Metabolic reprogramming and its clinical application in thyroid cancer (Review)

SHI-SHUAI WEN[1*], TING-TING ZHANG[1*], DI-XIN XUE[2], WEI-LI WU[2], YU-LONG WANG[1], YU WANG[1], QING-HAI JI[1], YONG-XUE ZHU[1], NING QU[1] and RONG-LIANG SHI[1]

[1]Department of Head and Neck Surgery, Fudan University Shanghai Cancer Center, Shanghai 200032; [2]Department of General Surgery, The Third Affiliated Hospital of Wenzhou Medical University, Rui'an, Zhejiang 325200, P.R. China

Received January 7, 2019; Accepted February 22, 2019

DOI: 10.3892/ol.2019.10485

Abstract. Warburg found that tumor cells exhibit high-level glycolysis, even under aerobic condition, which is known as the 'Warburg effect'. As systemic changes in the entire metabolic network are gradually revealed, it is recognized that metabolic reprogramming has gone far beyond the imagination of Warburg. Metabolic reprogramming involves an active change in cancer cells to adapt to their biological characteristics. Thyroid cancer is a common endocrine malignant tumor whose metabolic characteristics have been studied in recent years. Some drugs targeting tumor metabolism are under clinical trial. This article reviews the metabolic changes and mechanisms in thyroid cancer, aiming to find metabolic-related molecules that could be potential markers to predict prognosis and metabolic pathways, or could serve as therapeutic targets. Our review indicates that knowledge in metabolic alteration has potential contributions in the diagnosis, treatment and prognostic evaluation of thyroid cancer, but further studies are needed for verification as well.

Correspondence to: Professor Rong-liang Shi and Professor Ning Qu, Department of Head and Neck Surgery, Fudan University Shanghai Cancer Center, 270 Dong'an Road Shanghai 200032, P.R. China
E-mail: shirongliang@126.com
E-mail: jonathan_qn@163.com

*Contributed equally

Abbreviations: PTC, papillary thyroid carcinoma; FTC, follicular thyroid carcinoma; MTC, medullary thyroid carcinoma; ATC, anaplastic thyroid carcinoma; DTC, differentiated thyroid carcinoma; PDTC, poorly differentiated thyroid carcinoma; MCT, monocarboxylate transporter; CAF, cancer-associated fibroblasts; OXPHOS, oxidative phosphorylation; HK, hexokinase; LDH, lactate dehydrogenase; PK, pyruvatekinase; GLUT1, glucose transporter 1

Key words: thyroid cancer, metabolism, prognosis, predictive factor, targeted therapy

Contents

1. Introduction

Thyroid cancer is a common malignant tumor with a sharp increase in incidence worldwide (1). Thyroid cancer mainly includes four types: Papillary thyroid carcinoma (PTC), follicular thyroid carcinoma (FTC), medullary thyroid carcinoma (MTC), and anaplastic thyroid carcinoma (ATC) (2). PTC accounts for the largest component among them (>90%). The prognosis of thyroid cancer is closely related to its histological type. For example, the 10-year overall survival rate of PTC is estimated to be 98%, while the median survival of ATC is only 3-5 months (3). For thyroid cancer, surgical resectionis the most important treatment method. Different adjuvant treatments are effective for certain pathological subgroups, such as radioiodine for differentiated thyroid carcinoma (DTC) and chemotherapy for ATC.

Although most thyroid cancers have a good prognosis, approximately 10% of patients with well-differentiated thyroid cancer have a loss of response to radioactive iodine therapy, and poorly differentiated or undifferentiated tumors are more likely to cause disease recurrence and death (4,5). Therefore, it is necessary to investigate new methods of thyroid cancer treatment. Moreover, we observed that some well-differentiated thyroid cancer cases are significantly more aggressive than others, so it is difficult to predict the patient's course. This heterogeneity of thyroid cancer behavior and the inferior quality of life of patients indicate the importance of identifying prognostic markers.

Over a century ago, Warburg (6) found that tumor cells need more glucose than normal cells and tumor cells prefer glycolysis for glucose metabolism even under oxygen-sufficient conditions, rather than undergo mitochondrial oxidative phosphorylation to produce ATP. This is known as the 'Warburg

effect'. However, the special metabolic mode of tumor cells is not a passive change, but a positive change of expression of heredity to alter the metabolic mode for oncogenesis and neoplasm invasiveness. Tumor metabolism can serve as a potential target for the treatment of thyroid cancer. Moreover, tumor metabolism-related molecules may be a marker for the prognosis of thyroid cancer. Previous findings have shown that the development of thyroid cancer is associated with increased glucose uptake (7). Monocarboxylate transporter (MCT) on the tumor cell membrane and the translocation enzyme TOMM20 on the mitochondrial membrane were reportedly associated with the prognosis of thyroid cancer (8,9). The findings suggest that key molecules in tumor metabolism may be the factors involved in predicting the prognosis of thyroid cancer.

2. Cell metabolism in thyroid cancer

Multicompartment metabolism of thyroid cancer. Multicompartment mode revealed the translation of metabolic intermediates between different regions of cancer cells. Pavlides *et al* first proposed the 'Reverse Warburg effect', whereby cancer-associated fibroblasts (CAF) are induced by cancer cells to shift into aerobic glycolysis and produce L-lactic acid and ketone bodies, which is translated to cancer cells as fuels of oxidative phosphorylation (10). Metabolic coupling between glycolytic fibroblasts and cancer cells promotes tumor growth by increasing cancer cell proliferation and inducing resistance to apoptosis (11).

Transporters that translate intermediates between different compartments are important in the multicompartment mode. A noteworthy transporter is MCT, a class of membrane-bound proteins involved in the influx and outflow of small metabolites, such as lactic acid, and pyruvate and ketone bodies (12). MCT4 is responsible for CAF outputting Lactate. Lactate is then taken up by cancer cells via MCT1 (a two-way transporter) on cancer cells and transported to mitochondria through the mitochondrial outer membrane TOMM20 to produce ATP by oxidative phosphorylation (OXPHOS) (9). Therefore, TOMM20 and MCT1 can be used as biomarkers of OXPHOS and MCT4 can be used as a biomarker of glycolysis.

A high expression of MCT4 in head and neck canceris associated with tumor recurrence and more advanced staging (13). Curry *et al* (14) found that PTC tumor cells exhibit a uniform high expression of TOMM20, but have a low expression in normal thyroid and nodular goiter tissue adjacent to the tumor. There was a statistical difference in the expression of MCT4 in CAF between advanced PTC and non-advanced PTC. In another study on ATC, tumor tissues highly expressed both TOMM20 and MCT1 compared with non-tumor tissues, which was different from PTC (high expression of TOMM20 but low expression of MCT1) (9). The high expression of MCT1 means that it allows more pyruvate and lactic acid to enter tumor cells for high-intensity OXPHOS, leading to significant growth advantages in tumor cells (15). The difference in the expression of MCT1 between ATC and PTC probably explainsthe difference in prognosis.

Glucose metabolism. It is well known that unlike normal cells, tumor cells undergo aerobic glycolysis as the main form of glucose metabolism (16). Aerobic glucose metabolism is an inefficient metabolic pathway for the production of ATP. Researchers believe that the proportion of tumor cells in the aerobic glycolysis metabolic pathway is mainly due to its contribution to the proliferation and invasion of cancer cells, and enhancement of cancer cells to fight oxidative damage (16-18).

Nahm *et al* found that the expression levels of glycolytic-related proteins is differentin different thyroid cancer subtypes and is associated with prognosis (19). PTC patients with a high expression of glucose transporter 1 (GLUT1) had a shorter overall survival (OS), and hexokinase II-positive medullary carcinoma patients had a shorter OS and disease-free survival (DFS). MCT4-positive PTC patients had shorter OS than MCT4-negative ones. When GLUT1 and MCT4 were highly expressed, DFS and OS was significantly reduced in patients with poorly differentiated thyroid cancer. Several glycolytic-related molecules haveexhibited an important role in the metabolism of thyroid cancer, such as GLUT1, HK, PKM2 and lactate dehydrogenase (LDH).

GLUT1. GLUT1, a unidirectional transporter, is responsible for the transportation of glucose across the plasma membrane of mammalian cells. Extensive research has found that it is expressed in a variety of tumor cells and is associated with prognosis. Haber *et al* analyzed the expression of GLUT1 protein in 38 cases of benign thyroid disease and thyroid cancer (20). The results showed that GLUT1 expression was frequently upregulated in thyroid cancer, but weakly expressed in benign nodules and normal thyroid tissues. Nahm *et al* analyzed 556 cases of thyroid cancer, showing that GLUT1 expression was higher in ATC than PTC and higher in PTC than normal cells (19). They also found that the expression of GLUT1 in FTC was significantly higher than that of follicular adenoma (FA). Kim *et al* found that the expression of GLUT1 gene in ATC was significantly higher than that of differentiated cancer (21). In addition, the expression of GLUT1 in PTC was higher than FTC. The above results indicate that the expression level of GLUT1 may be positively correlated with the invasiveness of thyroid tumors. This is consistent with the results observed in other tumors (22). The phenomenon that ATC has a higher expression of GLUT1 than other types of thyroid cancer is probably due to the fact that ATC has the highest metabolic activity in thyroid cancer (23). Therefore, more GLUT1 is needed to take glucose for metabolism. High proliferative activity of the tumor causes hypoxia. Under hypoxic conditions, the expression of hypoxia-inducible factor-1 (HIF-1) is increased and GLUT1 is the target molecule of HIF-1 (24). Previous studies have demonstrated high HIF-1 nuclear staining in ATC (25), which supports this view. Moreover, ATC is a highly metastatic cancer. Its presence of high expression of GLUT1 is consistent with the known phenomenon that 'GLUT1 expression of some types of tumors is associated with distant metastasis' (26,27). In addition, 60% of ATC showed p53 mutations and p53 was involved in glycolytic regulation. GLUT1 is inhibited by wild-type p53, but due to p53 mutation, this regulation is disrupted (28).

HK. Hexokinase (HK) is the first rate-limiting enzyme in the glycolytic pathway. There are 4 subtypes of HK in mammals and HK2 has the greatest correlation with malignant

Table I. Comparison of expression of metabolism-related molecules between different subtypes of thyroid carcinoma.

Metabolism-related molecules	Comparison between different ssubtypes	Refs.
GLUT1	ATC > PTC > FTC > FA	(19,21)
HK2	PTC with $BRAF^{V600E}$ > PTC without $BRAF^{V600E}$	(19)
	Other subtypes > MTC	
PKM		
PKM2 mRNA	BCPAP and TPC1 > NC	(33)
PK activity:	BCPAP > TPC1	
LDH-A	ATC > PTC and FTC > NC	(37)
Serine/glycine	PDTC and PTC > MTC	(38)
Metabolism-related proteins	PTC > FTC	
	PTC with $BRAF^{V600E}$ > PTC without $BRAF^{V600E}$	
Glutamine metabolism-related proteins		(39)
Tumor and Stroma	ATC > other subtypes	
GLS1 and GDH		
Tumor ASCT2	MTC > FTC	
Tumor GLS1 and GDH	ATC > PTC > FTC > FA	
	PTC with $BRAF^{V600E}$ > PTC without $BRAF^{V600E}$	
TOMM20	ATC > NC	(9,14)
	PTC > NC	
MCT1	ATC > NC	(9)
	PTC < NC	

tumors (29). Nahm *et al* studied a total of 342 PTC samples and it was found that 50% of the PTC samples containing the $BRAF^{V600E}$ mutation had higher levels of HK2 (19). According to Hooft *et al*, HK expression in metastatic and primary DTC were similar (30). The expression of HK2 in MTC was lower than that of other thyroid cancer subtypes (19).

PKM2. Pyruvatekinase (PK) is one of the main rate-limiting enzymes in glycolysis (31). There are three different subtypes (R, L, M) in human body. PKM is widely distributed in tissues and has two isoforms, M1 and M2. Replacement of PKM2 in tumor cells with PKM1 results in a reversal of the Warburg effect, reduced lactic acid production and increased oxygen consumption (32). Coelho *et al* showed that in two types of human thyroid cancer cell lines, B-CPAP and TPC1, there was higher expression of PKM2 mRNA compared to non-tumor cells (33). There is no difference in PKM1 mRNA levels. However, the total PK activity of B-CPAP was higher than non-tumor cells and TPC1 cell line, indicating that the PK enzymatic reaction is dependent on *BRAF* mutations (33). It is believed that PKM isoform expression and changes of PK activity are associated with increased tumor growth rates. Feng *et al* showed that the expression of PKM2 in human PTC is associated with tumor progression and lymph node metastasis (34). Bikas *et al* also found overexpression of PKM2 in thyroid cancer cells (FTC-133 and B-CPAP) characterized by glycolytic dependence (35).

LDH. LDH converts pyruvate produced by glycolysis into lactic acid, which can be transported to the outside of the cell to avoid the accumulation of large amounts of lactic acid inside the cells and form an acidic microenvironment that is beneficial to cancer cells. Another important function of LDH is to oxidize the NADH coenzyme produced by glycolysis to NAD+ to maintain the aerobic glycolysis. Of five isozymes, LDH-A is the one closely related to tumor invasion (36). Coelho *et al* compared two PTC cell lines, B-CPAP and TPC1, and found no difference in LDH-A mRNA expression compared to non-tumor cells (33). However, the two tumor cell lines have a higher LDH activity and lactic acid production rate. Kachel *et al* showed a different result, that LDH-A is overexpressed in FTC and PTC compared to non-tumor tissue, and its level in ATC is even higher (37).

Amino acid metabolism of thyroid cancer

Serine/glycine metabolism. Sun *et al* reported that the expression of serine/glycine metabolism-related proteins in different thyroid cancer types is different through analyzing tissues of different thyroid cancer subtypes (38). The expression is higher in poorly differentiated thyroid carcinoma (PDTC) and PTC, and lower in MTC and FTC. In PTC, it is higher in tissues with $BRAF^{V600E}$ than those without BRAF mutation. Expression of serine/glycine metabolism-related proteins, including phosphoglycerate dehydrogenase (PHGDH), phosphoserine aminotransferase (PSAT), phosphoserine phosphatase (PSPH), serine hydromethyltransferase (SHMT), and glycine decarboxylase (GLDC), is different in different thyroid cancer subtype as mentioned below. Expression of PHGDH, PSAT1, PSPH and tumor SHMT1 is higher in PDTC and PTC, but lower in MTC. Matrix SHMT1 expression was highest in ATC and lowest in FTC. The expression of PSPH, tumor SHMT1 and matrix SHMT1 was higher in PTC than FTC. $BRAF^{V600E}$ mutant cells have higher PHGDH, PSAT1, PSPH, tumor SHMT1, and interstitial SHMT1 and GLDC expression than non-mutant cells.

Glutaminemetabolism. The three proteins that play an important role in glutamine metabolic pathway are amino acid transporter-2 (ASCT2), a transporter of glutamine into cancer cells; glutaminase 1 (GLS1), which converts glutamine into a glutamic acid; glutamate dehydrogenase (GDH), an enzyme that converts glutamic acid to alpha-ketoglutarate, the latter for the tricarboxylic acid cycle. Kim *et al* performed tissue microarray on 557 patients with different pathological types of thyroid cancer (39). The order of tumor GLS1 and GDH expression from high to low was ATC, PTC, FTC and FA. Tumor ASCT2 expression was higher in MTC but lower in FTC. Tumor GLS1 and tumor GDH expression was higher in the PTC with $BRAF^{V600E}$ mutation than PTC without the $BRAF^{V600E}$ mutation. Therefore, the more follicular differentiation, the more prone to low expression of GLS1 and GDH.

In other tumors, glutamine metabolism-related proteins (GLS1, GDH and ASCT2) have also been reported to be associated with tumor invasion (40). The possible mechanism is as follows. First, as mentioned earlier, ATC has higher metabolic activity than other subtypes of thyroid cancer. Glutamine metabolism plays an important role in tumor metastasis (41). Second, ATC has been shown to have higher HER-2 expression (42) and activation of the Wnt β-catenin pathway (43). HER-2 and β-catenin pathways are reported to be associated with increased glutamine metabolism (44,45).

BRAF mutation and metabolism of thyroid cancer. Since the first discovery of *BRAF* mutations in human cancer in 2002, its importance has become increasingly apparent in PTC (46). However, its mechanism is still under investigation. It has been observed that $BRAF^{V600E}$ mutations can lead to changes in tumor metabolism, which may be part of the reason for the worse prognosis of *BRAF* mutations.

In PTC, ^{18}F-FDG uptake has been shown to vary with pathological differentiation, although the molecular mechanisms responsible for this are unclear (47). It has also been suggested that the $BRAF^{V600E}$ mutation is associated with ^{18}F-FDG uptake rate and GLUT1 expression rate in PTC (48). Yoon *et al* found that *BRAF* mutations in PTC were significantly associated with ^{18}F-FDG PET/CT values (49). In addition,the expression of GLUT1 and GLUT3 in *BRAF*-positive PTCs was significantly increased. Chang *et al* also found that *BRAF* mutation is an independent factor in the uptake of PTC ^{18}F-FDG, especially for tumors >1 cm (50). Yoon *et al* showed that, the $BRAF^{V600E}$ mutation was independently associated with high ^{18}F-FDG uptake by preoperative PET/CT in PTC patients, but this relationship was not apparent in PTMC (51). Nagarajah *et al* compared the effects of BRAF mutations on ^{18}F-FDG uptake in DTC and PDTC (52). In DTC, $BRAF^{V600E}$-positive patients had significantly higher ^{18}F-FDG uptake than wild-type *BRAF* patients. In PDTC, only a few tumors were positive for $BRAF^{V600E}$, and their ^{18}F-FDG uptake was not significantly different from that of wild-type *BRAF* tumors. Nahm *et al* observed that the expression of HK2 and MCT-4 in *BRAF* mutation-positive PTC was higher than that in *BRAF*-negative patients (19). According to research by Sun *et al*, *BRAF* mutations, not only affect glucose metabolism in thyroid cancer cells, but also affect amino acid metabolism (38). The $BRAF^{V600E}$ mutant PTC expressed more serine/glycine metabolism-related proteins than wild-type *BRAF*. In summary, PTC with $BRAF^{V600E}$ mutations have a higher expression of metabolism-related proteins and increased ^{18}F-FDG uptake compared to non-mutants. This may explain the reason for PTC with positive *BRAF* mutations having a worse prognosis.

3. Tumor metabolism as the target of evaluation and treatment of thyroid cancer

Biomarkers for prognosis. In summary,we may draw the conclusion that metabolism-related molecules maybe used as biomarkers for the prognosis of thyroid cancer. None of the tumors with low fibroblast-expressing MCT4 staining showed advanced disease or invasive features. Glycolysis-related proteins such as GLUT1 and LDHA, and glutamine metabolism-related proteins such as GLS1, GDH and ASCT2, are associated with invasiveness and prognosis of thyroid cancer. HK2 is associated with the prognosis of MTC.

Glutamine metabolism as a therapeutic target. New targets are needed for the therapy of the radioactive iodine-refractory DTC, ATC and MTC. Current targeted therapies for thyroid cancer are tyrosine kinase inhibitors (TKIs) and monoclonal antibodies (mAbs) that inhibit the tyrosine kinase activity essential for the pathogenesis of thyroid cancer (53). However, clinical trial results of TKIs and mAbs are unsatisfactory, with only partial response rates ranging from 2 to 45% (53,54). A possible strategy is to reduce glutamine metabolic enzyme activity or reduce glutamine uptake. GLS1 inhibitors, including BPTES, CB-968 and CB-839, are in preclinical and clinical trials for the treatment of various tumors. BenSer has been reported to inhibit the proliferation of melanoma cells as an inhibitor of ASCT2 (55). Of note, inhibitors of the glutamine metabolic pathway need further research as a treatment for thyroid cancer.

Glucose metabolism as a therapeutic target. Studies targeting tumor glucose metabolism have continued for years, and in the field of thyroid cancer, glycolysis inhibitors such as 2-deoxyglucose have been shown to preferentially target ATC in animal models (56). Radioactive iodine-refractory thyroid tumors may be suitable for metabolic-related targeted therapies because they show positive in ^{18}FDG-PET scans (57). Moreover, MCT1 inhibitors are also being tested for the treatment of malignant tumors and may be valuable for the treatment of ATC (58).

OXPHOS inhibitors may be effective anti-cancer drugs in thyroid cancer. Previously, there were no strong OXPHOS inhibitors approved by the FDA. In PTC patients, there are data indicating that the weak OXPHOS inhibitor metform in is active in PTC. Metformin has a higher response rate, as was evidenced in a retrospective cohort of subjects with DTC (59). Metformin induces apoptosis in cancer cells and reduces tumor growth in a PTC xenograft model (60). In DTC patients, a single institutional observation study showed that individuals treated with metformin had smaller tumor size, indicating their potential to inhibit tumor growth. However, the beneficial effects of metformin on thyroid cancer may not be due to mitochondrial effects, but through its insulin sensitization. In addition, metformin may reduce the level of TSH, which in turn inhibits the growth of thyroid cancer cells.

4. Conclusion

Although there has been some progress in the study of thyroid tumor metabolism in recent years, there are still many gaps to fill. The current research indicates that oncogenes and tumor suppressor genes directly affect cell energy metabolism, leading to phenotype changes conducive to tumor progression. The differential expression of metabolic-related molecules in thyroid cancer with different prognosis and the association between the degree of expression and prognosis suggest that the prognosis of thyroid cancer maybe predicted viametabolic-related molecules. Treatments and drugs targeting tumor metabolism are also under development, and some of them have achieved phased progress, which is likely to open new pathways for thyroid cancer treatment. Consequently, more investigations will be conducted in this field.

Acknowledgements

Not applicable.

Funding

This study was supported by grants from the National Natural Science Foundation of China (no. 81702649 to NQ; nos. 81572622 and 81272934 to QHJ; nos. 81472498 and 81772851 to YLW).

Availability of data and materials

Not applicable.

Author's contributions

SSW, TTZ, YXZ, NQ and RLS conceived and designed the review. SSW, TTZ, YW and QHJ drafted and revised the manuscript. DXX, WLW and YLW contributed to the search and collection of documents. All authors approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Wiltshire JJ, Drake TM, Uttley L and Balasubramanian SP: Systematic Review of Trends in the Incidence Rates of Thyroid Cancer. Thyroid 26: 1541-1552, 2016.
2. Navas-Carrillo D, Ríos A, Rodríguez JM, Parrilla P and Orenes-Piñero E: Familial nonmedullary thyroid cancer: Screening, clinical, molecular and genetic findings. Biochim Biophys Acta 1846: 468-476, 2014.
3. Jillard CL, Scheri RP and Sosa JA: What is the optimal treatment of papillary thyroid cancer? Adv Surg 49: 79-93, 2015.
4. Pacini F, Cetani F, Miccoli P, Mancusi F, Ceccarelli C, Lippi F, Martino E and Pinchera A: Outcome of 309 patients with metastatic differentiated thyroid carcinoma treated with radioiodine. World J Surg 18: 600-604, 1994.
5. Nikiforova MN and Nikiforov YE: Molecular genetics of thyroid cancer: Implications for diagnosis, treatment and prognosis. Expert Rev Mol Diagn 8: 83-95, 2008.
6. Warburg O: On the origin of cancer cells. Science 123: 309-314, 1956.
7. Fagin JA: How thyroid tumors start and why it matters: Kinase mutants as targets for solid cancer pharmacotherapy. J Endocrinol 183: 249-256, 2004.
8. Eilertsen M, Andersen S, Al-Saad S, Kiselev Y, Donnem T, Stenvold H, Al-Shibli K, Richardsen E, Busund LT and Bremnes RM: Abstract 2377: MCT1 and MCT4 in NSCLC: Overexpression of MCT1 in tumor and stroma is an independent prognostic marker for NSCLC survival. Cancer Res 73 (Suppl 8): 2377, 2013.
9. Johnson JM, Lai SY, Cotzia P, Cognetti D, Luginbuhl A, Pribitkin EA, Zhan T, Mollaee M, Domingo-Vidal M, Chen Y, *et al*: Mitochondrial metabolism as a treatment target in anaplastic thyroid cancer. Semin Oncol 42: 915-922, 2015.
10. Pavlides S, Whitaker-Menezes D, Castello-Cros R, Flomenberg N, Witkiewicz AK, Frank PG, Casimiro MC, Wang C, Fortina P, Addya S, *et al*: The reverse Warburg effect: Aerobic glycolysis in cancer associated fibroblasts and the tumor stroma. Cell Cycle 8: 3984-4001, 2009.
11. Witkiewicz AK, Whitaker-Menezes D, Dasgupta A, Philp NJ, Lin Z, Gandara R, Sneddon S, Martinez-Outschoorn UE, Sotgia F and Lisanti MP: Using the 'reverse Warburg effect' to identify high-risk breast cancer patients: Stromal MCT4 predicts poor clinical outcome in triple-negative breast cancers. Cell Cycle 11: 1108-1117, 2012.
12. Feron O: Pyruvate into lactate and back: From the Warburg effect to symbiotic energy fuel exchange in cancer cells. Radiother Oncol 92: 329-333, 2009.
13. Ullah MS, Davies AJ and Halestrap AP: The plasma membrane lactate transporter MCT4, but not MCT1, is up-regulated by hypoxia through a HIF-1alpha-dependent mechanism. J Biol Chem 281: 9030-9037, 2006.
14. Curry JM, Tassone P, Cotzia P, Sprandio J, Luginbuhl A, Cognetti DM, Mollaee M, Domingo M, Pribitkin EA, Keane WM, *et al*: Multicompartment metabolism in papillary thyroid cancer. Laryngoscope 126: 2410-2418, 2016.
15. Kennedy KM, Scarbrough PM, Ribeiro A, Richardson R, Yuan H, Sonveaux P, Landon CD, Chi JT, Pizzo S, Schroeder T, *et al*: Catabolism of exogenous lactate reveals it as a legitimate metabolic substrate in breast cancer. PLoS One 8: e75154, 2013.
16. Villar VH, Merhi F, Djavaheri-Mergny M and Durán RV: Glutaminolysis and autophagy in cancer. Autophagy 11: 1198-1208, 2015.
17. Kianercy A, Veltri R and Pienta KJ: Critical transitions in a game theoretic model of tumour metabolism. Interface Focus 4: 20140014, 2014.
18. Pacini N and Borziani F: Cancer stem cell theory and the warburg effect, two sides of the same coin? Int J Mol Sci 15: 8893-8930, 2014.
19. Nahm JH, Kim HM and Koo JS: Glycolysis-related protein expression in thyroid cancer. Tumour Biol 39: 1010428317695922, 2017.
20. Haber RS, Weiser KR, Pritsker A, Reder I and Burstein DE: GLUT1 glucose transporter expression in benign and malignant thyroid nodules. Thyroid 7: 363-367, 1997.
21. Kim S, Chung JK, Min HS, Kang JH, Park DJ, Jeong JM, Lee DS, Park SH, Cho BY, Lee S, *et al*: Expression patterns of glucose transporter-1 gene and thyroid specific genes in human papillary thyroid carcinoma. Nucl Med Mol Imaging 48: 91-97, 2014.
22. Davis-Yadley AH, Abbott AM, Pimiento JM, Chen DT and Malafa MP: Increased expression of the glucose transporter type 1 gene is associated with worse overall survival in resected pancreatic adenocarcinoma. Pancreas 45: 974-979, 2016.
23. Erickson LA, Jin L, Wollan PC, Thompson GB, van Heerden J and Lloyd RV: Expression of p27kip1 and Ki-67 in benign and malignant thyroid tumors. Mod Pathol 11: 169-174, 1998.
24. Pereira KM, Chaves FN, Viana TS, Carvalho FS, Costa FW, Alves AP and Sousa FB: Oxygen metabolism in oral cancer: HIF and GLUTs (Review). Oncol Lett 6: 311-316, 2013. (Review).
25. Burrows N, Resch J, Cowen RL, von Wasielewski R, Hoang-Vu C, West CM, Williams KJ and Brabant G: Expression of hypoxia-inducible factor 1 alpha in thyroid carcinomas. Endocr Relat Cancer 17: 61-72, 2010.

26. Jiwa LS, van Diest PJ, Hoefnagel LD, Wesseling J, Wesseling P and Moelans CB; Dutch Distant Breast Cancer Metastases Consortium: Upregulation of Claudin-4, CAIX and GLUT-1 in distant breast cancer metastases. BMC Cancer 14: 864, 2014.
27. Zuo J, Wen J, Lei M, Wen M, Li S, Lv X, Luo Z and Wen G: Hypoxia promotes the invasion and metastasis of laryngeal cancer cells via EMT. Med Oncol 33: 15, 2016.
28. Schwartzenberg-Bar-Yoseph F, Armoni M and Karnieli E: The tumor suppressor p53 down-regulates glucose transporters GLUT1 and GLUT4 gene expression. Cancer Res 64: 2627-2633, 2004.
29. Moreno-Sánchez R, Rodríguez-Enríquez S, Saavedra E, Marín-Hernández A and Gallardo-Pérez JC: The bioenergetics of cancer: Is glycolysis the main ATP supplier in all tumor cells? Biofactors 35: 209-225, 2009.
30. Hooft L, van der Veldt AA, Hoekstra OS, Boers M, Molthoff CF and van Diest PJ: Hexokinase III, cyclin A and galectin-3 are overexpressed in malignant follicular thyroid nodules. Clin Endocrinol (Oxf) 68: 252-257, 2008.
31. Christofk HR, Vander Heiden MG, Wu N, Asara JM and Cantley LC: Pyruvate kinase M2 is a phosphotyrosine-binding protein. Nature 452: 181-186, 2008.
32. Di Cristofaro J, Marcy M, Vasko V, Sebag F, Fakhry N, Wynford-Thomas D and De Micco C: Molecular genetic study comparing follicular variant versus classic papillary thyroid carcinomas: Association of N-ras mutation in codon 61 with follicular variant. Hum Pathol 37: 824-830, 2006.
33. Coelho RG, Cazarin JM, Cavalcanti de Albuquerque JP, de Andrade BM and Carvalho DP: Differential glycolytic profile and Warburg effect in papillary thyroid carcinoma cell lines. Oncol Rep 36: 3673-3681, 2016.
34. Feng C, Gao Y, Wang C, Yu X, Zhang W, Guan H, Shan Z and Teng W: Aberrant overexpression of pyruvate kinase M2 is associated with aggressive tumor features and the BRAF mutation in papillary thyroid cancer. J Clin Endocrinol Metab 98: E1524-E1533, 2013.
35. Bikas A, Jensen K, Patel A, Costello J Jr, McDaniel D, Klubo-Gwiezdzinska J, Larin O, Hoperia V, Burman KD, Boyle L, *et al*: Glucose-deprivation increases thyroid cancer cells sensitivity to metformin. Endocr Relat Cancer 22: 919-932, 2015.
36. Sonveaux P, Végran F, Schroeder T, Wergin MC, Verrax J, Rabbani ZN, De Saedeleer CJ, Kennedy KM, Diepart C, Jordan BF, *et al*: Targeting lactate-fueled respiration selectively kills hypoxic tumor cells in mice. J Clin Invest 118: 3930-3942, 2008.
37. Kachel P, Trojanowicz B, Sekulla C, Prenzel H, Dralle H and Hoang-Vu C: Phosphorylation of pyruvate kinase M2 and lactate dehydrogenase A by fibroblast growth factor receptor 1 in benign and malignant thyroid tissue. BMC Cancer 15: 140, 2015.
38. Sun WY, Kim HM, Jung WH and Koo JS: Expression of serine/glycine metabolism-related proteins is different according to the thyroid cancer subtype. J Transl Med 14: 168, 2016.
39. Kim HM, Lee YK and Koo JS: Expression of glutamine metabolism-related proteins in thyroid cancer. Oncotarget 7: 53628-53641, 2016.
40. Kim S, Jung WH and Koo JS: The expression of glutamine-metabolism-related proteins in breast phyllodes tumors. Tumour Biol 34: 2683-2689, 2013.
41. Chen J, Lee HJ, Wu X, Huo L, Kim SJ, Xu L, Wang Y, He J, Bollu LR, Gao G, *et al*: Gain of glucose-independent growth upon metastasis of breast cancer cells to the brain. Cancer Res 75: 554-565, 2015.
42. Murakawa T, Tsuda H, Tanimoto T, Tanabe T, Kitahara S and Matsubara O: Expression of KIT, EGFR, HER-2 and tyrosine phosphorylation in undifferentiated thyroid carcinoma: Implication for a new therapeutic approach. Pathol Int 55: 757-765, 2005.
43. Oyen WJ, Bodei L, Giammarile F, Maecke HR, Tennvall J, Luster M and Brans B: Targeted therapy in nuclear medicine - current status and future prospects. Ann Oncol 18: 1782-1792, 2007.
44. Cadoret A, Ovejero C, Terris B, Souil E, Lévy L, Lamers WH, Kitajewski J, Kahn A and Perret C: New targets of beta-catenin signaling in the liver are involved in the glutamine metabolism. Oncogene 21: 8293-8301, 2002.
45. Youngblood VM, Kim LC, Edwards DN, Hwang Y, Santapuram PR, Stirdivant SM, Lu P, Ye F, Brantley-Sieders DM and Chen J: The ephrin-A1/EPHA2 signaling axis regulates glutamine metabolism in HER2-positive breast cancer. Cancer Res 76: 1825-1836, 2016.
46. Xing M: Molecular pathogenesis and mechanisms of thyroid cancer. Nat Rev Cancer 13: 184-199, 2013.
47. Delbeke D, Coleman RE, Guiberteau MJ, Brown ML, Royal HD, Siegel BA, Townsend DW, Berland LL, Parker JA, Hubner K, *et al*: Procedure guideline for tumor imaging with ^{18}F-FDG PET/CT 1.0. J Nucl Med 47: 885-895, 2006.
48. Barollo S, Pennelli G, Vianello F, Watutantrige Fernando S, Negro I, Merante Boschin I, Pelizzo MR, Rugge M, Mantero F, Nacamulli D, *et al*: BRAF in primary and recurrent papillary thyroid cancers: The relationship with (131)I and 2-[(18)F] fluoro-2-deoxy-D-glucose uptake ability. Eur J Endocrinol 163: 659-663, 2010.
49. Yoon M, Jung SJ, Kim TH, Ha TK, Urm SH, Park JS, Lee SM and Bae SK: Relationships between transporter expression and the status of BRAF V600E mutation and F-18 FDG uptake in papillary thyroid carcinomas. Endocr Res 41: 64-69, 2016.
50. Chang JW, Park KW, Heo JH, Jung SN, Liu L, Kim SM, Kwon IS and Koo BS: Relationship between ^{18}F-fluorodeoxyglucose accumulation and the BRAF V600E mutation in papillary thyroid cancer. World J Surg 42: 1-9, 2017.
51. Yoon S, An YS, Lee SJ, So EY, Kim JH, Chung YS and Yoon JK: Relation between F-18 FDG uptake of PET/CT and BRAF^{V600E} mutation in papillary thyroid cancer. Medicine (Baltimore) 94: e2063, 2015.
52. Nagarajah J, Ho ALR, Tuttle RM, Weber WA and Grewal RK: Correlation of BRAF^{V600E} Mutation and Glucose Metabolism in Thyroid Cancer Patients: An ^{18}F-FDG PET Study. J Nucl Med 56: 662-667, 2015.
53. Locati LD, Licitra L, Agate L, Ou SH, Boucher A, Jarzab B, Qin S, Kane MA, Wirth LJ, Chen C, *et al*: Treatment of advanced thyroid cancer with axitinib: Phase 2 study with pharmacokinetic/pharmacodynamic and quality-of-life assessments. Cancer 120: 2694-2703, 2014.
54. Sherman SI, Wirth LJ, Droz JP, Hofmann M, Bastholt L, Martins RG, Licitra L, Eschenberg MJ, Sun YN, Juan T, *et al*; Motesanib Thyroid Cancer Study Group: Motesanib diphosphate in progressive differentiated thyroid cancer. N Engl J Med 359: 31-42, 2008.
55. Wang Q, Beaumont KA, Otte NJ, Font J, Bailey CG, van Geldermalsen M, Sharp DM, Tiffen JC, Ryan RM, Jormakka M, *et al*: Targeting glutamine transport to suppress melanoma cell growth. Int J Cancer 135: 1060-1071, 2014.
56. Sandulache VC, Skinner HD, Wang Y, Chen Y, Dodge CT, Ow TJ, Bankson JA, Myers JN and Lai SY: Glycolytic inhibition alters anaplastic thyroid carcinoma tumor metabolism and improves response to conventional chemotherapy and radiation. Mol Cancer Ther 11: 1373-1380, 2012.
57. Robbins RJ, Wan Q, Grewal RK, Reibke R, Gonen M, Strauss HW, Tuttle RM, Drucker W and Larson SM: Real-time prognosis for metastatic thyroid carcinoma based on 2-[^{18}F]fluoro-2-deoxy-D-glucose-positron emission tomography scanning. J Clin Endocrinol Metab 91: 498-505, 2006.
58. Polański R, Hodgkinson CL, Fusi A, Nonaka D, Priest L, Kelly P, Trapani F, Bishop PW, White A, CritchlowSE, *et al*: Activity of the monocarboxylate transporter 1 inhibitor AZD3965 in small cell lung cancer. Clin Cancer Res 20: 926-937, 2014.
59. Klubo-Gwiezdzinska J, Costello J Jr, Patel A, Bauer A, Jensen K, Mete M, Burman KD, Wartofsky L and Vasko V: Treatment with metformin is associated with higher remission rate in diabetic patients with thyroid cancer. J Clin Endocrinol Metab 98: 3269-3279, 2013.
60. Cho SW, Yi KH, Han SK, Sun HJ, Kim YA, Oh BC, Park YJ and Park DJ: Therapeutic potential of metformin in papillary thyroid cancer in vitro and in vivo. Mol Cell Endocrinol 393: 24-29, 2014.