dependent on *de novo* lipogenesis for cell viability (**Figure 2**).

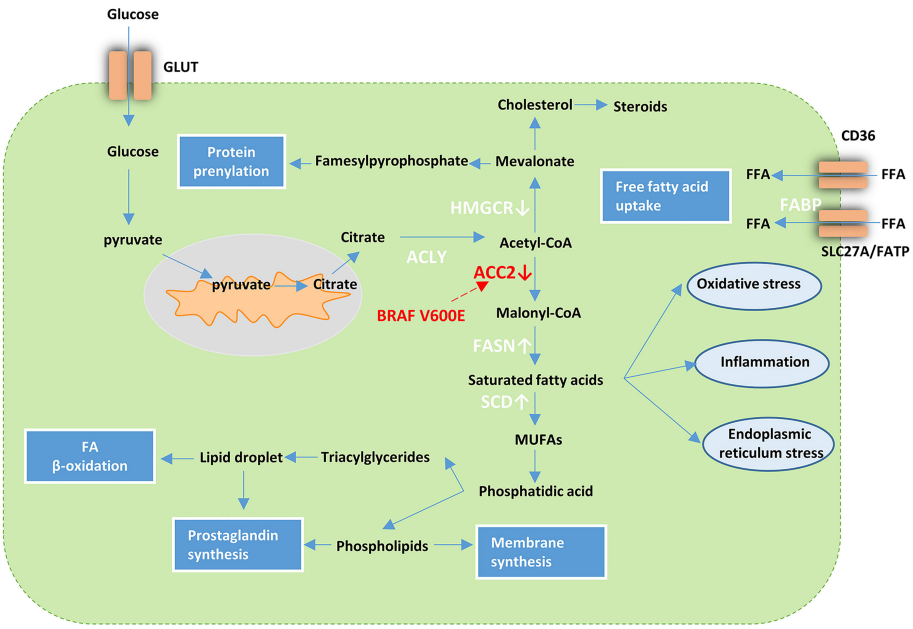

FIGURE 2 | Lipid metabolism in cancer cells. Tumor cells increase FFA uptake *via* upregulation of fatty acid transport receptors and chaperones such as Solute Carrier SLC27A/FATP, CD36, and FABP. In addition, metabolic reprogramming that facilitates glycolysis can activate *de novo* lipid synthesis. Acetyl-CoA derived from citrate can be further processed into a variety of lipid species with the help of various enzymes. FASN and SCD are upregulated while ACC2 and HMGCR are downregulated in TC. $BRAF^{V600E}$ influences the lipid metabolism in PTC *via* downregulation of ACC2. GLUT, glucose transporter; HMGCR, 3-hydroxy-3-methylglutaryl-CoA reductase; fatty acid synthase ACLY; ACC2, Acetyl-CoA carboxylase 2; FASN fatty acid synthase; SCD, stearoyl-CoA desaturase-1; MUFAs, monounsaturated fatty acids; FFA, free fatty acid; FABP, fatty acid binding protein; SLC27A, Solute Carrier Family 27; FATP, Fatty Acid Transporter.

Enhancement of Protein Synthesis

As a crucial component of all cells and tissues of the human body, proteins are the material basis of life. Proteins have many functions in organisms, including catalysis, locomotion, transport, mechanical support, immunity, regulation. Protein synthesis consists of five steps, including amino acid activation, initiation of polypeptide chain synthesis, peptide chain extension, peptide chain termination and release, and post-synthesis processing and modification of the protein. This process expresses the genetic information on messenger RNA (mRNA) transcribed from DNA in the form of proteins. As tumor cells are more metabolically active and divide more frequently than normal cells, they require more proteins.

As mentioned above, the PI3K-Akt-mTOR pathway is activated in various kinds of carcinoma. This pathway is also closely associated with protein synthesis. Tumor cells keep their protein synthesis positive to meet the growth needs through this pathway. In addition, tumor cells have different genetic mutations that activate the synthesis of certain proteins and perform certain functions.

Ribosomes, ribonucleoprotein particles in cells, are mainly composed of numerous distinct proteins and rRNA and are responsible for protein synthesis. In recent decades, many studies have demonstrated the causal associations between inherited mutations affecting ribosome biogenesis and increased cancer risk. Recent studies have shown that dysregulated ribosome biogenesis plays a broader role in the development and progression of most cancers (93–98). Some studies have also assessed the relationship between ribosomes and TC. Saiselet et al. reported that the expression of genes involved in the negative regulation of cell death/apoptosis was also downregulated in five TC cell lines (WRO, FTC133, BCPAP, TPC1, and K1) (99). Jeong et al. discovered the high expression of LXRβ in TC, which was coordinately associated with ribosome-related genes (100).

Abnormalities in Nucleic Acid Biosynthesis

Nucleic acid is a biological macromolecule with a nucleotide as its basic unit, which has a complex spatial structure and important biological functions. Nucleic acids can be classified as deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). DNA, which is found in the nucleus and mitochondria, carries genetic information and is passed down through generations through replication. Cell and organismal traits are determined by this genetic information. The two basic pathways of nucleotide synthesis are *de novo* synthesis and remediation. The *de novo* synthesis of nucleotides from simple materials such as ribose phosphate, amino acids, one-carbon units, and CO_2 is the main synthesis pathway in the human body. The *in vivo* use of free bases or nucleosides can generate nucleotides through a simple reaction process known as the salvage pathway. Tumor cells use both pathways because they require significant amounts of nucleic acids for rapid growth. As mentioned above, the catabolism of glutamine is particularly active in tumor cells;

thus, increased amounts of the breakdown products of glutamine are observed when compared with those in normal cells. Ammonia produced by the breakdown of glutamine participates in the ammonia cycle and can be used for the biosynthesis of nucleotides and proteins (101–105).

Tumor cells increase nucleotide synthesis to satisfy their need for growth and proliferation (106). Therefore, the activity of nucleotide synthetase, especially deoxyribonuclease, is higher in tumor cells than that in normal cells (107). The expression of deoxyribonuclease in normal cells fluctuates with changes in the cell cycle. Cancer cells have lost normal regulation and the expression levels are constitutively high, leading to increased DNA synthesis (24). The expression levels of genes involved in DNA replication were upregulated in TC cell lines such as BCPAP and 8505C (99). The occurrence of thyroid tumors is related to abnormal nucleic acid synthesis caused by a variety of gene mutations. The activation of BRAF mutations is a major oncogenic driver of many cancers, especially TC (108, 109). BRAF is the predominant mutation (30–40%) in PTC and is considered an initiating event in papillary thyroid carcinogenesis. Another human gene involved in thyroid carcinogenesis is TERT, which contributes to the distant metastasis (110–112).

TC CELL METABOLISM AND THE TME

Tumor Cell Metabolism Shapes the Inflammatory TME

The two major characteristics of the TME are hypoxia and acidification, which are closely related. Tumor cells increase glycolysis to adapt to the hypoxic microenvironment. The lactate produced by glycolysis, in turn, acidifies the TME. In addition, the incomplete vasculature of tumor tissue prevents the timely elimination of metabolites, which is also related to the acidification of the TME. Active metabolism in TME cells can also lead to increased toxic concentrations of certain metabolites, such as increased levels of adenosine, kynurenine, ornithine, reactive oxygen species, and potassium. These metabolites have profound effects on suppressing the tumor immune response. During tumor development, the TME changes continuously with tumor growth and develop its cellular contents by releasing various recruiting factors, leading to the accumulation of specific types of immune cells in the TME, also affects the functions of these immune cells and the complex relationship between these cells and tumor cells. Thus, tumors are no longer simply a problem of cancer cells. Co-evolution occurs between tumor cells and the surrounding stromal cells, forming an inseparable community. Under the influence of tumor cells, tumor stromal fibroblasts, macrophages, and neutrophils become tumor-associated fibroblasts (CAFs), tumor-associated macrophages (TAMs), and tumor-associated neutropenia.

Metabolic Crosstalk in the TC Microenvironment

Nutrient Competition

The high metabolic activity of cancer cells and the disordered vasculature in the TME can contribute to a microenvironment featuring nutrient depletion and hypoxia, which established a metabolic competition between cancer cells and infiltrating immune cells. This series of changes and metabolic reprogramming plays a significant role in promoting tumor growth and immune escape. Chen et al. compared human normal thyroid and PTC samples and identified metabolites in carbohydrate metabolism, including glucose, that consistently decreased in PTC (113). The lack of glucose impaired the function of immune cells such as TAMs and T cells by regulating mTOR and GAPDH. Glycolysis promotes effector T cell (Teff cell) function by sustaining the production of IFNγ. Decreased mTOR activity diminishes IFNγ at the transcriptional level in $CD8^+$ T cells and, thus, impairs T cell function (114, 115). Besides glucose, amino acids also play a role in driving and fueling T cell function and differentiation. The neighboring immune cells in solid tumors are outcompeted due to arginine uptake and catabolism which primarily shifts toward cancer cells (116). Leone et al. reported that tumor cells exposed to glutamine antagonist showed decreased viability, proliferation, and cell cycle progression while Teff cells produce a long-lived, highly activated phenotype by markedly upregulating oxidative metabolism (117).

Secreted Metabolites

The accumulation of metabolites such as lactate, kynurenine, and other metabolic by-products of cancer metabolism can be detrimental to immune cells, leading to tumor immunosuppression. Indoleamine 2, 3-dioxygenase (IDO), a rate-limiting enzyme in tryptophan oxidation, promotes tryptophan uptake from the TME and generates kynurenine, which inhibits tryptophan import. Therefore, the amino acids of T cells are depleted and result in immunosuppression and induced T cell apoptosis. IDO-expressing tumor cells are not rejected by specific T cells through the secretion of kynurenines, which can suppress cytotoxic effector functions *via* the downregulation of TCR CD3 ζ-chain and induced $FOXP3^+$ regulatory T cell (Treg) differentiation. IDO upregulation impaired the function of NK cell function and boost the high infiltration of $FOXP3^+$ Tregs in thyroid carcinoma (118, 119). In addition, $Foxp3^+$ Tregs in lymphocytes facilitate thyroid tumor growth and invasion (120). A large amount of lactate can also cause acidosis in the microenvironment and weaken immune cell function (121). Arts et al. showed that TC-derived lactate-mediated TC-induced TAM reprogramming and inflammation through Akt/mTOR-dependent glycolysis, an increase in inflammation characteristics, and changes in cell metabolism (122). The accumulation of lactate is also detrimental to the function and antitumor response of T and NK cells by inhibiting proliferation and cytokine production (123). These studies suggested that patients with cancer should be cautious when using lactate preparations, as lactate may promote tumor growth.

Tumor cells also secrete vascular endothelial growth factor (VEGF) into the TME, resulting in the upregulation of 6-phosphofructo-2-kinase/fructose-2, 6-biphosphatase 3 (PFKFB3) in endothelial cells, which activates PFK-1 to promote the glycolytic phenotype as well as proliferation (124). Colegio et al. demonstrated that lactate produced by tumor cells promotes M2 macrophage polarization by a HIF1a-dependent mechanism. In turn, VEGF and Arginase-1 secreted by

M2-polarized macrophages signal back to tumor cells and promote tumor growth (125).

Metabolic Coupling

In TME, the energy metabolism of CAFs shifts to aerobic glycolysis under the influence of cancer cells. The lactate, ketone body, or pyruvate released by these CAFs can be used as an energy source by epithelial cancer cells to enter the TCA cycle and produce ATP through OXPHOS. This phenomenon is called the reverse Warburg effect. Lactate produced by CAFs is exported *via* the monocarboxylate transporter (MCT)-4 into the TME and taken up by tumor cells *via* the MCT-1 transporter. Such metabolic coupling has been reported in several tumor types including head and neck cancer (126). In addition, the metabolic coupling between PTC cells and adjacent fibroblasts can result in aggressive behavior owing to the large-scale production lactate, which is transported outside the cell by MCT4 (127). CAFs also increased the anabolic metabolism of glutamine which can be consumed by cancer cells to sustain nucleotide generation and OXPHOS. In contrast, glutamate secreted by cancer cells promoted the production of glutathione (GSH), thereby maintaining redox balance and ECM remodeling in CAFs (128). The results of Mestre-Farrera et al. indicated that glutamine deprivation promoted CAFs migration and invasion, which, in turn, promotes tumor epithelial cells to move to nutrient-rich areas (129). CAFs release paracrine signals to induce metabolic reprogramming and epigenetic changes, causing changes similar to KRAS-driven oncogenic transformations (130). Tumors cells release factors such as PDGF and TGF-β, resulting in metabolic reprogramming of CAFs toward aerobic glycolysis (131, 132). Fozzatti et al. described the significant increase of GLUT-1 in human fibroblasts *in vitro* when cultured in ATC cells-derived conditioned media. Strikingly, conditioned media obtained from these activated fibroblasts promoted cell proliferation and invasion of follicular TC cell line (133). Rabold et al. performed transcriptome, metabolome, and lipidome analyses on TC-induced macrophages in a human coculture model. The lipidome analysis showed increased total lipid and intracellular lipid content of tumor-induced macrophages, especially phosphoglycerides and sphingolipids. Remarkably, this metabolic shift in lipid synthesis contributes to their protumoral functional characteristics: a block of key enzymes of lipid biosynthesis in tumor-induced macrophages reversed elevated inflammatory cytokines and the ability to produce ROS, two well-known pro-tumoral factors in the TME (134).

These studies show the complicated and dynamic interaction that exists between thyroid tumors and immune cells in TME, which results in the promotion of thyroid tumorigenesis (**Figure 3**).

PROGNOSTIC BIOMARKERS AND TREATMENT

Prognostic Indicators

In conclusion, the expression of metabolism-related molecules revealed the differences in invasiveness and prognosis between different TC subtypes (**Figure 4**). Numerous studies have demonstrated the relationship between the prognosis of thyroid carcinoma and glycolysis-related proteins such as GLUT, LDHA, MCT1 (32, 135, 136). Some studies have indicated that GLUT contributed to the increased glucose uptake observed during carcinogenesis (135, 137). The differentiated extent of thyroid cancer is negatively correlated with the expression of GLUTs. Poorly differentiated types such as ATC have high expression levels of GLUT (mainly GLUT-1); in contrast, well-differentiated tumors such as FTC and PTC usually have low GLUT-1 expression levels (45, 137–140). Glutamine, serine, glycine, and other amino acid metabolism-related proteins can also be used as prognostic indicators for thyroid tumors. Stromal GDH positivity was an independent factor associated with poor prognosis. In follicular variant PTC, stromal serine hydromethyl transferase 1 expression was associated with shorter disease-free survival. The serine/glycine metabolism-related molecules phosphoglycerate dehydrogenase, glycine decarboxylase, and phosphoserine phosphatase positivity were associated with shorter overall survival (57, 58, 60, 141). IDO, which was associated with the aggressive features of papillary thyroid microcarcinoma, may disrupt antitumor immunity and contribute to tumor progression by increased infiltration of $FOXP3^+$ Treg cells (142).

Metabolism Targeted Therapy

At present, cancer therapeutic regimens face the problem of drug resistance which may associate with metabolic reprogramming in tumor. Therefore, combination therapies that target various tumor cell properties showed great potential value. Metabolic inhibitors in combination with targeted therapy or chemotherapy hold promise for increasing anticancer drug sensitivity.

Glucose Metabolism as a Therapeutic Target

The energy supply of tumor cells differs from that of normal cells. This unique energy supply pathway is mainly due to increased glycolytic enzyme expression and activity levels. Theoretically, inhibiting specific glycolytic metabolic enzymes with high expression levels can cut off the energy supply of tumor cells, while normal tissues are not affected. When the glycolytic pathway is inhibited, normal tissue cells can utilize fatty acid and amino acid production through alternative pathways. Some glycolytic enzymes, such as HK-II LDHA, and PKM2, are highly expressed in malignant tumors. These highly expressed glycolytic enzymes can be used as targets for tumor treatment (143). Due to tumor cell heterogeneity and TME variability, the expression and activity of glycolytic enzymes may change. Consequently, the therapeutic effect of a single glycolytic enzyme target may not be as good as that for the combination of multiple glycolytic enzyme targets. Combinations involving the inhibition of glycolysis and OXPHOS, or glycolysis and glutaminolysis have been proven in multiple preclinical cancer models to effectively suppress tumor growth (144–148). Glyoxalase I (GLO I) is a rate-limiting enzyme that is involved in the detoxification of cytotoxic methylglyoxal formed in glycolysis. The combination of GLO I inhibitor with shikonin, a PKM2 specific inhibitor, could suppress the cellular proliferation and induction of apoptosis (149).

Various HK2 inhibitors have been identified, including 2-deoxyglucose(2-DG), 3-bromopyruvate (3-BP), and lonidamine (LND). In thyroid tumors, glycolytic inhibitors also show unique

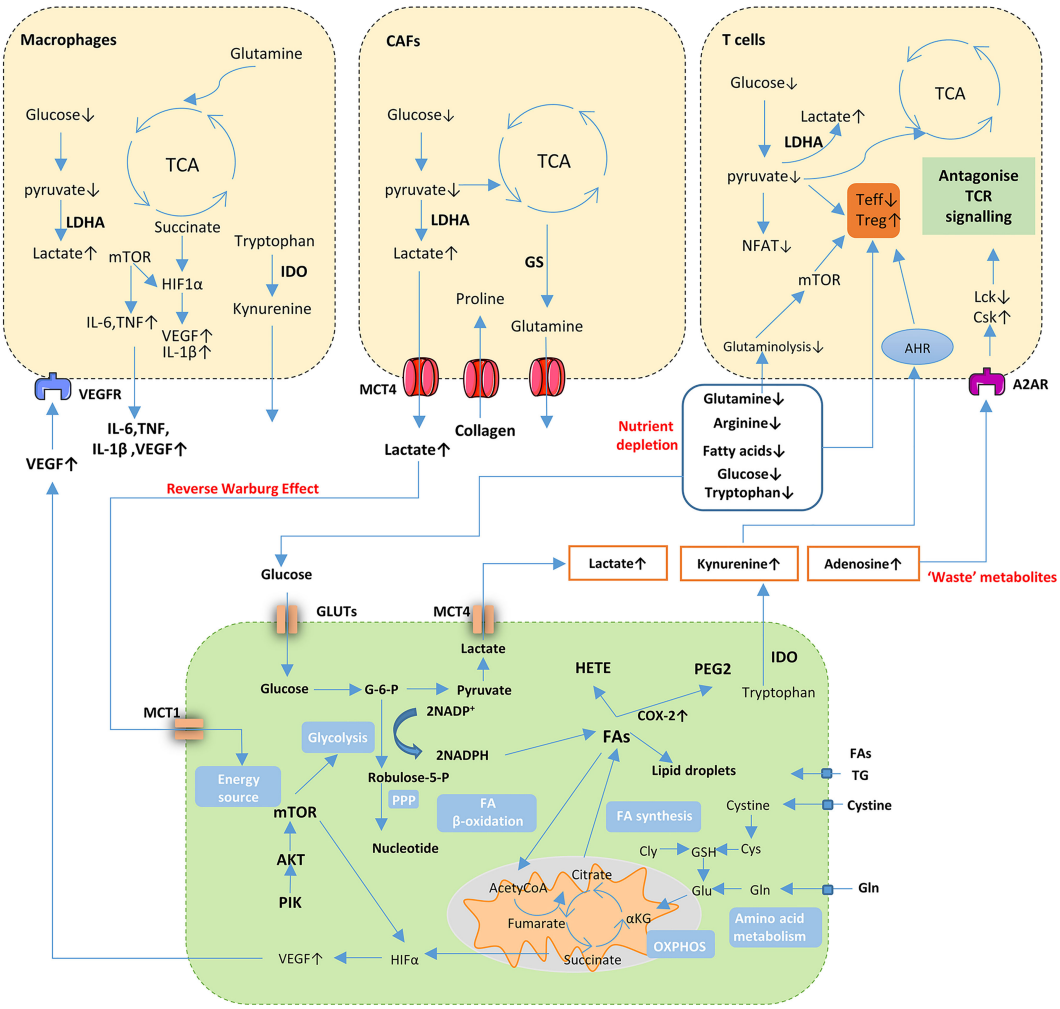

FIGURE 3 | Cancer cell metabolism and crosstalk in the TME. Cancer cells undergo metabolic changes including activation of aerobic glycolytic, enhanced FA synthesis and increased uptake of glutamine supply for bioenergetics through tricarboxylic acid (TCA) cycle and support biosynthesis of proteins. Nutrient depletion, accumulation of 'waste' metabolites and aberrant signaling molecules in TME influence the function and proliferation of both cancer cells and immune or stromal cells. Gln, glutamine; Glu, Glutamate; Cys, cysteine; GSH, glutathione; Cly, glycine; TG, triglyceride; FA, fatty acids; PPP, pentose phosphate pathway; NADH, nicotinamide adenine dinucleotide; NADPH, nicotinamide adenine dinucleotide phosphate; HETE, thromboxane hydroxiepoxyeicosate-traenoic acid; PEG2, prostaglandin E2; COX-2, cyclooxygenases-2; G-6-P, glucose-6-phosphate; IDO, Indoleamine 2, 3-dioxygenase; MCT, monocarboxylate transporter; GLUT, glucose transporter; VEGF, vascular endothelial growth factor; LDHA, lactate dehydrogenase A; GS, glutamine synthetase; NFTA, nuclear factor of activated T cells; AHR, aryl hydrocarbon receptor; A2AR, Adenosine 2A receptor; Csk, C-terminal Src kinase; Lck, lymphocyte-specific protein tyrosine kinase; Teff, effector T cells; Treg, regulatory T cells.

therapeutic effects. Glycolytic inhibition with 3-BP suppress tumor growth and extends survival in a murine model of ATC when combined with the ketogenic diet (150). It has been previously shown that glycolytic inhibitors 2DG significantly enhanced the antitumor effects of other medical treatments and radiotherapy (151–154). Phase I/II clinical trials have been performed for 2-DG as a single-agent therapy in solid tumors and hormone-refractory prostate cancer. However, further research was halted owing to the significant toxicities and limited efficacy (NCT00633087) (155). LND also reached phase II and III clinical trials for the treatment of several tumor types but showed only modest clinical activity and a lack of specificity. Moreover, due to concerns regarding liver enzyme abnormalities, further research was halted (156, 157). Targeted therapy is a common treatment for thyroid tumors. When blocking platelet-derived growth factor receptor by imatinib, the pro-oncogene $BRAF^{V600E}$ promotes thyroid tumor cell glycolysis *via* the upregulation of HK2 expression, resulting in drug resistance. However, glucose uptake and metabolism in thyroid tumor cells were downregulated when $BRAF^{V600E}$ was blocked by vemurafenib. In terms of tumor growth, combination therapy of imatinib and vemurafenib was much more effective than single therapy and led to a near abolition of the tumors (158). The combination of imatinib

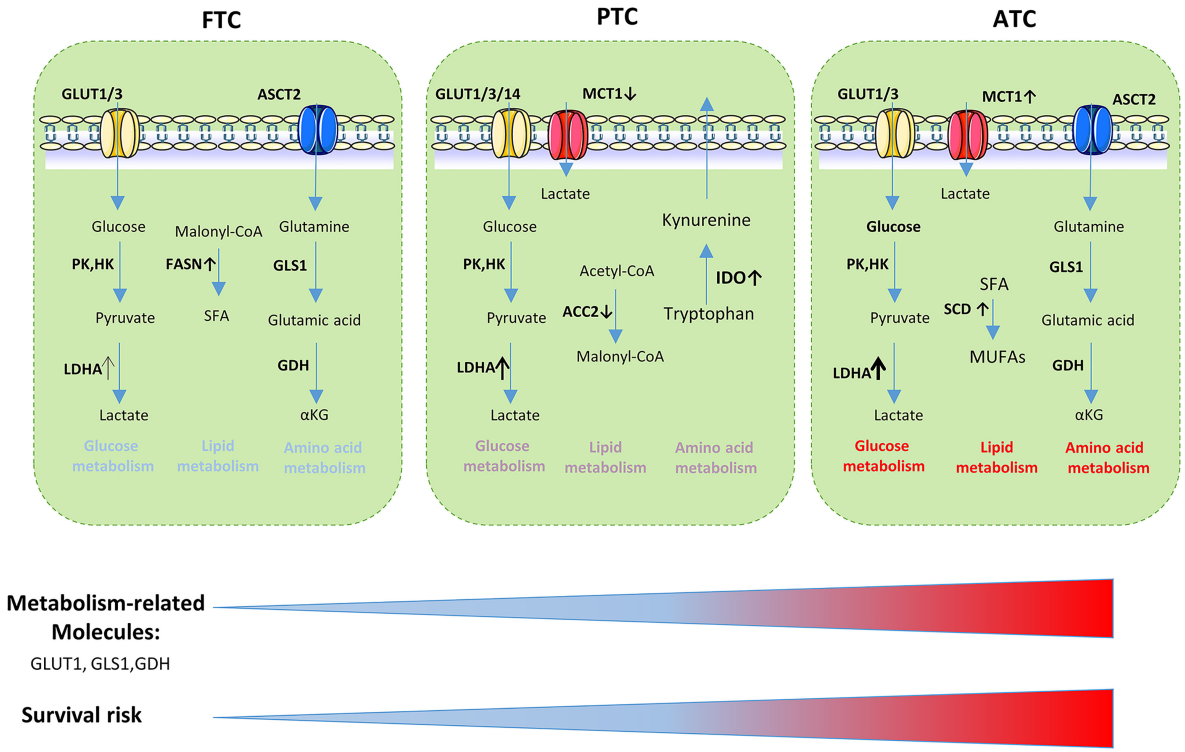

FIGURE 4 | Metabolism-related molecules is related to the aggressiveness of thyroid cancer and survival risk. GLUT, glucose transporter; LDHA, lactate dehydrogenase A; PK, Pyruvate kinase; HK, hexokinase; SFA, saturated fatty acids; ASCT, amino acid transporter; FASN, fatty acid synthase; GLS1, glutaminase 1; GDH, glutamate dehydrogenase; ACC2, Acetyl-CoA carboxylase 2; IDO,Indoleamine 2, 3-dioxygenase; SCD1, stearoyl-CoA desaturase-1; MUFAs, monounsaturated fatty acids.

and HK2 inhibitors may solve the problem of drug resistance and also provide better efficacy in TC.

LDH is a critical metabolic enzyme that is considered a hallmark of aggressive malignancies. Radiotherapy is a common therapy in thyroid cancer, indicating the combination therapy of LDHA inhibitor and radiotherapy may be efficient in thyroid cancer. Chen et al. find LDHA suppression monotherapy decreased cellular proliferation and stunted tumor growth temporarily in ATC but cannot achieve tumor cure, due to the maintenance of residual viable cells. Only the combination therapy of chronic LDHA suppression and radiation can achieve a functional cure (159). Various LDHA inhibitors have been developed, such as dichloroacetate (DCA), gossypol, oxamate and FX-11 (160–162). The lactate transporter MCT links intracellular lactate with the TME and plays an indispensable role in tumor lactate metabolism. AZD3965 is an inhibitor of the MCT-1/MTC-2 lactate transporter and reached phase I clinical trials for both solid tumors and large B-cell lymphoma (NCT01791595). However, MCT inhibition also impairs T cell proliferation (**Table 2**).

Amino Acid Metabolism as a Therapeutic Target

Amino acids are an essential component of tumor cells and are closely related to tumor development. Thus, amino acid metabolism may provide a new therapeutic perspective. Lasparaginase is approved by the Food and Drug Administration for the frontline treatment of acute lymphoblastic leukemia (163). Other treatments for amino acid deprivation have also shown encouraging results in clinical trials in several solid malignancies (164–167). The mitochondrial enzyme GLS plays a crucial role in glutaminolysis. Among the GLS inhibitors, CB-839 is more potent, selective and shows greater bioavailability. In phase I clinical trials, CB-839 showed preliminary signs of clinical activity with an acceptable safety profile in multiple tumor types including triple-negative breast cancer, non-small cell lung adenocarcinoma, renal cell carcinoma, mesothelioma, and tumors with mutations in enzymes in the TCA cycle (NCT02071862) (168).

Since tumor cells require glutamine, one possible strategy is to treat tumors by preventing or interfering with glutamine metabolism by tumor cells. The blockade of glutamine in tumor-bearing mice inhibited cancer cell oxidation and glycolytic metabolism, resulting in hypoxia, acidosis, and reduced nutrient consumption (117). However, some studies showed that increasing the intake of glutamine in tumor-bearing rats did not elevate the growth rate of tumors; moreover, clinical work has also shown that glutamine supplementation in patients with tumors improved chemotherapy efficacy and reduced the adverse reactions (169–173). IDO, the ratelimiting enzyme in tryptophan catabolism, is highly expressed in TC cells and suppresses the function of NK cells.

TABLE 2 | Metabolism-targeting cancer therapies.

Target pathway and protein		Agent	Study phase	Effects	Interventions	References	Status
Glucose metabolism	HK2	2-DG	Phase II	Limited efficacy on tumor growth and significant toxicities	Single agent	NCT00633087	Terminated
		LND	Phase III	Limited efficacy and produced more myalgias and fatigue	Combined with epirubicin	(150)	
		3-BP	Preclinical	Suppresses tumor growth and improves survival *in vivo*	combined with the ketogenic diet	(143)	
	MTC1	AZD3965	Phase I		Single agent	NCT01791595	Completed
	LDHA	DCA	Phase I		Single agent	NCT01163487	Completed
		Gossypol	Phase I/II	Safe and well tolerated but shown limited activity.	Single agent	(1153)	
		Oxamate	Preclinical	Inhibits the viability of cancer cells in a dose- and time-dependent manner		(155)	
		FX-11	Preclinical	Block aerobic glycolysis and growth cancer *in vitro*	Single agent	(154)	
Amino acid metabolism	GL1	CB-839	Phase II		Combined with Paclitaxel	NCT03057600	Completed
	IDO	Epacadostat	Phase III	Effect remains uncertain.	Combined with Pembrolizumab	NCT02752074	Completed
		Indoximod	Phase II		Combined with Chemoradiotherapy	NCT04049669	Recruiting
Lipid metabolism	ACC	ND-654	Preclinical	Inhibits the tumor development *in vivo*, improve survival rate	Single agent; combined with the sorafenib	(68)	
	SCD	SSI-4	Preclinical	Regulate tumor-initiating cells and sorafenib resistance	Combined with sorafenib	(182)	
		Betulinic acid	Preclinical	Induces rapid cell death	Single agent	(184)	
		MF-438	Preclinical	Achieve better control	Combined with cisplatin	(183)	

IDO inhibitors such as epacadostat have reached phase III trials and show promising efficacy in combination therapies by linking metabolism and immunomodulation. Therefore, IDO inhibitors are likely to be useful for the treatment of thyroid tumors (174).

Lipid Metabolism as a Therapeutic Target

ACC is a rate-limiting enzyme for *de novo* lipid synthesis and inhibition of fatty acid oxidation. Rescue of ACC2 may be a new molecular strategy to overcome the resistance of refractory PTC to $BRAF^{V600E}$ inhibitors (90). SCD is an aliphatic acyl desaturase that catalyzes the transformation of saturated fatty acids into MUFAs by inserting cis-double bonds at the Δ9 position of the carbon chain (175). MUFAs play a role in cell growth, survival, differentiation, metabolic regulation, and signal transduction. SCD has been observed in a wide range of cancer cells (176–179) and this increase is closely associated with cancer aggressiveness and poor prognosis (180–183). Previous research established SCD reduces cell proliferation and invasion by blocking cell migration and membrane fluidity (184–187). In ATC, therapeutic and genetic-targeted inhibition of SCD enzyme activity promoted a significant reduction in cell proliferation and induced cell death, while normal thyroid cells were unaffected (91). SCD inhibitors such as SSI-4, betulinic acid, and MF-438 that proved effective in antitumor effect (188–190) may show a promising efficiency in the treatment of thyroid cancer.

CONCLUSION AND PERSPECTIVE

The crucial of metabolic reprogramming in tumor development and metastasis is increasingly recognized (**Table 3**). The complicated relationship between tumor cell metabolism and the TME is also important. Tumor cell metabolism can cause acidification of the TME and can also recruit immune cells to change immune cell metabolism in the TME. However, the immune microenvironment can also act on tumor cells to promote the immune escape of tumor cells.

Although there has been some progress in the study of metabolic reprogramming of TC in recent years, there remain

TABLE 3 | Metabolic reprogramming between proliferation and metastasis in thyroid cancer.

Metabolism pathways		Function	Reference	Evidence
Glucose metabolism	LDHA	Migration, invasion, tumor growth	(26)	*In vivo and in vitro*
	HK2	Proliferation, migration	(41)	*In vitro*
Amino acid metabolism	IDO	Tumor growth and invasion	(135)	Clinical relevance
Lipid metabolism	SREBP1, SCD, FASN and ACC	Extrathyroidal extension, lymph node metastasis, migration and invasion	(61)	Clinical relevance, *in vitro*
	SCD1	Proliferation and viability	(84)	*In vitro*

many gaps to fill. Some outstanding questions still need to be addressed for the development of specific metabolic targeted therapy. More studies are needed to determine how thyroid tumor cell metabolism interacts with immune cells in the microenvironment, which metabolic targets can be blocked specifically for TC treatment, the possible side effects of metabolism inhibitors, and the solutions to these challenges.

AUTHOR CONTRIBUTIONS

Conceived the work: LB and ZP. Wrote the manuscript: LB. Generated data for figures: TX and XL. Revised the manuscript: MG and PH. All authors contributed to the article and approved the submitted version.

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