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Molecular Mechanisms of Glucose Uptake Regulation in Thyroid Cancer

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Abstract

Common capabilities of thyroid malignant cells are accelerating metabolism and increasing glucose uptake to optimize energy supply for growth. In tumor cells, keeping the power load required for cell survival is essential and glucose transporters are capable of promoting this task. GLUT-1 and GLUT3 are promising goals for the development of anti-cancer strategies. The lack of oncosuppressors has dominant effect on the membrane expression of GLUT1 and glucose uptake. Overexpression of hypoxia-inducing factors, in thyroid cancer, modulates the expression of some glucose transporter genes. Although the physiology of the thyroid gland has been excellently explained, metabolic regulation in thyroid cancer is inevitable. In this section, we investigated the proliferation pathways of pivotal regulators and signal molecules around GLUT regulation in thyroid cancer, including PTEN, p53, MicroRNA, iodide, BRAF, HIF-1, PI3K-Akt, TSH, c-Myc, and AMPK. Impaired energy regulation and cell metabolism are the most critical symptoms of most cancers. As a result, understanding the mechanisms of glucose transport in the normal and pathological tissues of the thyroid may be very crucial and offer tremendous insights into the science of analysis and remedy of thyroid disease.

Keywords: thyroid cancer, glucose uptake, regulator, glucose transporter

1. Introduction

In glucose metabolism, glucose transport in the plasma membrane, known as the rate-limiting step, is mediated by carriers belonging to the facilitative glucose transporter (GLUT) and the sodium-coupled glucose co-transporter (SGLT) proteins families. While SGLTs require energy to perform the task of glucose transport, GLUT allows glucose to be transported below its concentration gradient without energy dependence [1]. GLUT1 is one of the fourteen GLUT isoforms that have a strong affinity for glucose and express unusual expression of plasma membranes [2, 3]. High expression of GLUT1 is positively correlated with proliferation index and is equivalent to malignant characteristic. In this case, there are poor foresight in different types of cancer, including prostate [4], thyroid [5, 6], colon [7, 8], melanoma [9], liver [10], breast [11, 12], and ovary [13, 14].

Almost many cancer cells change cellular metabolism due to high proliferation rates, which can lead to a stressful metabolic phenotype. Tumor cells are able to alter metabolism from oxidative to glycolytic phenotype. This effect is called Warburg, which is a specific metabolic feature of the tumor and a major metabolic feature. Research on tumor metabolism suggests that rapid cell proliferation, tumor progression, and resistance to cell death should be maintained by altering cellular metabolism in which glycolysis and glutaminolysis are regulated [15]. Glucose transfer occurs in neoplastic cells across the plasma membrane, the first step in limiting the rate of glucose metabolism. There is evidence that a decrease in GLUT1 can suppress cell proliferation, so regulating glucose transporter expression and activity has a significant effect on glucose supply in cancer cells [16]. Several studies have shown the immunohistochemistry of GLUT 1 in cancer cell research [17–19]. High expression of GLUT1 on plasma membranes is related to exactly the same degree of differentiation. Also, the biological invasion of thyroid cancer (TC) is commonly occurred in ATC compared to other different types. GLUT1 is located on the plasma membrane and their expression can be assessed by using PET [20].

One hallmark of cancer cells; especially TC cells are showing high glucose uptake than the normal thyroid samples. Tumor cells regenerate their metabolism by increasing the transportation of glucose to promote cell survival. Malignant cells increase the transportation of glucose through the cell membrane by inducing a family of facilitative glucose-transporting proteins (GLUTs) that are highly classifiable in terms of tissue-specific distribution and different tendencies to glucose and different transport capacities. In most cases, thyroid cancer cells often show overexpression of the GLUT1 and GLUT3 proteins that respond to hypoxia. Malignant cells are typically less able to utilize oxidative metabolism, but aerobic glycolysis is rapidly increased and oxidative phosphorylation remains constant. Increased glycolysis is the main source of energy in cancer cells, but due to the lower energy function in the glycolytic pathway, malignant cells increase the rate of glucose transport in the plasma membrane to compensate for the energy obtained [21–25].

Recently, the relationship between tumor differentiation and glucose metabolism in thyroid cancer has been investigated. The metabolic profile of glucose is differently related to differentiation in well-differentiated and poorly differentiated thyroid cancer. During Suh H. Y. et al. studies based on genetic mutation, the metabolic profile of TC cells was not simply linked with differentiation. The expression of GLUT had an opposite relationship with differentiation in TC. Glycolysis enhancing had a positive relationship with the well-differentiated TC, and on the other hand, showed a negative relationship with poorly differentiated TC. In the papillary type of TC, glycolysis signature showed a positive correlation with differentiation rate, while GLUT signature had a negative correlation with differentiation rate. On the other hand, in the poorly differentiated type of TC, both GLUT and glycolysis showed a negative relationship with the differentiation rate. Their results were in agreement with previous investigations because poorly differentiated type with overexpression of GLUT requires more glucose uptake. In general, it is considered that the relationship between the differentiation and glycolysis may follow a U-shape pattern. The results of different rates for GLUT and glycolysis in PTC were the BRAFV600E mutation status. The PTC cells containing BRAFV600E mutation had high GLUT signature and low glycolysis signature than PTC cells that did not contain BRAFV600E mutation [26].

It is reported that GLUT1, GLUT3, GLUT4, and GLUT10 are expressed in all thyroid parenchymal cells, without attention to their histological status. GLUT1 is more expressed in thyroid cancer tissues than in normal and benign samples obtained from the same patient. Other GLUTs have not been reported to be altered in comparison to GLUT1 in the same patient's pathological tissues. These results

indicated that GLUT1 is theoretically responsible for the observed increase in glucose uptake during carcinogenesis [27, 28]. Overexpression of hexokinase I and increased intracellular glucose phosphorylation in thyroid tumors have been shown to be a signal of tumor invasion. The degree of tumor differentiation in thyroid cancer is consistent with the expression of GLUTs. While poorly differentiated types (anaplastic) have a high expression of GLUT (mainly GLUT1), in contrast, well-differentiated tumors (follicular and papillary) often have a weak expression of GLUT1. GLUT-3 has been reported to be predominant in papillary thyroid cancer [20, 29]. Based on the results of the research, there was a significant expression of GLUT1, GLUT3, and GLUT4 in the cytoplasm and/or membrane of PTC. In PTC cells, GLUT3 and GLUT4 expression pattern were higher than GLUT1 one [30].

The expression of GLUT1 and GLUT3 induced by hypoxia is not similar in benign and malignant thyroid tissues as well as non-neoplastic samples. The dissimilarity in expression levels of GLUT1 and GLUT3 are related to the sample histology. The hypoxia-induced GLUT1 and 3 have a role in the progress of PTC and may be contributed to the panel of significant markers of thyroid cancer. High expressions of GLUT1 and GLUT3 proteins showed a direct relationship with high levels of GLUT1 and GLUT3 mRNA in similar samples of TC. In spite of that, in some of the neoplasm samples, the GLUT1 or GLUT3 band and also mRNA levels were very low. The best interpretation for these detections is the influence of the hypoxia-induced GLUTs by the cancer cell microenvironment and oxygen-related transcription factors [31].

Unusual expression of GLUT proteins is controlled by multiple signal transduction pathways, including the phosphoinositide 3-kinase (PI3K) / AKT pathway [32]. In the thyroid glands, AMPK plays an important physiological role in the uptake of thyroid iodide and can play a role in carcinogenesis. It is recently found that in TC cells, AMPK can increase glucose uptake through the inducing of GLUT 1 and hexokinase (HK) activity [33, 34]. Lack of PTEN expression can lead to the AKT pathway inhibition that was linked with superficial expression of GLUT1 and the possibility of TC diagnosis by FDG-PET [35].

Thyroidectomy and radioactive iodine therapy are common treatments for patients with thyroid cancer but often are not more effective. Recent advances in molecular therapies aimed to understand the molecular pathogenesis of thyroid cancer were promising in the development of early detection and appropriate treatment strategies for thyroid cancer. This is mainly due to the detection of molecular alterations [36]. Although the physiological function of the thyroid gland is well established, its metabolic compatibility is unclear, especially in thyroid cancer. This review argues for recent significant advances and key factors, including inhibiting or stimulating glucose uptake in thyroid cancer that may be useful for future therapeutic purposes in this disease.

2. Targeting glucose transportation in cancer cells

It has been well known from the time of Warburg's hypothesis that cancer cells were found to show the high need for energy and metabolism. It has been reported that almost 90% of cancers showed high glucose metabolism. In addition, these cells, despite having oxygen, can reduce the oxidative phosphorylation pathway and are in favor of the pyruvate conversion to lactate. ATP synthesis is not the top priority of the upregulation of glucose transport. Glycolysis is approximately 18 times more efficient than the oxidative phosphorylation process, so cancer cells need more glucose uptake into cells to compensate for low ATP production [37–39]. Although the Warburg effect was observed more than 80 years ago, its

Figure 1.
Positive and negative regulators of glucose uptake.

interpretation is still argumentative and evolving. Cancer cells do not tend to convert all of the glucose from regulated transport into pyruvate, but rather turn some of the metabolic mediators of glucose into the pentose phosphate pathway (PPP), which is a metabolic pathway, branched off from glycolysis that provides metabolic intermediates for the synthesis of biomass [40–42]. At present, clinical and basic science studies have shown that the Warburg effect is a potential and intelligent cancer research area [43]. Targeting glucose metabolism and transport has been suggested as a useful target for cancer therapeutic intervention [39, 44, 45]. Glycolytic switching in cancer, in addition to greater potential for invasion and metastasis [46], increases the susceptibility of cancer to external interference due to their greater dependence on aerobic glycolysis [47–49]. The discovery of GLUT inhibitors may indicate the development of drugs that can be used as anticancer agents, possibly in addition to conventional chemotherapy or new immunotherapies for further study [50]. There is strong evidence that the expression, activity, and intracellular movement of GLUTs as malignant biomarkers are regulated by different signaling molecules and pathways. In this study, we investigated the proliferation pathways of key positive and negative regulators and signal molecules including PI3K-Akt, HIF-1, MicroRNA, PTEN, AMPK, BRAF, c-Myc, TSH, iodide, and p53, which consist of GLUT regulation in thyroid cancer cells (**Figure 1**).

3. Negative regulation of glucose uptake

3.1 PTEN

PTEN (phosphatase and tensin homolog deleted on chromosome 10) is known as a protein and lipid phosphatase that suppresses tumors and negatively regulates cell growth and metabolism. This gene is often mutated in many advanced human cancers [51]. PTEN expression and activity may be affected by intragenic mutations or epigenetic silencing and post-translational changes. Histone de-acetylation is one of the factors that shut down the genetic process that affects PTEN expression. Researches have shown that inhibition of histone deacetylase can save PTEN

expression and reduce the AKT pathway as well as glucose transport [52]. Loss of PTEN as tumor suppressor gene, possessing an inhibitory role on PI3K / AKT signaling pathway, has also been involved in FTC progression.

Scientific researchers have identified the relationship between plasma PTEN levels and sporadic PTC and their involvement as biomarkers. The observation of PTEN promoter hypermethylation in approximately 50% of PTCs and 100% of FTCs proposes that it may have a contribution to thyroid carcinogenesis [53, 54]. Glucose uptake signaling pathways that occurred during thyroid cancer is poorly recognized since now. Genetic manipulations showed that PTEN as an oncosuppressor agent have participation in GLUT1 expression and glucose uptake in TC cells. Lack of PTEN expression can block the AKT pathway and is associated with the possibility of rapid detection of thyroid cancer by FDG-PET. PTEN binds to SNX27 and prevents it from accessing the VPS26 retromer complex, thus blocking GLUT1 glucose transporter recycling to the plasma membrane, leading to impaired cellular glucose uptake [55, 56]. PTEN can also affect glucose metabolism by dephosphorylating the insulin-1 receptor substrate, thus inhibiting insulin signals and insulin growth factors that are also associated with glucose metabolism [52].

The PI3k class I (PI3KC1) -AKT pathway and AKT downstream effector AS160 (GTPase rab activator) are involved in GLUT1 cell surface exposure in thyroid cancer cells [57, 58]. PTEN lipid phosphatase activity is a determinant of PTEN inhibitory action on the AKT pathway which antagonizes the activation of the AKT pathway. This can reduce the availability of phosphatidylinositol [3–5] -tris phosphate (PIP3), which is a phosphate donor for AKT phosphorylation. This prevents the expression of GLUT1 in the plasma membrane and ultimately the anti-cancer function. It has not been revealed whether PTEN protein phosphatase activity also affects PI3K activity and GLUT1 regulation on plasma membranes. It has been reported that even the AKT pathway can be regulated by PTEN through protein phosphatase activity [52].

3.2 P53

Environmental, genetic, and hormonal factors are the main roots of human malignancy incidence [59], among which genetic factors indicate an extraordinary role in carcinogenesis. Different types of incidence and progression of thyroid cancer are characterized by the gradual accumulation of somatic mutations and/or gene rearrangement with different frequencies and properties [60, 61]. Today, the absence of p53 family members indicates the pathogenesis of poorly differentiated thyroid tumors. Inactive P53 is a genetic variant that distinguishes anaplastic thyroid cancer from well-differentiated thyroid cancer. The p53 mutation usually occurs in undifferentiated thyroid tumors (50–80% in ATCs) [60, 62]. In addition, recent studies have shown that genetic variation of p53 is distinguished in 40% of papillary thyroid cancer and 22% of follicular thyroid cancer [63, 64].

PTEN and P53 play a key role in driving GLUT1 in the plasma membrane. They are key regulators of glucose metabolism and autophagy, which are the most common deleted or mutated suppressors in human cancer [65–67]. Expression of PTEN and P53 can be the cause of glucose uptake and glycolytic enzymes inhibition, stimulation of apoptotic cell death, and mitochondrial oxidation induction, accordingly counteracting with the Warburg effect. They block the PI3k-AKT-mTOR signaling, so it can regulate cell growth. TC cells with an unusual expression of PTEN or p53 are more likely to consume glucose. These two regulators have been shown to stimulate tumor cells to overcome hypoxia-induced metabolic stress and glucose depletion. It also inhibits caspase-dependent apoptosis, autophagy, promotes cell migration, and invasion [68–70].

Point mutations in p53, which occurred in the domain of its binding to DNA, have been associated with malignancy and have abolished its inhibitory activity on the transcriptional activity of GLUTs. Among the GLUTs, GLUT1 and GLUT4 gene promoters are the dominant types that are affected by the P53 mutation in a dose-dependent manner. This results in an increase in glycometabolism and cellular energy, which is known to facilitate tumor cell growth. P53 has shown a significant inhibitory effect on GLUT4 compared to GLUT1. This may be due to the fact that GLUT1 is a general “housekeeping” transporter of glucose, whereas GLUT4 is a tissue-specific and insulin-sensitive glucose carrier [71, 72].

3.3 MicroRNA

MicroRNAs (miRNAs) are classified into oncogenic and tumor suppressor miRNAs. Onco-miRNAs are elevated in human cancers that inhibit cell growth and apoptosis, whereas tumor-suppressive miRNAs are downregulated in human cancers and can prevent cancer progression [73–75]. MiRNAs are non-coding, evolutionarily conserved RNAs that bind to the 3'-UTRs of messenger RNAs and are referred to as negative regulators following transcription [76]. Recent research suggests that a TC invasion is frequently characterized by a lack of miRNA regulation. MiR-146b, MiR-221, and MiR-222 are invasive PTC predictors [77–79].

MiR-718, which is a known negative regulator of proliferation, metastasis, and glucose metabolism, exhibits anti-cancer activity in PTC. MiR-718 can diminish the intensity of PTC cells by inhibiting the Akt–mTOR messaging pathway. MiR-718 expression was significantly decreased in malignant samples compared to normal papillary thyroid tissue. Due to the study of miR-718's influence on PDK1, p-Akt, Akt, and p-mTOR, it was determined that p-Akt and p-mTOR were reduced following PTC treatment with MiR-718. MicroRNA was found to have a detrimental influence on the primary stages of the Akt–mTOR signaling pathway. It follows the regulation of the proliferation, migration, and invasion of PTC cells. The Akt–mTOR signaling pathway has been shown to play an important role in tumor cell glucose metabolism and phenotypic severity. Overexpression of MiR-718 has a significant effect on reducing energy production in PTC cells. Taken together, these results suggest that microRNAs such as miR-718 negatively regulate metabolic activity in thyroid cancer cells [80, 81].

MiR-125a-5p has been demonstrated to act as a tumor suppressor and glucose metabolism regulator in a range of malignancies, most notably TC [82]. Due to the fact that lactate is the end product of glycolysis in tumor cells and can be easily measured, its detection shows the rate of glucose metabolism. MiR-125a-5p reduces lactate synthesis, ATP production, and glucose uptake in TC cells, resulting in a blockage of glycolysis, decreased migration, and cell invasion. The MiR-125a-5p/CD147 axis has been suggested to possibly play an important role in the aerobic glycolysis of thyroid cancer cells. Because GLUT1, HK2, MCT1, and MCT4 are important glycolysis-related proteins, their expression levels are significantly regulated by the miR-125a-5p/CD147 axis (**Figure 2**) [83, 84].

3.4 Iodide

Iodide is responsible for regulating the activity of thyroid cells. The number of glucose carriers in the plasma membrane can be reduced by the iodine auto-regulation function of iodine. In fact, it not only affects glucose metabolism through the oxidation pathway but also through an inhibitory effect on the glucose-facilitating transport system. Iodide is able to inhibit TSH-induced stimulation of glucose transport. The role

Figure 2.
 Metabolic diversity between the Normal and cancer cells of the thyroid. Normal cells primarily consume glucose through the oxidation of pyruvate to CO₂ by the TCA cycle. TC cells convert most glucose to lactate, regardless of the availability of O₂, through the overexpression of some special glucose metabolism-related proteins. MiR-125a-5p blocks the effect of CD147 on lactate transporters such as MCT1/MCT4 that is resulted in low viability, migration, and invasion of TC cells.

of thyroid hormone in the automatic regulation of iodine has also been recognized, but T3 and T4 do not block glucose transportation. Iodide can block the V_{max} of glucose transport without any interference on K_m. Therefore; iodine has not any function through the affinity to glucose, but can result in a low number of available transporter sites. As a consequence, the inhibitory role of iodine on glucose uptake in thyroid tissues may be crucial in both physiological and pathological status, as well as metabolism and nucleic acid mediators [85]. Poor differentiation is associated with upregulation of GLUT1 in TC cells that led to severe malignant biological phenotypes. The dedifferentiation process of FTC cells is associated with iodine loss. In addition, it was reported that thyroid malignancies become more eager for glucose during the dedifferentiation. This inverse communication between iodine and glucose (measured by ¹⁸FFDG PET/CT) was determined as the flip-flop phenomenon (**Figure 3**). This pattern is distinguished in different patients as well as in different locations of the tumor in one patient [20, 86].

3.5 BRAF

BRAF is a cytoplasmic serine–threonine protein kinase that shows a crucial role in thyroid carcinogenesis. Finding of BRAF mutation as a common change in TC is important knowledge. The BRAF mutation may initiate the transition of PTC to ATC [87]. The differentiated thyroid cancers with mutant-type BRAF show more levels of GLUT-1 than those with wild-type BRAF. These results suggest that tumor cells with BRAF genetic variants may have higher uptake of ¹⁸F-FDG.

It has been recognized that there is a link between mutant BRAF and down-stream stimulation of MAPK. The c-Myc linkage targets HIF-1a that resulted to high glucose metabolism [88]. The incidence of BRAF V600E mutations may participate in glycolytic phenotypes associated with overexpression of GLUT1. In this case, GLUT1 is the target of the RAF / MEK / ERK activated pathway. This contribution leads to cancer cells growth [89, 90]. BRAF and MAP/ERK kinase inhibitors give the assurance in cancer therapy linked with BRAF mutations [91].

Figure 3.
Molecular basis of flipflop phenomenon.

4. Positive regulation of glucose uptake

4.1 HIF-1

Hypoxia is an important feature of invasive malignancies that causes malignant phenotypes and activates the physiological adaptation of cancer cells. This helps the tumor to survive and also to progress the diseases. Examples of this adaptation for cancer cells include the glucose transporter 1 gene (GLUT1), which increases glucose uptake for glycolysis [92]. Evidences suggest that the high rate of HIF-1 α signaling observed in many tumors can lead to tumor metastasis, poor prognosis, or therapy. It is important to note that HIF-1 α signaling is induced by low oxygen uptake as well as by oncogenic stimulation through abnormal growth mediators or lack of tumor suppressors [93]. The level of HIF-1 α protein and the upregulation of reporter gene activity is equal to the increase in GLUT1 levels. HIF-1 α expression is increased in FTC-133 cells with PTEN mutation. There is an important correlation between PI3K/AKT and HIF-1 α that may be particularly associated with disease progression in thyroid cancer [86].

There is no sign of HIF-1 α expression in normal thyroid tissue, but it is highly expressed in the most invasive differential thyroid cancers. In PTC, MTC, and FTC, overexpression of HIF-1 is associated with poor prognosis and distant metastasis [15, 93]. Thyroid hormones can activate the PI3K and MAPK signal cascades. In addition, thyroid hormones have the task of directly regulating HIF-1 α expression by stimulating these signal transduction pathways. A TR β mutation binds to the PI3K-regulatory subunit p85 α following high signaling of PI3K and causes thyroid tumorigenesis, which may result in high HIF-1 α expression [93].

HIF-1 contributes to the Warburg effect by increasing glycolysis. It is performed through the stimulation of all glycolytic enzymes, as well as increasing their substrates affinity [83]. HIF-1 also can increase the GLUTs level and decrease mitochondrial metabolism, which may be important in inhibiting ROS production and protecting cancer cells from death [94, 95]. HIF-1 has been suggested to help the Warburg effect by stimulating a number of glycolysis-mediated genes [96, 97], including GLUT1 and GLUT3, which contain hypoxia-reactive elements (HRE) in their promoters [98, 99].

In addition, HIF-1 can show a direct effect on the expression of all 12 enzymes required for glycolysis, or glucose and lactate transporters. These factors showed high expression in TC. In general, these results suggest that TC cells showed the Warburg effect by altering the energy supply by increasing the glycolysis pathway and decreasing mitochondrial function [100]. The close association of HIF-1 α with metabolic pathways may be a welcome goal for better treatment of thyroid cancer [92].

4.2 PI3K/AKT

The phosphatidylinositol 3-kinase (PI3K)-Akt pathway is a family of growth factor-activated lipid and protein kinases that are involved in the regulation of growth and survival processes [101]. The PI3K/Akt pathway was initially associated with thyroid cancer due to the proclivity of patients with Cowden's syndrome to develop thyroid cancer. Due to the fact that Akt phosphorylates a vast number of downstream cytoplasmic and nuclear mediators, it is involved in the regulation of a variety of activities, including glucose metabolism. Increased PI3K/Akt expression appears to be connected with a poor prognosis in a variety of malignancies. Although the PI3K/Akt pathway plays a crucial role in endocrine malignancies, it has received less attention than other types of tumors [102].

The PI3K/Akt pathway mediates increased glucose uptake and overexpression of GLUT in cancers and is also involved in stimulating glucose transport in normal insulin-responsive tissues to increase glucose uptake [103]. PTEN functions as a tumor suppressor by blocking the PI3K/AKT pathway. The absence of this inhibitor can result in enhanced PI3K signaling, which can result in carcinogenesis. In malignancies, overactivation of Akt in the absence of a suppressor may result in enhanced glucose absorption. The serine/threonine kinase Akt, which is downstream of PI3K, is implicated in mediating the Warburg effect and triggering the expression of GLUTs such as GLUT1, GLUT3, and GLUT5 [101, 103–105]. It also acts as a regulator of GLUT4 transport around the plasma membrane, which facilitates glucose transport [103].

The effect of oncogenes on the metabolic change of cells to maintain cell proliferation is a major aspect of thyroid tumors [106]. In many tumors, activation of the PI3K / AKT pathway may be associated with mutations in RAS [107] leading to increased glycolysis flux [108, 109]. The PI3K / AKT pathway in the transfer of the GLUT1 cytoplasm to the plasma membrane in thyroid cells is very significant [15, 32]. According to the list of somatic mutations in cancer, PI3K/Akt pathway mutations are more prevalent in follicular and anaplastic thyroid tumors but are less prevalent in papillary thyroid cancer.

PI3K/Akt signaling has been implicated in thyroid carcinogenesis in animal studies. Thyroid cancer incidence is dramatically reduced in patients with Akt deficiency. Additionally, there is considerable evidence that AKT activation occurs in human thyroid cancer [96, 110, 111]. Numerous medicines targeting the PI3K/Akt signaling pathways are now being explored in phase I to III clinical studies. Temsirolimus and everolimus have been discovered to be very effective in the treatment of thyroid cancer [112].

4.3 TSH

TSH is an abbreviation for Thyroid Stimulating Hormone, a hormone that plays a critical role in the regulation of the activity and metabolism of normal thyroid cells. Its stimulation increases glucose metabolism to enhance iodide transport and thyroid hormone synthesis (T3 and T4) [15]. Increased glucose uptake in tumor cells may reflect changes in gene expression or increased transmission to the cell surface. According to study, thyroid cells enhance their glucose absorption in response to thyroid-stimulating hormone activity. TSH, on the other hand, does not appear to have a substantial effect on GLUT gene expression, indicating that TSH alters glucose uptake through shifting/transferring GLUT rather than boosting GLUT gene expression [27]. TSH significantly increased the cellular absorption of 2-deoxy-D-glucose and the glucose transport tracer 3-O-methyl-D-glucose, both of which were labeled with carbon-14. Additionally, it has been demonstrated that enhanced glucose transfer may be a factor in increased GLUT1 transfer to the thyroid cell surface. These findings may help for explanation of the increased absorption of FDG with high TSH [113].

TSH can promote glucose absorption in normal thyroid tissue. TSH stimulation has an effect on adenylate cyclase, increasing the levels of cAMP. The results indicated an increase in glucose metabolism in a well-differentiated rat cell line FRTL-5. TSH-induced increase in 18F-FDG accumulation is dependent on phosphatidylinositol-3-kinase (PI3-kinase) in FRTL-5 cells. TSH or cAMP influence glucose absorption in thyroid cancer cells. This is depending on the activity of the PI3-kinase triggered by the mutant K-ras oncogene. TSH-induced glucose uptake was studied in ML-1 and FRTL-5 cell lines. This diversity is due to the clinical heterogeneity of various tumor morphologies and the degree of differentiation of tumor cells. Increased PI3-kinase activity, which may be induced by oncogenes such as mutant Ras, is responsible for glucose uptake in dedifferentiated thyroid cancer, indicating possible pathogenesis for thyroid malignancies (**Figure 4**) [107, 108, 114].

TSH affects FDG absorption in a time and concentration-dependent manner through TSH receptors. At high TSH levels, glucose absorption is enhanced in well-differentiated thyroid carcinomas, which are typically still sensitive to TSH. TSH receptor messenger RNA expression in thyroid malignancies has been linked to the degree of differentiation, and poorly differentiated thyroid carcinomas may lack TSH receptors [115, 116]. Thyroid malignancies have been shown to contain somatic mutations in the TSH receptor gene as well as other CAMP cascade alterations, thus even when the TSH receptor is expressed, malignant tissue may respond to TSH stimulation differently than normal tissue. As a result, not all thyroid tumors are likely to accumulate FDG in TSH stimulation to the same degree as normal thyroid tissue [113]. The link between FDG uptake and TSH levels is of therapeutic relevance and might lead to new treatments. The link between FDG uptake and TSH levels is clinically significant and may result in significant misinterpretations in therapeutic studies [114].

4.4 c-Myc

c-MYC, a proto-oncogene, is a known cause of cancer. Myc has been demonstrated to directly influence glucose metabolism genes. The glucose transporter GLUT1, hexokinase 2 (HK2), phosphofructokinase (PFKM), and enolase 1 are the most essential of these [117–119]. Recently, it was demonstrated that glucose metabolism inhibitors targeting MYC inhibited the expression of GLUT-1, LDH-A, and MCT1 in cancer cell lines, coupled with lower MYC activity, hence inhibiting cell proliferation and tumor formation. Is it [120]. Myc controls the expression of genes involved in the

Figure 4. According to Riesco-Eizaguirre and Santisteban, and Rivas and Santisteban, a proposed signal transduction pathway in the thyrocyte exist [36, 43]. The absorption of ^{18}F -FDG triggered by TSH is mediated via adenylyl cyclase (AC) and cAMP, as well as Ras, PI3K, and Akt. PKA regulates iodide absorption. The mitogen-activated protein (MAP) kinase pathway is hypothesized to control cell proliferation by involving B-type Raf (BRAF), extracellular signal-regulated kinase, and mitogen-activated protein kinase.

transfer of glucose, its catabolism to triose and pyruvate, and lastly to lactate. Due to the fact that glycolytic genes also respond directly to HIF-1, a collaboration between Myc and HIF has been seen in a number of cancers with genetic abnormalities [16, 120, 121]. In normoxia, Myc can accelerate glucose oxidation and lactate generation. Myc inhibits mitochondrial respiration with HIF-1 in order to create phosphoinositide-dependent kinase-1 and eventually favors anaerobic glycolysis (Figure 5) [122].

In addition to thyroid cancer, overexpression of c-Myc has been detected in a variety of other malignancies, where it promotes the expression of glucose metabolism genes. The c-Myc gene is a transcription factor that is associated with alterations in cellular metabolism and cancer. The initial connection between c-Myc and glycolysis was its influence on the positive regulation of an enzyme involved in the conversion of pyruvate from glycolysis to lactate. Additionally, c-Myc targets included glucose transporter-1, hexokinase 2, phosphofructokinase, and enolase 1 (Figure 5) [122].

Figure 5. *Myc and HIF-1 are involved in the regulation of glucose metabolism and the Warburg effect. Myc and HIF-1 are shown to influence (dotted lines) glucose metabolism genes (glucose transporter Glut1, HK2, PKM2, LDHA, and PDK1), preferring glucose to lactate conversion (glycolysis). Myc is also shown to increase glutamine metabolism via the modulation of glutaminase and transporters (SLC1A5) (GLS).*

4.5 AMPK

The reactive oxygen species (ROS) as upstream signals of AMP kinase (AMPK) can alter cellular metabolism and increase the Warburg effect by upregulation of AMPK. AMPK is a metabolic cytosolic enzyme that senses stress and is activated by a lack of energy for the regulation of metabolism and cell growth [123]. In contrast, ROS production is not controlled by AMPK. This is proven by inhibiting AMPK phosphorylation and evaluating ROS production under these conditions. AMPK plays an essential role in cell cycle arrest and has a strong anti-growth effect in various cancer cell lines.

In the thyroid gland, it plays a serious physiological role in the absorption of thyroid iodide in vitro and in vivo and can play a role in severe invasive thyroid cancer. When activated, AMPK promotes energy generation pathways and restores intracellular ATP levels, while simultaneously inhibiting energy consumption processes. AMPK activation also enhances glucose absorption in non-cancerous cells and papillary thyroid cancer cells, mostly in the first step of the glycolysis process. AMPK has been shown to increase glucose absorption in thyroid cells without requiring TSH by increasing both GLUT 1 expression and hexokinase (HK) activity.

This definitely suggests that AMPK regulates glucose absorption by thyrocytes via a different pathway. Two mechanisms that influence glucose metabolism include enhanced glucose transport to cells and increased glucose phosphorylation. Three kinases, including the liver kinase B1 homolog (serine/threonine protein kinase LKB1), calcium/calmodulin-dependent protein kinase kinase (CaMKK), and TGF-beta-activated kinase 1 (TAK1), may be involved in the control of thyrocyte glucose absorption. The capacity of AMPK to influence glucose metabolism may be valuable in discovering novel pathways involved in thyroid function regulation in the future [34, 124]. Inhibiting AMPK activation in tumor cells can enhance the Warburg

effect. mTOR is significantly elevated in AMPK deficient models. Additionally, HIF-1 promotes the expression of HK2 and GLUT1, as well as glucose absorption by tumor cells. AMPK activation appears to contribute to the glucose metabolism seen in certain PTC cells. The active phosphorylated form of AMPK is expressed at a greater level in PTC tumor cell samples than in non-tumor tissue samples. Finally, more studies are necessary to clarify the role of AMPK in human thyroid cancer, particularly in metabolic regulation mechanisms such as cell proliferation, apoptosis, and survival [125–127].

5. Conclusion

While cancer was generally defined as aberrant cell growth, emerging data indicate that cancer is also a metabolic disorder. Metabolomics investigations, in addition to conventional approaches, are likely to be employed in the near future for the detection and classification of various forms of thyroid malignancies, most likely introducing altered metabolic pathways as treatment targets [128]. Thyroid cancer has a greater quick prevalence grade than any other kind of cancer in several countries [129]. Thyroid cancer cells have a high degree of metabolic complexity, indicating that they are capable of reprogramming glucose metabolism in response to nutritional restriction circumstances in the hypoxic tumor microenvironment. Malignant cells undergo metabolic alterations in order to get sufficient energy to continue growth signaling. Metabolic alterations such as increased glucose uptake are reported in invasive thyroid carcinoma for this purpose. Understanding the mechanisms of glucose transport to normal and pathological tissues of the thyroid can provide effective insights into the diagnosis and treatment of thyroid cancer treatments [27, 130].

Anticancer treatment is based on two main aspects. One is the traditional aspect of conventional chemotherapy, which is examined non-specifically against general cell processes. Another method is targeted molecular therapies, which include drugs designed to inhibit specific components of deregulated signaling pathways in cancer [131]. Deregulation of cellular metabolism as a hallmark of cancer may indicate changes in different signaling pathways. The metabolic change suggests a survival score for tumor cells [132]. Despite the number of various thyroid cancer biomarkers, only a few of them are clinically useful. Because one of these molecules may be ineffective on its own in many circumstances, the combination of two or more biomarkers can be quite helpful in detecting and predicting thyroid cancer [133]. The regulation of GLUTs is reviewed in this article in relation to critical amplification and survival pathways including as PI3K-Akt, HIF-1, MicroRNA, PTEN, AMPK, BRAF, c-Myc, and p53. Combination therapy is promising to enhance the efficacy of cancer treatment and cope with the multiple genetic alterations in different cancer cells. It involves simultaneous administration of more than one type of treatment such as two or more chemotherapies or merging chemotherapy with radiation/ adjuvant therapy.

Because glucose uptake into cancer cells is a limiting step in glycolysis, nutritional restriction in tumors through targeting GLUTs by inhibiting their glucose transport channel with small molecules might be an acceptable approach [134]. Recently, the concept of cancer chemotherapy targeting glucose transporters has been highlighted [1]. Glucose transport inhibitors have been demonstrated to be potential anticancer medicines that need more investigation and clinical trials. As more information on cancer metabolism becomes available, we will be able to produce more effective anti-cancer treatments [39]. The discovery of the method of impaired glucose uptake through glucose-transporting proteins may alter the

metabolism of malignant cells and thus disrupt tumor growth. If this hypothesis is confirmed, glucose-transporting proteins could become significant targets for cancer treatment [127]. Shifting the balance between cancer and stromal cells or the metabolic cooperation between different TC cell populations is a promising therapeutic strategy, but still needs further study. Finally, a better description of the metabolic phenotype under TC subtypes is clearly needed to provide a treatment option for poorly differentiated and refractory TC [130].

While conventional treatments such as surgical thyroidectomy and radioiodine therapy have been the main aspect of thyroid cancer treatment, they are frequently ineffective. As a result, treatment approaches against these sorts of malignancies must be recast in order to achieve modern drugs. Currently, the levels of GLUT1 or GLUT3 expression may give crucial information about the aggressiveness and growth of a tumor, as well as patient survival. The potential use of GLUTs as therapeutic targets is an exciting topic for future research in combination therapy.

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