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Review

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Review of pharmacological inhibition of thyroid cancer metabolism

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Abstract

Thyroid cancer (TC) is the most common malignancy of the endocrine system and has been rapidly increasing in incidence over the past few decades. Aggressive TCs metastasize quickly and often levy poor prognoses, as they are frequently resistant to first-line treatment options. Patients diagnosed with aggressive, dedifferentiated TC have a prognosis of under a year with the most current treatment modalities. Like many cancers, TCs also exhibit altered cell metabolism, which enhances the cell's ability to generate energy, protect against reactive oxygen species, and synthesize macromolecules such as lipids, proteins, and nucleotides for proliferation. Genetic and enzyme profiling of TC tissues and cell lines have uncovered several dysregulated metabolic pathways such as glycolysis, the pentose phosphate pathway, glutamine metabolism, and pyrimidine synthesis. These aberrations are most often due to overexpression of rate-limiting enzymes or metabolite transporters. Metabolic pathways pose attractive therapeutic targets in aggressive TC and may serve to work in tandem with standard therapeutics such as kinase inhibitors depending on the genetic, metabolic, and signaling backgrounds of individual tumors. Further studies are needed to clearly delineate altered metabolic targets across TC subtypes for implementing therapeutic metabolic inhibitors that have shown success in other aggressive tumors.

Keywords: Thyroid cancer, tumor metabolism, metabolic inhibitors, Warburg effect, cell signaling

INTRODUCTION

Thyroid cancer (TC) is the most common endocrine malignancy and is a concern due to the rapidly increasing incidence[1]. There are specific subtypes of TC that differ in appearance, genetic drivers, prognosis, and effective treatment options. Papillary thyroid cancer (PTC) is the most common subtype and is often diagnosed in people under 55 years of age[2]. PTC still resembles a normal thyrocyte and is well differentiated. Resection is currently the most effective treatment option with radioactive iodine (RAI) therapy serving as an ablation for remaining TC tissue[3]. PTC is canonically driven by consistently active BRAF via a *V600E* mutation[1]. Follicular thyroid cancer (FTC) is usually more aggressive than PTC and is often diagnosed in patients between 40 and 60 years old[4]. It is most often treated with surgery and typically carries a good prognosis. However, drug resistance and distant metastases can develop. FTC is unique amongst the TC subtypes as BRAF mutations are rare[5]. FTC is canonically driven by phosphoinositide 3-kinase (PI3K) signaling, usually through activating mutations in PI3K and copy number gains in receptor tyrosine kinases and Akt[1,6]. Poorly differentiated (PDTC) and anaplastic thyroid cancers (ATC) are highly aggressive and metastatic. PDTC and ATC are driven by $BRAF^{V600E}$, PI3K signaling, *TERT* promoter mutations, and mutated or loss of p53 expression[7-9]. The average lifespan for individuals diagnosed with PDTC/ATC is six months, amongst the shortest timeframe of all solid tumors[4,10]. Current therapies only extend survival to eleven months at best[3,10,11]; therefore, there is a clear and significant need for new treatment modalities in aggressive TCs for which current treatment regimens fail to significantly enhance disease-free survival.

Metabolic inhibitors pose as attractive potential options to address this need, as they have garnered significant treatment success in other tumor types, most notable antifolates in leukemias[12]. Cancer cells display a markedly different metabolic landscape, which parallels the altered signaling landscape these cells typically exhibit[13]. It is now known that many cancer cells demonstrate high glycolytic profiles with dysregulated oxidative phosphorylation and mitochondrial dynamics[14]. The increased rate of glycolysis not only supplies rapid ATP for the cell but also provides metabolic intermediates for protecting against reactive oxygen species and synthesizing nucleotides, lipids, and proteins for new daughter cells[13,14]. Although multiple metabolic processes have been shown to be dysregulated in TC, there has not been great attention on targeting these pathways for therapeutic intervention, particularly in cases of aggressive and often drug-resistant ATC. This review serves to summarize results in metabolism across the spectrum of TC differentiation while highlighting key areas that deserve further investigation that could potentially yield promising therapeutic efficacy.

GLYCOLYSIS

Glucose transporters

Glucose transporters (GLUT) are the first rate-limiting step in glycolysis [Figure 1] and often regulate cellular metabolism in general by limiting intracellular glucose flux[15]. There are 14 distinct isoforms of GLUTs which vary based on tissue localization and affinity for glucose[15]. Normal thyroid cells express GLUT 1, 3, 4, and 10[16-19]. GLUT 4 and 10 have not been found to be overexpressed in TC, but GLUT 1 and 3 are overexpressed in multiple forms of TC[16,17,19]. GLUT1 expression is inversely correlated with TC differentiation, as ATC has been shown to have the highest GLUT1 expression[16,17]. Furthermore, there appears to be a strong correlation between $BRAF^{V600E}$ and GLUT1 expression, possibly suggesting that TC cells driven by MAPK signaling require a high flux of glucose to fuel proliferation[19,20]. GLUT3 is expressed even more than GLUT1 in some PTC tumors and was overexpressed in well differentiated TC cell lines[21].

There have been several GLUT inhibitors investigated for limiting glucose import in cancer cells. Although not specific for GLUTs, the flavonol quercetin directly binds to GLUT1 and can limit GLUT4 localization to

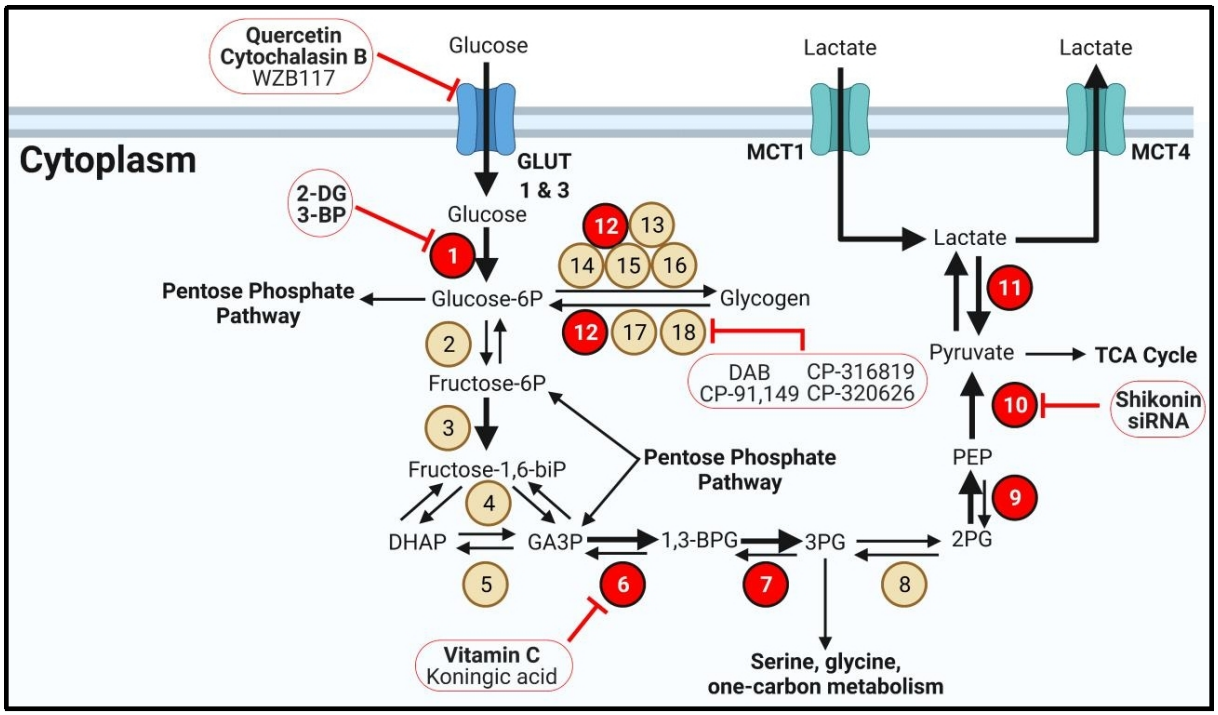

Figure 1. Glycolysis and glycogen metabolism. Glycolytic enzymes and transporters are dysregulated in many forms of thyroid cancer. Bold text for transporters indicates overexpression. Bold arrows indicate increased metabolite flux. Beige circles indicate enzymes not shown to be aberrantly expressed in TC. Red circles display overexpressed enzymes in TC. Inhibitors are outlined in red circles with conjoining red inhibitor (T) bars. Inhibitors in bold have demonstrated efficacy in TC models. Enzyme/transporter key: 1. Hexoxinase; 2. Glucose-6-phosphate isomerase; 3. Phosphofructokinase-1; 4. Aldolase A; 5. Triose phosphate isomerase; 6. Glyceraldehyde-3-phosphate dehydrogenase; 7. Phosphoglycerate kinase 1; 8. Phosphoglycerate mutase; 9. Enolase; 10. Pyruvate kinase; 11. Lactate dehydrogenase, 12. Phosphoglucomutase-1; 13. UDP-glucose pyrophosphorylase 2; 14. Glycogenin; 15. Glycogen synthase 1; 16. Glycogen branching enzyme; 17. Glycogen debranching enzyme; 18. Glycogen phosphorylase. MCT: Monocarboxylate transporter.

the plasma membrane via inhibiting PI3K[22-24]. Quercetin induced apoptosis in PTC cells *in vitro*[25]. Cytochalasin B, a mycotoxin that binds in the central cavity of GLUT1, significantly limited glucose uptake in PTC cells[26]. Recently, more selective and potent GLUT inhibitors have been developed such as Glutor. Glutor is highly potent and selective for GLUT 1 and 3 and has demonstrated success at inhibiting growth *in vitro* with nearly 100 cancer cell lines but not TC cells[27].

Once glucose has entered the cell, it is irreversibly phosphorylated by hexokinases (HK) to generate glucose-6-phosphate (G6P), preventing it from being exported[15]. High HK expression is correlated with $BRAF^{V600E}$ status as well as poor survival in PTC patients[28]. Furthermore, PDTC and ATC almost always have the highest HK expression in TC[18,28]. The most well-studied HK inhibitor is 2-deoxyglucose (2-DG), a glucose analog that is unable to be phosphorylated. 2-DG limited PTC, FTC, and ATC growth *in vitro* and reduced tumor size in an ATC xenograft[29-31]. 3-bromopyruvate is a similar inhibitor of HK that reduced PDTC growth *in vitro* but is not currently in any clinical trials[32]. Although HK is an attractive target as the first rate-limiting step in glycolysis, unwanted toxicity may prove to be a difficult challenge to manage clinically. Additionally, glycolysis is crucial for the activation of T cells, dendritic cells, natural killer cells, and B cells to initiate an immune response[33,34]. Targeting specific metabolic pathways that are uniquely dysregulated in an individual tumor may limit unwanted deleterious effects on the immune system.

JOURNEY TO PYRUVATE

Following glucose phosphorylation and isomerization via glucose phosphate isomerase, phosphofructosekinase-1 generates fructose-1,6-bisphosphate (fructose-1,6-biP)[15,35]. Two molecules of glyceraldehyde-3-phosphate (GA3P) are generated from fructose-1,6-biP via aldolase A and triose phosphate isomerase[15,35]. Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) converts GA3P to 1,3-bisphosphoglycerate (1,3-BPG) and forms ATP in the process. GAPDH is overexpressed in PTC and FTC and is a promising drug target[31]. Kumagai *et al.*[36] reported that koningic acid, a GAPDH inhibitor, inhibited proliferation of leukemia cells in addition to murine breast, Ehrlich ascites, and fibrosarcoma cells *in vitro* as well as Ehrlich ascites *in vivo*. Interestingly, vitamin C has been found to inhibit PTC, FTC, and ATC growth *in vitro*; Su *et al.*[37] reported that pharmaceutical grade injections of vitamin C slowed ATC tumor growth by inducing reactive oxygen species and inhibiting MAPK and PI3K signaling via GAPDH inhibition.

1,3 BPG then generates ATP and 3-phosphoglycerate (3PG) by phosphoglycerate kinase (PGK1) which was highly expressed in a PTC model (B-CPAP cells) as well as PTC tissue[38,39]. Following isomerization via phosphoglycerate mutase, enolase generates phosphoenolpyruvate (PEP)[15,35]. Enolase 1 (ENO1) is expressed ubiquitously while enolase 2 (ENO2) is typically found in neurons and has been recommended as a tumor marker for its high expression in some cancers[40]. ENO1 is overexpressed in the B-CPAP cell line while ENO2 was highly expressed in B-CPAP and FTC-133 cells[31,39]. Since cancer cells rely so heavily on glycolysis for ATP and the metabolic intermediate pyruvate, these reactions in glycolysis provide promising targets for pharmacological intervention in TC.

Pyruvate kinase

The final rate-limiting step of glycolysis is pyruvate kinase (PKM1)[15,35]. While PKM1 is expressed in most tissues and serves only to phosphorylate PEP, PKM2 is frequently overexpressed in cancers and acts as a strict checkpoint to regulate the metabolic demands of cancer cells[41,42]. PKM2 is often found as a tetramer, in which it forms pyruvate from PEP. Unlike PKM1, PKM2 is allosterically regulated by fructose-1,6-biP to enhance enzymatic activity on PEP to increase the rate of glycolysis in cancer cells[42-44]. A key difference between isozymes is that the PKM2 tetramer is stabilized by the presence of serine and succinyl-5-aminoimidazole-4-carboxamide-1-ribose 5-phosphate (SAICAR), important intermediates of one carbon metabolism and purine synthesis[45]. When nucleotide levels are high, the cell is able to employ these two metabolites to encourage glycolysis for ATP and NADH production. When serine and SAICAR levels are low, PKM2 adopts its dimer form which has a dramatically reduced affinity for PEP. As a dimer, PKM2 moonlights as a protein kinase for over one hundred substrates such as EGFR, HER2, FGFR, cell-cycle proteins, and notable to TC, ERK[46]. ERK is not only phosphorylated by PKM2 but it phosphorylates PEP in a positive feedback loop to encourage adopting the PKM2 dimer form. As a dimer, glycolysis bottlenecks as PEP levels rise, favoring the reverse reactions via partial gluconeogenesis to 2PG and 3PG. 3PG is then anabolized to serine via three reactions which will favor the tetrameric form of PKM2, continuing glycolysis[15,35]. PKM2 represents a critical junction in cancer metabolism by simultaneously regulating glycolysis and nucleotide metabolism while phosphorylating several tumor promoters. There is only one PKM1/2 inhibitor available, shikonin. Shikonin inhibits multiple cell processes in addition to PKM2 but was effective at slowing FTC growth *in vivo*[47,48]. Additionally, siRNA against PKM2 demonstrates robust activity at inhibiting PTC growth *in vitro* and *in vivo*[49].

FATE OF PYRUVATE IN THE CYTOPLASM

Pyruvate can be funneled into the tricarboxylic acid (TCA) cycle for further ATP generation or may be converted to lactate to replenish glycolytic intermediates[15]. In highly glycolytic tumors such as aggressive,

dedifferentiated TC, pyruvate is frequently converted to lactate by lactate dehydrogenase (LDH)[39,50]. This reaction is significant for regenerating NAD+ from NADH[15]. The NAD+ can then serve as a cofactor for GAPDH in glycolysis, further generating ATP. LDH is a tetramer frequently composed of LDHA and LDHB subunits. LDHA is typically expressed in the liver and skeletal muscle while LDHB is found in the kidneys and heart muscle[15]. Importantly, LDHA preferentially converts pyruvate to lactate, generating NAD+, while LDHB performs the opposite reaction[15]. The predominantly expressed isotype may shed light onto the preferential route of metabolism in cancer cells. There are seemingly conflicting reports on LDH expression and function in TC. Mirebeau-Prunier *et al.*[51] found that FTC cells and tissue samples exhibit high LDHB/LDHA ratios based on mRNA levels of each isoform. Kachel *et al.*[52] reported that LDHA protein is mildly overexpressed in FTC and PTC but not ATC compared to non-tumor tissues, while only ATC demonstrated significantly higher transcript levels of LDHA. Similarly, Coelho *et al.*[53] discovered that PTC cell lines showed no differences in LDHA transcript levels compared to normal thyroid cells. Paradoxically, both sets of PTC cells demonstrated higher lactate production rates[53]. Taken together, these three studies may reflect a lack of correlation between LDH transcript expression with protein expression and that post translational modifications are highly important for LDH activity. Indeed, Kachel *et al.*[52] showed that FGFR1 mediated phosphorylation and activity of LDHA, and p-LDHA was markedly elevated in PTC, FTC, and ATC tumors. Cells that maintain a high LDHA/LDHB isozyme ratio may favor converting pyruvate to lactate to continue glycolysis. Excess lactate can then be exported to the stroma via monocarboxylate transporter 4 (MCT4) to prevent reconversion to pyruvate and acidify the tumor microenvironment (TME)[54]. Inhibiting lactate production and export could help balance the pH of the TME to protect infiltrating immune cells. Indeed, limiting TME lactate levels protects naïve T cells from apoptosis[33]. A cancer cell that maintains a high LDHB/LDHA ratio, however, may rely on lactate produced by cancer associated fibroblasts (CAFs) that is imported via MCT1[54,55]. The lactate is then converted to pyruvate and NADH. This phenomenon has been coined the "reverse Warburg effect", in which cancer cells are able to exploit the high energy lactate from CAFs for anabolism without requiring ATP investment to oxidize glucose[56]. There is strong evidence supporting MCT expression in TC. Patient derived samples revealed that PTC, FTC, and ATC all express MCT4 for lactate export, with ATC having the highest expression of all types of TC[28]. However, MCT1 was only found expressed at an appreciable level in samples from ATC patients[55]. This is unsurprising, as all types of TC expressed a method for exporting lactate from highly glycolytic cells. The MCT1/4 expression pattern may reveal an avenue of metabolic plasticity in ATC, in which these highly dedifferentiated, aggressive tumors are able to shuttle lactate in and out of the cell depending on the precise metabolic demand that is met by pyruvate dehydrogenation.

GLYCOGEN METABOLISM

In a well-fed state, cells may store excess glucose in the form of glycogen, which is normally found in high quantities in the liver, muscle, and brain[15]. However, many cancers have been found to metabolize glycogen outside of these tissue types[57-60]. To date, there have been no direct reports of glycogen in TC, yet glycogen can be detected in bovine and canine thyroids[61]. Furthermore, there are rare cases of clear cell thyroid carcinomas, aggressive tumors filled with solid deposits that may contain glycogen[62]. Phosphoglucose mutase (PGM1) appears to be one of the few reported enzymes that is overexpressed in the pathway, as shown in PTC and FTC cells[31]. Although not a rate-limiting enzyme, PGM1 represents an important step in glycogen metabolism that acts in both anabolism and catabolism[63]. PGM1 converts G6P to glucose-1-phosphate (G1P) and then to uridine diphosphate glucose via UDP-glucose pyrophosphorylase 2 for incorporation into glycogen. Glycogen synthase 1 forms 1-4 α glycosidic linkages with UDP-glucose onto an already formed glycogen granule initiated by the self-glycosylating primer, glycogenin. Glycogen branching enzyme (GBE) forms 1-6 α linkages to create branches of G1P monomers[15,35]. In a starved state, the cell relies on glycogen phosphorylase (PYG) to cleave 1-4 α glycosidic bonds to liberate G1P monomers from

the ends of glycogen chains. Glycogen debranching enzyme assists in this process by removing G1P 1-6 α glycosidic bonds formed by GBE[64].

There are several inhibitors designed to target the rate-limiting enzyme of glycogen breakdown, PYG. 1,4-dideoxy-1,4-amino-D-arabinitol (DAB) is a potent PYG inhibitor and the only one that directly inhibits the PYG active site[65,66]. DAB prevented hypoxia-induced cell survival in colorectal and breast cancer cells following glucose deprivation[63]. The remaining PYG inhibitors discussed here bind to the allosteric "indole" pocket of PYG, named for the indole structure these inhibitors contain[58,60]. CP-91,149 was designed to treat diabetes and was able to significantly decrease blood glucose levels in obese mice without inducing hypoglycemia in lean mice[67]. CP-91,149 is a pan PYG inhibitor that reduced cell viability in models of hepatocellular, prostate, and lung carcinoma[68-70]. Excitingly, CP-91,149 was highly synergistic with the BRAF inhibitor sorafenib in hepatocellular carcinoma, which is the standard therapy for ATC[69]. Additionally, CP-316819 enhanced melatonin cytotoxicity in Ewing sarcoma cells, and CP-320626 induced apoptosis in pancreatic carcinoma cells[71,72]. Although PYG inhibitors have demonstrated robust success *in vitro*, these promising results have yet to be validated for *in vivo* tumor models, let alone in any TC model. Therefore, glycogen metabolism represents an exciting but unexplored avenue of therapeutic intervention in TC.

THE PENTOSE PHOSPHATE PATHWAY

In addition to supplying energy and reducing equivalents in the form of ATP and NADH, glycolysis is used to generate the building blocks for nucleotide synthesis and protecting against reactive oxygen species (ROS) via the pentose phosphate pathway (PPP) [Figure 2][73,74]. G6P can be diverted to the PPP via glucose 6 phosphate dehydrogenase (G6PDH). This enzyme forms 6-gluconophospholactone and regenerates NADPH from NADP+. NADPH is used in fatty acid synthesis and reduces redox enzymes[15,35,73,74]. G6PDH is the rate-limiting step in the PPP and represents an attractive target in cancer cell metabolism, particularly in TC which has been shown to overexpress the enzyme in PTC, FTC, and ATC cells[31,75]. 6-aminonicatinomide (6-AN) is a selective, competitive inhibitor of G6PDH that demonstrated success in inducing apoptosis in PTC and ATC models[75]. Following conversion to 6PG via 6-phosphogluconolactonase, 6-phosphogluconate dehydrogenase (6PGDH) forms another equivalent of NADPH as well as the intermediate ribulose-5-phosphate (RL5P)[73]. 6PGDH was found to be significantly expressed in PTC fine-needle aspirations as well as cell culture models of ATC following doxorubicin treatment, possibly representing an evolutionary drug resistance mechanism[76,77]. This resistance was overcome by inhibiting 6PGDH with physcion, which re-sensitized ATC cells to doxorubicin[76]. RL5P is converted to an epimer via ribulose-5-phosphate 3-epimerase (forming xylulose-5-phosphate, X5P) or isomer using ribose-5-phosphate isomerase (forming ribose-5-phosphate, R5P) depending on the balance of products and metabolic requirements in the cell[15,35,73,74]. R5P serves as the building block for forming nucleotides. One equivalent of R5P and two equivalents of X5P are required to regenerate the glycolytic intermediates GA3P and F6P. These interconversions are performed by transketolase and transaldolase[35,73,74]. Transketolase is overexpressed in PTC and ATC cells, and inhibition by oxythiamine suppressed PTC and ATC growth and exhibited drug additivity with 6-AN[75]. The PPP is a crucial metabolic pathway in cancer cells for forming nucleotides, a requirement for DNA synthesis and cell division, and combating excessive levels of ROS. Inhibitors of this pathway have demonstrated impressive success in ATC cell culture models, warranting further investigations *in vivo*.

FATE OF PYRUVATE IN THE MITOCHONDRIA

In a highly glycolytic cancer cell, pyruvate is most frequently converted to lactate[78-80]. However, pyruvate can also generate acetyl-CoA for use in the TCA cycle. High pyruvate levels favor transport into the

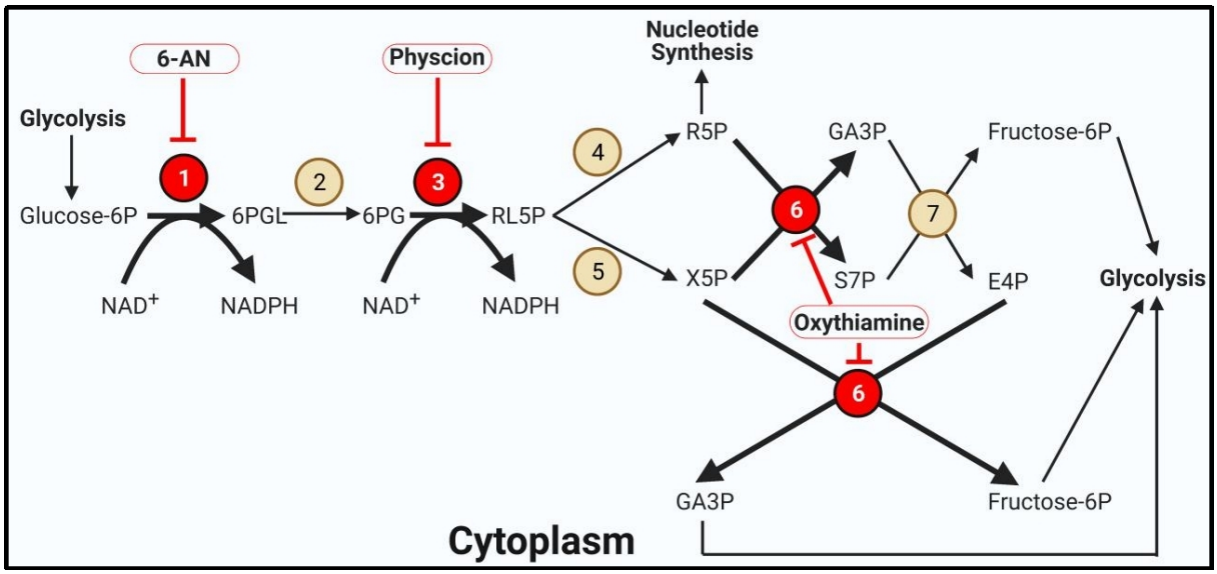

Figure 2. The pentose phosphate pathway. The pentose phosphate pathway is highly active in thyroid cancer. Bold arrows indicate increased metabolite flux. Beige circles indicate enzymes not shown to be aberrantly expressed in TC. Red circles display overexpressed enzymes in TC. Inhibitors are outlined in red circles with conjoining red inhibitor (T) bars. Inhibitors in bold have demonstrated efficacy in TC models. Enzyme key: 1. Glucose-6-phosphate dehydrogenase; 2. 6-Phosphogluconolactonase; 3. 6-Phosphogluconate dehydrogenase; 4. Ribose-5-phosphate isomerase; 5. Ribulose-5-phosphate 3-epimerase; 6. Transketolase; 7. Transaldolase.

mitochondria via mitochondrial pyruvate carrier 1 and 2[81]. High concentrations of NAD+, PEP, and pyruvate encourage the dehydrogenation to acetyl-CoA via pyruvate dehydrogenase (PDH)[15,35]. Along with acetyl-CoA, PDH forms another molecule of NADH from NAD+. The acetyl-CoA is then able to progress in the TCA cycle[15,35]. In reality, this reaction does not occur at an appreciable rate in cancer cells due to the rare instance of the cell having a high NAD+/NADH ratio[82]. Instead, mitochondrial pyruvate is more likely to be irreversibly converted to oxaloacetic acetate (OAA) via pyruvate carboxylase, which requires ATP and bicarbonate[83]. OAA may be used to refuel the TCA cycle if mutations in isocitrate dehydrogenase or succinate dehydrogenase cause a broken TCA cycle [Figure 3][83]. In some cancers, the mitochondrial isoform of PEP carboxykinase (PEPCK) converts OAA to PEP for transport to the cytoplasm via the mitochondrial citrate carrier (CIC)[84]. This is the only method for a cell to convert pyruvate back to PEP for gluconeogenesis[15,35].

Interestingly, Vincent *et al.*[84] reported that out of several types of solid tumors they investigated, PTC samples had the highest expression of PEPCK, and 3-Mercaptopropionic acid inhibited PEPCK in lung cancer cells. Despite this observation, PEPCK inhibition remains an unexplored target in TC. Finally, CIC is overexpressed in PTC and ATC, at least in part through dysregulation in a lncRNA-miRNA axis[85]. ShRNA targeted against CIC resulted in reduced PTC and ATC cell migration *in vitro*[85].

THE TCA CYCLE

In cancer cells, the TCA cycle serves as a hub for anaplerosis and fatty acid metabolism, often being co-opted by overexpression or mutations of key enzymes to fuel cancer progression. Citrate is formed from OAA and acetyl-CoA via citrate synthase. Citrate can be converted to isocitrate via aconitase and then to alpha ketoglutarate (αKG) via isocitrate dehydrogenase (IDH)[15,35]. However, isozymes of IDH are frequently mutated in several cancers, causing the first stall in the TCA cycle[86-88]. IDH mutations form the oncometabolite 2-hydroxyglutarate (2-HG) at higher rates than wildtype IDH, which competitively inhibits several nuclear proteins such as histone and RNA demethylases and DNA methylation and repair

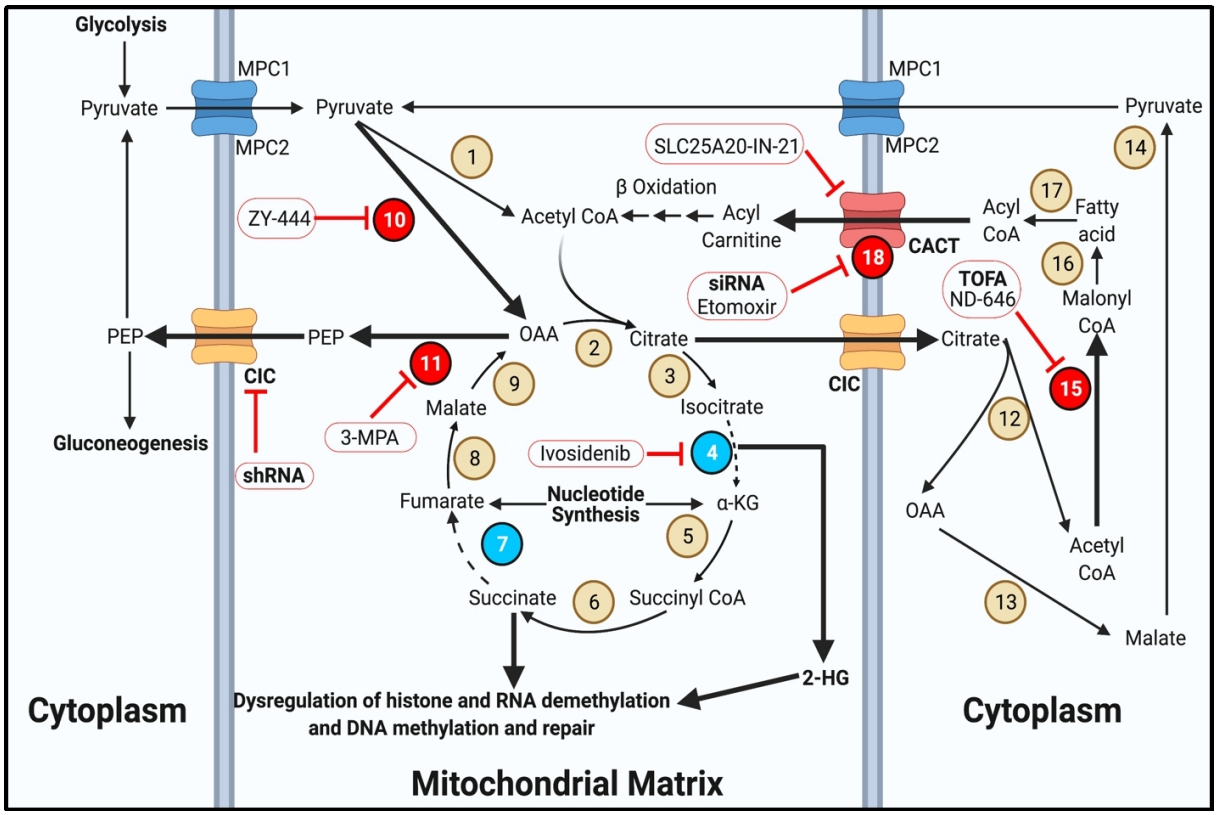

Figure 3. TCA cycle and fatty acid metabolism. The TCA cycle and fatty acid metabolism serve to replenish intermediates for metabolic pathways in thyroid cancer. Bold text for transporters indicates overexpression. Bold arrows indicate increased metabolite flux. Beige circles indicate enzymes not shown to be aberrantly expressed in TC. Red bubbles display overexpressed enzymes in TC. Cyan bubbles indicate mutated or underexpressed enzymes in TC. Inhibitors are outlined in red circles with conjoining red inhibitor (T) bars. Inhibitors in bold have demonstrated efficacy in TC models. Enzyme/transporter key: 1. Pyruvate dehydrogenase; 2. Citrate synthase; 3. Aconitase; 4. Isocitrate dehydrogenase; 5. Alpha ketoglutarate dehydrogenase; 6. Succinyl-CoA synthetase; 7. Succinate dehydrogenase; 8. Fumarase; 9. Malate dehydrogenase 2; 10. Pyruvate carboxylase; 11. Phosphoenolpyruvate carboxykinase 2; 12. ATP-citrate lyase; 13. Malate dehydrogenase 1; 14. Malic enzyme; 15. Acetyl-CoA carboxylase; 16. Fatty acid synthase; 17. Acyl-CoA synthetase; 18. Carnitine palmitoyltransferase 1. CIC: Mitochondrial citrate carrier; CACT: carnitine acylcarnitine translocase; MPC: mitochondrial pyruvate carrier.

enzymes[86,88]. 2-HG is likely best studied in glioblastoma, in which high levels of 2-HG have been shown to induce vascularization via epigenetic reprogramming[87]. There have been numerous reports of IDH1 mutations in TC patients representing at least seven unique amino acid substitutions across PTC, FTC, and ATC subgroups[89,90]. Regardless of these specific IDH1 mutations promote the 2-HG formation, high levels of wildtype IDH increased 2-HG levels in PTC[91]. Continuing in the cycle, αKG forms succinyl-CoA by alpha ketoglutarate dehydrogenase and then succinate by succinyl-CoA synthetase[15,35]. Succinate is normally converted to fumarate via succinate dehydrogenase (SDH), then to malate via fumarase, and finally back to OAA by malate dehydrogenase 2[15,35]. SDH, a bona fide tumor suppressor, is frequently mutated or underexpressed in cancers[92,93]. There are reports of several single nucleotide polymorphisms in *SDHB* and *SDHD* in PTC and FTC patients[94,95]. Additionally, tumors with wildtype *SDHx* exhibited lower expression of *SDHB* and *SDHD* compared to matched normal tissue, suggesting a mutually exclusive mechanism for succinate buildup[93,94]. This second break in the TCA cycle can cause an increase in succinate levels which acts in a similar fashion to 2-HG in the nucleus[93]. Although SDH function cannot be restored in TC patients, IDH inhibitors are effective treatment options in other cancers. The pan IDH inhibitor ivosidenib significantly reduced tumor burden in patients with IDH mutations and is approved for

use in AML[96]. IDH inhibitors may be useful in treating TC tumors harboring IDH mutations or elevated 2-HG levels.

FATTY ACID METABOLISM

Fatty acids have long been accepted to play an oncogenic role in cancer. They represent a rich carbon source that can be synthesized *de novo* or taken up from the bloodstream to contribute to hormone synthesis, membrane expansion, energy storage, and cell signaling[97-99]. In ATC, fatty acid synthesis is crucial for maintaining endoplasmic reticulum homeostasis and the unfolded protein response[100,101]. Fatty acids are first synthesized from citrate produced in the TCA cycle. Citrate is exported to the cytoplasm via CIC where it is split into acetyl-CoA and OAA via malate dehydrogenase 1. The liberated malate is converted to pyruvate via malic enzyme[15,35]. Excess acetyl-CoA in the cytoplasm is converted to malonyl CoA via the rate-limiting enzyme, acetyl-CoA carboxylase (ACC), which is overexpressed in PTC, FTC, and ATC[102]. Although not tested in TC, ND-646 can specifically inhibit ACC[103]. The ACC inhibitor TOFA [5-(tetradecyloxy)-2-furoic acid], inhibited PTC, FTC, and ATC growth *in vitro*, which was reversible with the addition of palmitic acid[102]. Several rounds of fatty acid synthase will form long chain fatty acids in the cytoplasm. When the cell reaches a low energy state, fatty acids are catabolized to acyl CoA via acyl-CoA synthetase. Acyl-CoA is converted to acyl-carnitine via carnitine palmitoyltransferase 1 (CPT1) for entry into the mitochondria via carnitine acylcarnitine translocase (CACT)[15,35]. CPT1 is overexpressed in several cancers, including PTC[104]. Although the classic CPT1 inhibitor etomoxir does not appear to have been tested in TC models, siRNA against CPT1 decreased PTC growth[104]. CACT can be overexpressed in FTC tumors harboring a PPAR-PAX8 fusion, but the specific CACT inhibitor, SLC25A20-IN-21, has not been investigated in cancer models[105,106]. Acyl-carnitine requires conversion back to acyl-CoA via CPT2 and several rounds of beta oxidation using multiple enzymes to liberate acetyl-CoA for use in the TCA cycle[15,35]. Fatty acid metabolism represents an exciting if underrepresented area in TC metabolism.

NUCLEOTIDE SYNTHESIS

Highly proliferative cancer cells require an abundance of nucleotides for replicating the genome. Although some of this high nucleotide requirement is met by diet and bloodstream uptake, the vast majority is synthesized *de novo*[73,107-111]. Nucleotide synthesis makes use of several metabolites from central metabolic pathways [Figure 4]. The PPP is required for the ribose base and NADPH as a reducing agent; glutamine and aspartate donate nitrogen, and glycine and serine donate specific carbon atoms for the nucleoside base[15,35]. Although specific purine metabolism enzymes do not appear to be overexpressed in TC, pyrimidine enzymes are shown to be aberrantly expressed in multiple models of TC.

Pyrimidine synthesis

Pyrimidine synthesis begins with R5P following conversion to phosphoribosylpyrophosphate (PRPP). Five additional steps requiring glutamine transform PRPP to UMP[15,35]. UMP is phosphorylated to UDP via uridine-cytidine kinase 2 (UCK2), which is overexpressed in PTC (TCGA)[112]. Flavokawain B from the kava plant has activity against UCK2 and was effective against FTC *in vivo*[113]. UDP can be phosphorylated to UTP and converted to CTP using glutamine and CTP synthetase (CTPS), which is overexpressed in PTC (TCGA)[112]. CTPS can be inhibited using the nucleoside analog gemcitabine which is incorporated into replicating DNA strands[114]. Gemcitabine is currently in a phase II clinical trial for differentiated and metastatic PTC and FTC[115], while *in vitro* efficacy has been demonstrated in ATC[116]. Inhibiting CTPS is an attractive target because in addition to preventing CTP synthesis, UTP is necessary for glycogen synthesis, and excess UTP has potential for incorporation into DNA, forming mismatches with GTP[35,117-119]. UDP can also be reduced and phosphorylated in sequence to form dUMP, which is converted to dTMP by thymidylate synthase (TYMS)[15,35]. TYMS is overexpressed in a variety of cancers including PTC and

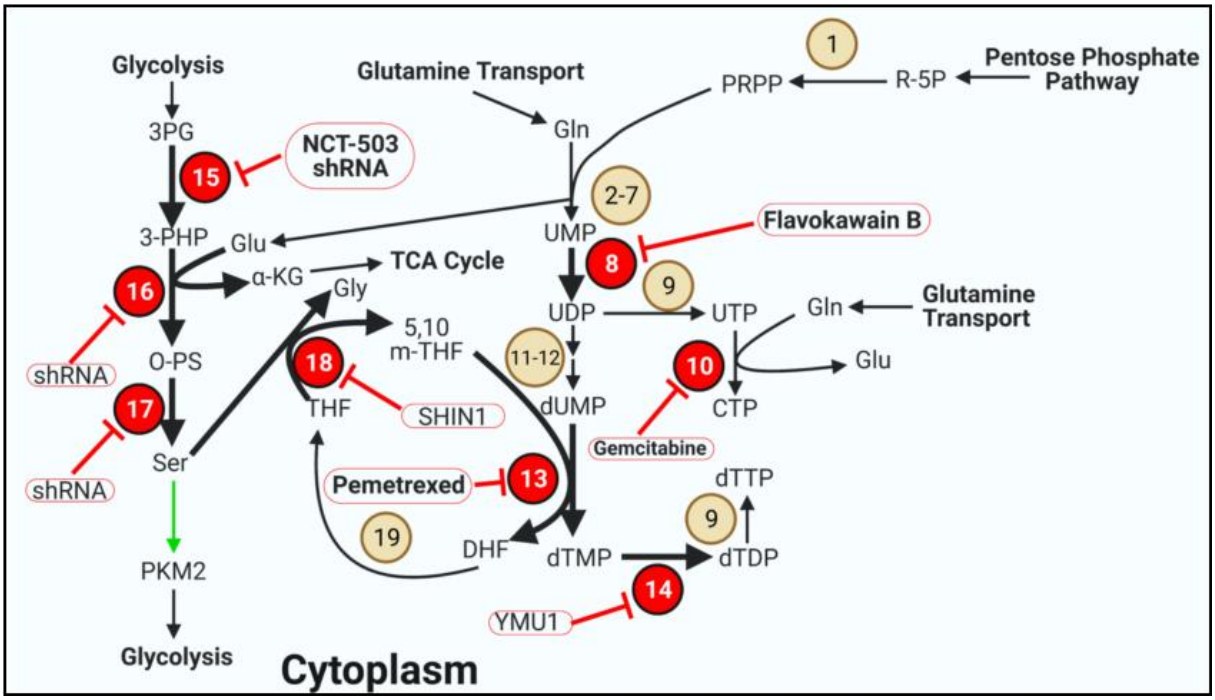

Figure 4. Pyrimidine synthesis and one carbon metabolism. Several enzymes involved in pyrimidine synthesis and one carbon metabolism are overexpressed in thyroid cancer. Bold arrows indicate increased metabolite flux. Beige circles indicate enzymes not shown to be aberrantly expressed in TC. Red circles display overexpressed enzymes in TC. Inhibitors are outlined in red circles with conjoining red inhibitor (T) bars. Inhibitors in bold have demonstrated efficacy in TC models. Green arrows indicate allosteric regulation of the indicated enzyme. Enzyme/transporter/metabolite key: 1. PRPP synthetase; 2. Carbamoyl-phosphate synthetase 2; 3. Aspartate transcarbamoylase; 4. Dihydroorotase; 5. Dihydroorotate dehydrogenase; 6. Orotate phosphoribosyltransferase; 7. Orotidine-5 - phosphate decarboxylase; 8. Uridine-cytidine kinase 2; 9. Nucleoside diphosphate kinase A; 10. CTP synthetase; 11. Ribonucleotide reductase; 12. dUTP diphosphatase; 13. Thymidylate synthase; 14. Deoxythymidylate kinase; 15. Phosphoglycerate dehydrogenase; 16. Phosphoserine aminotransferase 1; 17. Phosphoserine phosphatase; 18. Serine hydroxymethyltransferase 1; 19. Dihydrofolate reductase. PKM2: Pyruvate kinase 2.

FTC[112,120]. TYMS is an attractive metabolic target and one of the earliest targets in cancer using antifolates[121]. Now there are several TYMS inhibitors such as pemetrexed, which also has activity against dihydrofolate reductase (DHFR). Pemetrexed was well tolerated in a Phase Ib safety evaluation in advanced/metastatic TC and is in a phase II clinical trial in combination with paclitaxel for aggressive TC[122,123]. dTDP is phosphorylated to dTTP via deoxythymidylate kinase (DTYMK), which is also overexpressed in PTC[112]. YMU1 is a specific inhibitor of DTYMK that was effective at sensitizing breast, colorectal, and bone cancer cells to doxorubicin while reducing colon cancer growth *in vivo*[119].

ONE CARBON METABOLISM

Several of the steps outline in nucleotide metabolism build upon the nitrogenous and ribonucleotide bases a few atoms at a time. These carbons are provided by glycine and folate derivates which are generated from serine[15,35,107-110]. Highly active serine synthesis is a hallmark of cancer metabolism and represents attractive targets for therapy, particularly in TC in which all three enzymes are overexpressed in PTC and ATC[124]. 3PG generated in glycolysis is converted to 3-PHP by phosphoglycerate dehydrogenase (PGDH)[15,35]. Both NCT-503 and shRNA demonstrated robust success in inhibiting PGDH to reduce PTC and ATC cell viability[125]. 3-PHP is converted to O-PS by phosphoserine aminotransferase 1 (PSAT1), generating αKG from OAA in the process. O-PS is dephosphorylated to serine via phosphoserine phosphatase (PSPH)[15,35]. While there are currently no specific inhibitors for PSAT1 or PSPH, shRNA against each enzyme were

effective at inhibiting breast and lung cancer respectively[126,127]. Serine is converted to glycine in the cytoplasm via serine hydroxymethyltransferase 1 (SHMT1) to donate a methylene group to tetrahydrofolate (THF), forming 5,10 m-THF in the process[35]. SHMT1 is high in PTC and ATC and can be inhibited with SHIN1, which has a high affinity for both isoforms of SHMT[124,128]. The 5,10 m-THF is then used for dTMP generation via TYMS, forming dihydrofolate (DHF) in the process. DHF is converted back to THF via DHFR, which requires NADPH to be re-oxidized[15,35].

GLUTAMINE METABOLISM

Glutamine is recognized as one of the most important amino acids in cancer metabolism[129]. It acts as a carbon and nitrogen source for a variety of important biosynthetic pathways. Glutamine is the most abundant amino acid in serum and is taken up by the cell by a few transporters, most notably alanine, serine, cysteine transporter 2 (ASCT2) [Figure 5][130]. ASCT2 expression is correlated with $BRAF^{V600E}$ and is expressed the highest in PDTC tumors[131]. Small molecules such as L-γ-Glutamyl-p-nitroanilide, phenylacetate, and V-9302 are selective inhibitors for blocking ASCT2-mediated glutamine transport[132-135]. Notably, phenylacetate inhibited PTC and FTC growth *in vitro*[136]. Once in the cell, glutamine can immediately be used in several steps of nucleotide synthesis to donate nitrogen atoms to the ribose base[35,111,129]. In the cytoplasm, glutamine can be exchanged for neutral non-branched amino acids via LAT1 which was highly expressed in PTC and ATC[137]. JPH203, a LAT1 inhibitor, slowed TC growth *in vitro* and inhibited ATC growth in xenograft models[137,138]. Glutamine can also be converted to glutamate by glutaminase (GLS1/2), which is highly expressed in PTC, FTC, and ATC[131,139]. Glutaminase inhibitors such as CB-839 and BPTES have already demonstrated success at inhibiting PTC and ATC growth *in vitro*[140,141]. Glutamate and aspartate can be transaminated to αKG and OAA via aspartate aminotransferase. These anaplerotic reactions are essential for replenishing TCA cycle intermediates from excess glutamate and aspartate[15,35]. Glutamate can directly be converted to αKG in the mitochondria via glutamate dehydrogenase (GDH), which is overexpressed in PTC, FTC, and ATC[131]. GDH is inhibited by epigallocatechin gallate, which worked well in PTC and FTC to slow growth[142].

THYROID CANCER METABOLISM AND CELL SIGNALING INTEGRATION

It is important to understand the metabolic landscape of an individual tumor to strategically inhibit aberrant metabolic pathways [Figure 6]. PTC and ATC tumors typically exhibit overactive MAPK signaling due to $BRAF^{V600E}$[1]. Hyperphosphorylation of the downstream targets of BRAF, MEK and ERK, leads to increased cell proliferation, survival, and inhibition of apoptosis by regulating oncogene transcription[143]. Constitutively activated BRAF strongly correlates with enhanced expression of all three serine synthesis genes[124]. Whether this observation is simply a correlation, or if these genes are directly regulated by MAPK signaling is unknown. At least in PTC, PKM2 is highly expressed, which increases the rate of glycolysis, and PKM2 is further activated by high serine levels[45,46,49]. Low serine levels cause PKM2 to adopt a dimer configuration to support serine and nucleotide synthesis. This is further promoted by ERK-mediated phosphorylation, and p-PKM2 can phosphorylate ERK in return to enhance oncogenic signaling[42,44,46]. This serine-PKM2-ERK axis may represent an unexplored metabolic switch in TC tumors driven by $BRAF^{V600E}$. In contrast to PTC, FTC (and ATC) tumors demonstrate highly active PI3K signaling. The tumor promoters Akt and mTORC1 are phosphorylated as a result of aberrant PI3K activity and have major roles in macromolecule synthesis. Akt stimulates fatty acid and glycogen synthesis while mTORC1 promotes protein synthesis by regulating translation factors and inhibits autophagy[1,6,144-146]. Accordingly, FTC tumors have been shown to upregulate fatty acid metabolism via ACC and CACT[102,105], the glycogen buildup and breakdown enzyme PGM1[31], and enzymes for amino acid metabolism such as ASCT2, GLS, and GDH[131,139]. There may be a connection between the aberrant signaling landscape in FTC tumors and these specific metabolic pathways. FTC tumors may be primed to store carbon in the form of glycogen and fatty

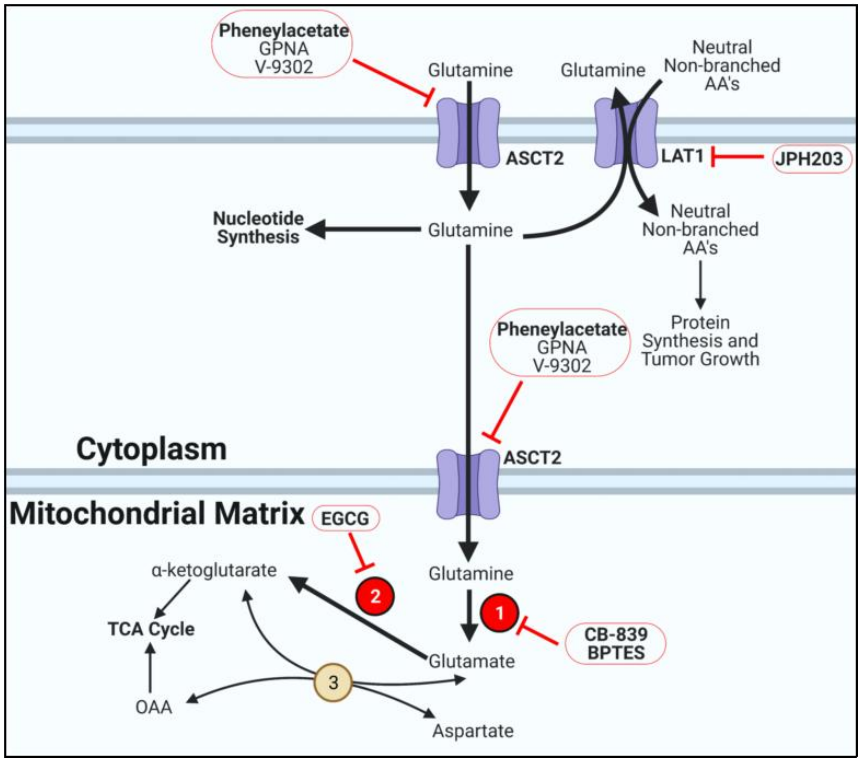

Figure 5. Glutamine metabolism. Thyroid cancer cells overexpress glutamine transporters and enzymes to fuel tumor progression. Bold arrows indicate increased metabolite flux. Beige circles indicate enzymes not shown to be aberrantly expressed in TC. Red circles display overexpressed enzymes in TC. Inhibitors are outlined in red circles with conjoining red inhibitor (T) bars. Inhibitors in bold have demonstrated efficacy in TC models. Enzyme key: 1. Glutaminase; 2. Glutamate dehydrogenase; 3. Aspartate aminotransferase.

acid via Akt. Metformin, a pan-metabolic inhibitor, activates AMPK to inhibit mTOR1 and decrease blood glucose and insulin levels. Metformin was effective at inhibiting PTC, FTC, and ATC growth *in vitro* and is currently in a phase II clinical trial in combination with RAI for differentiated TC[31,147-149].

MAPK signaling converges with PI3K signaling to regulate the expression and function of MYC and HIF1A. Akt and mTORC1 upregulate MYC expression via enhancing translation[150-152], and Akt signaling also inhibits phosphorylation of MYC at thr58, preventing degradation[150,153]. MAPK signaling phosphorylates MYC at ser62, extending the half-life[150,153]. PI3K and MAPK signaling both enhance HIF1A expression through increased translation. MYC and HIF1A are considered the Warburg effect gatekeepers, as both MYC and HIF1A are frequently overexpressed in TC and increase the expression of several rate-limiting enzymes in glycolysis such as GLUTs, HK, PGK1, LDH, and MCTs as well as G6PDH and GLS[18,50,151,152,154,155]. Unsurprisingly, nearly all of these genes are increased in PTC, FTC, and ATC, which represent important steps for carbon flux through glycolysis and the PPP and nitrogen acquisition from glutamine. This complex interplay between cell signaling and metabolism in cancer cells may be exploited for strategic drug combinations that work against both oncogenic processes in aggressive TC.

CONCLUSION

Cancer cells must extensively reprogram metabolism for successful tumorigenesis. Rerouted metabolism is essential for generating energy in the form of ATP, quenching ROS in the form of NADPH, generating nucleotides *de novo*, forming adequate amino acid levels for protein and DNA synthesis, and storing carbon in the form of fatty acids and glycogen. These pathways in cancer cell metabolism are attractive targets for

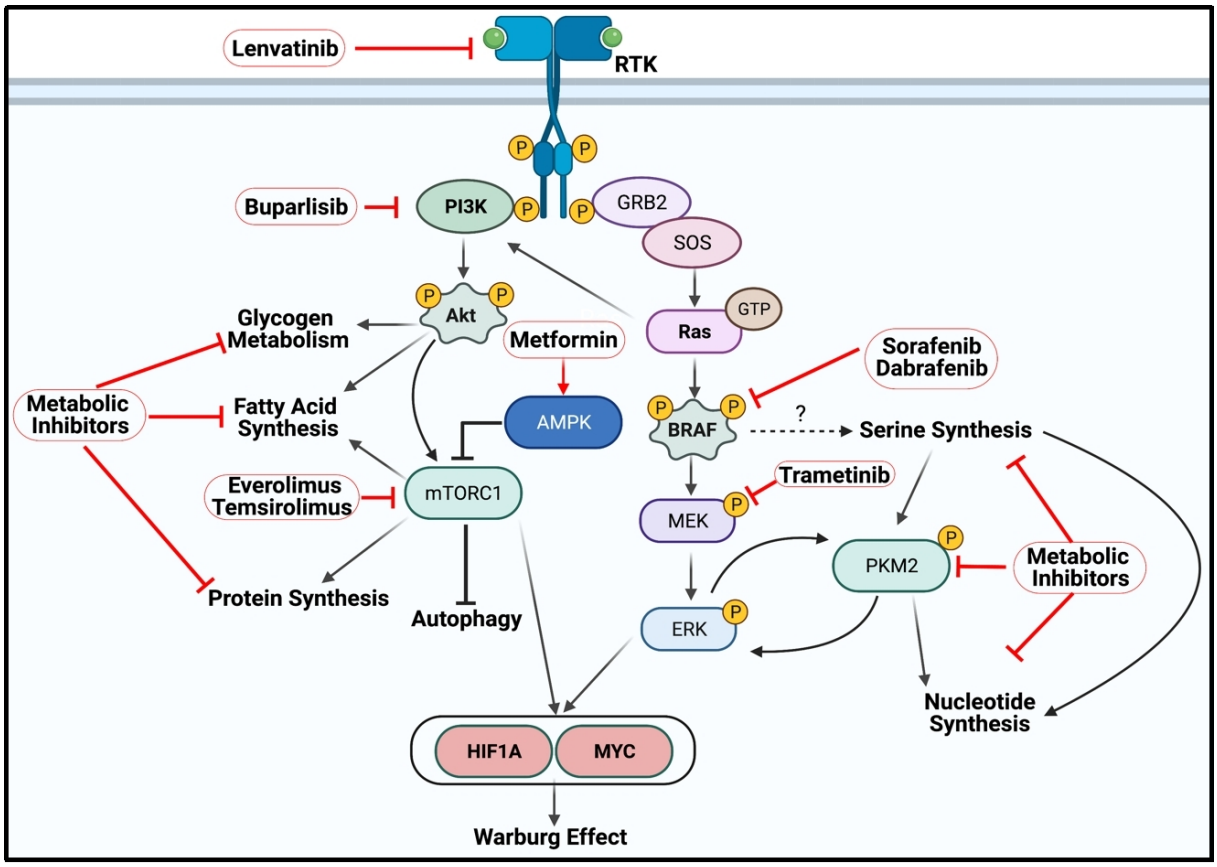

Figure 6. Thyroid cancer oncogenesis frequently invokes activation of PI3K-Akt-mTOR signaling in FTC and ATC and MAPK signaling in PTC and ATC. PI3K signaling is often induced by PI3K activating mutations and copy number variations in Akt and RTKs. The PI3K pathway induces changes in cell metabolism by regulating glycogen storage via Akt, protein synthesis and autophagy via mTORC1, and fatty acid metabolism from Akt and mTORC1, which is regulated by AMPK. BRAF is often constitutively activated in PTC and ATC tumors via the V600E gain-of-function mutation which is correlated with high expression of enzymes in serine synthesis. Downstream of BRAF is ERK, which phosphorylates pyruvate kinase 2 (PKM2) to promote nucleotide synthesis and ERK phosphorylation. Aggressive TCs such as ATC often harbor Ras mutations that activate both sets of pathways. PI3K and MAPK signaling increases expression and stability of the transcription factors hypoxia-inducible factor 1 alpha (HIF1A) and MYC, which in turn increase expression of enzymes in glycolysis, PPP, and amino acid metabolism to promote the Warburg effect. Kinase inhibitors marked in bold have demonstrated varying levels of success in aggressive TC, but drug resistance and tumor recurrence often develop, suggesting the need for combined therapies.

chemotherapeutic intervention. Although metabolic inhibitors have demonstrated robust success *in vitro*, high toxicity could be seen *in vivo* if not strategically administered. Metabolic inhibitors would likely be most efficacious when administered to patients with mutations or amplifications in specific metabolic enzymes, as opposed to targeting a ubiquitous enzyme such as hexokinase[156].

Numerous metabolic inhibitors in many types of cancers have received admirable success and are advancing in clinical trials. These metabolic inhibitors are even more successful when paired with specific kinase inhibitors or broad-spectrum chemotherapies in certain tumors. Sorafenib and lenvatinib are the first-line therapies for aggressive ATC[3,10]. However, these kinase inhibitors as well as the MEK inhibitor trametinib have disappointing long-term efficacy[157]. The most effective current treatment modalities extend the patient lifespan to only eleven months in ATC, yet the strategic combination of metabolic and kinase inhibitors has not been attempted *in vivo*[158,159]. For example, combining lower doses of kinase inhibitors with nucleotide synthesis inhibitors in aggressive, BRAF-driven TC tumors may prove to be an effective synergistic drug strategy that also limits toxicity. Likewise, kinase inhibitors targeted against PI3K and

mTOR such as buparlisib, everolimus, and temsirolimus have demonstrated only modest success in advanced TC[160-164]. Patients exhibited reduced tumor burden initially, but drug resistance and relapse inevitably occurred. As the field in TC metabolism advances, we will need a more thorough delineation of enzyme expression patterns and metabolite levels to formulate the most specific and effective targeted strategies for improving clinical outcomes.

DECLARATIONS

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Authors' contributions

Drafted the manuscript and figures: Davidson CD
Provided assistance with planning, conceptualizing, and editing: Carr FE

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Conflicts of interest

Both authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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