Thyroid Cancer Metabolism: A Review

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Abstract

Metabolic dysregulation within the tumor microenvironment (TME) is critical to the process of tumorigenesis in various cancer types. Thyrocyte metabolism in papillary and anaplastic thyroid cancer, however, remains poorly characterized, and studies analyzing the role of multicompartment metabolism in thyrocyte oncogenesis are sparse. We present a review of the current knowledge on cellular metabolism in non-cancerous and cancerous thyroid tissues, focusing on the monocarboxylate transporters MCT1 and MCT4, and on a transporter of the outer mitochondrial membrane TOMM20. Understanding the metabolic phenotype of tumor cells and associated stromal cells in thyroid cancer can have profound implications on the use of biomarker staining in detecting subclinical cancer, imaging as it relates to expression of various transport proteins, and therapeutic interventions that manipulate this dysregulated tumor metabolism to halt tumorigenesis and eradicate the cancer. Future studies are required to confirm the prognostic significance of these biomarkers and their correlation with existing staging schemas such as the AGES, AMES, ATA and MACIS scoring systems.

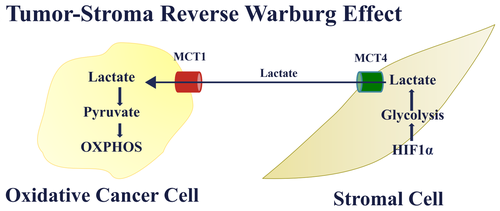
Introduction

Thyroid cancer is the most common endocrine malignancy in the United States, with the fifth highest incidence of all cancers affecting females [1] and the highest prevalence of any malignancy affecting women under 35 years old. Thyroid cancer has increased in incidence by 5.4-6.5% per year between 2006 and 2010 [1]. Some are predicting it to become the third most common cancer among American women by 2019, surpassing uterine and colorectal cancers [2].

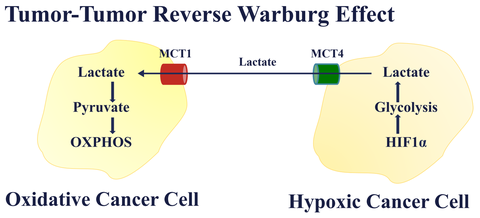
Primary cancer is the most common type of thyroid malignancy, and papillary thyroid cancer (PTC) is the most common histologic type, representing 90% of all thyroid malignancies [2]. Other subtypes include: follicular, medullary, and anaplastic. Prognosis depends greatly on histologic type. Estimated 5-year survival rate for PTC is 98% [2], compared to anaplastic thyroid carcinoma [3], which has a median survival of only 3-5 months [4]. This prognostic disparity emphasizes the importance of classifying the type of thyroid cancer as the primary step in assessment, which is usually diagnosed via fine needle aspiration (FNA). However, cytologic patterns determined by FNA, or even histologic patterns identified by biopsy, may be inconclusive in some cases. Therefore, knowledge regarding the significance of various molecular biomarkers in different metabolic compartments of the tumor can aid in thyroid cancer diagnosis.

Despite a 98% 5-year survival rate, a recent study by Applewhite *et al*. found that quality of life of thyroid cancer survivors was worse than expected; it was similar to patients with colon cancer, glioma, and gynecologic cancer, and worse than patients with breast cancer [5]. Furthermore, some cases of well-differentiated thyroid cancer are significantly more aggressive than others, making it difficult to predict a patient's course. This heterogeneity of thyroid cancer behavior and unfavorable quality of life for survivors emphasizes the importance of discovering predictive and prognostic biomarkers for thyroid cancer. Once corroborated by future studies, this information can ultimately guide management and impact surgical considerations in patients who are clinically in a gray area of whether to proceed with total thyroidectomy, lobectomy, or, in the case of an indeterminate cancer diagnosis, more conservative measures like close observation and follow-up ultrasounds [6]. In this review, we discuss metabolism in thyroid cancer with an emphasis on our current knowledge of metabolism in the different compartments that constitute the tumor.

Figure 1 **A. Tumor-Stroma Reverse Warburg Effect**



B. Tumor-Tumor Reverse Warburg Effect



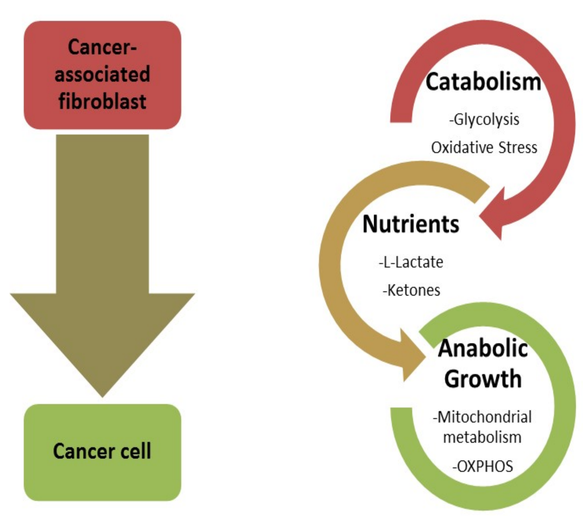
Tumor metabolism and tumor microenvironment (TME)

Warburg effect: Preferential use of glycolysis with generation of lactate compared to the more energy efficient pathway of oxidative phosphorylation (OXPHOS).

Reverse Warburg effect: Aerobic glycolysis occurring in the cancer-associated fibroblasts (CAFs), as opposed to the tumor cells themselves, results in the production of high-energy metabolites such as lactate and pyruvate. Cancer cells at the leading edge of growth exploit nearby glycolytic CAFs to utilize these metabolites, which are ultimately transferred to epithelial cancer cells via inflammation and high levels of reactive oxygen species (ROS) acting as second messengers. Lactate and pyruvate then undergo mitochondrial metabolism, resulting in increased ATP production, which promotes tumor progression (**see Figure 1A and 1B**). This shift toward aerobic glycolysis occurring in the CAFs and the coupling of different tumoral metabolic compartments is coined the "reverse Warburg effect" [5]. This interplay between synergistic metabolic compartments facilitates cancer cell anabolism via the catabolic activity of adjacent tumor fibroblasts (**Figure 2**).

In order to facilitate their metabolic requirements, solid tumors often reprogram and manipulate their surrounding "condemned tissue," composed of cancerous cells, adjacent epithelial, stromal, and immune cells and their surrounding matrix. Collectively, these components make up the TME, which serves as a conduit for the cytokine signaling needed to meet the cancer cells' high metabolic requirements. Various signaling pathways, such as NF-kb, HIF-1α, and VEGF continue to be explored as therapeutic targets in the TME [1-2].

Figure 2



Tumor metabolism and TME in thyroid cancer

This paradigm of shuttling high-yield metabolites from stromal fibroblasts to fuel cancer cell growth and metastasis has resulted in increased research of various transport proteins. Among these transport proteins are monocarboxylate transporters (MCT), which are a class of membrane bound proteins involved in the influx and efflux of small metabolites such as lactate, pyruvate and ketone bodies [3]. **MCT4** is responsible for the export of lactate from CAFs. Lactate is then taken up by cancer cells via **MCT1**, a bidirectional transporter, and transported to mitochondria via a translocase of the outer mitochondrial membrane (**TOMM20**), leading to the generation of ATP via OXPHOS [4]. TOMM20 is a central component of the receptor complex responsible for the recognition and translocation of cytosolically-synthesized mitochondrial proteins and has been shown to be an indicator of functional mitochondrial mass and of OXPHOS activity [5-7]. Therefore, TOMM20, as well as MCT1, can be used as markers of OXPHOS, and MCT4 a marker of glycolytic metabolism and oxidative stress. Further, these biomarkers have been shown to have prognostic significance: MCT4 is associated with poor outcomes in other cancers [8], and in head and neck cancer specifically, MCT4+ tumor stromal cells were associated with higher tumor stage (p<0.03), poorer clinical outcome (tumor recurrence; p<0.0001) and greater FDG-PET avidity (p<0.04). MCT1 positivity, on the other hand, is prognostic in renal cell cancer and non-small cell lung cancer [9-10].

Results

Our group previously characterized tumor metabolism in thyroid cancers specifically looking at TOMM20, MCT4 and MCT1. We interrogated, by IHC, non-cancerous (NCT), PTC, and ATC tissue for these biomarkers, and review our discoveries on the metabolic profiles of these tissue types (**Figure 3**). In all non-tumor thyroid tissue and multinodular goiter samples, TOMM20 expression was low. Fibroblasts in NCT and nodular goiter (NG) specimens demonstrated low MCT4 expression as well [11]. No NCT samples had high expression of MCT1 (p<0.0001) [12]. In summary, IHC of NCT and NG tissue samples demonstrated low staining of all 3 biomarkers: stromal MCT4, cancer cell TOMM20 and cancer cell MCT1. In follicular adenoma (FA) specimens, all of the adenomatous thyrocytes demonstrated high expression of TOMM20 compared to adjacent non-tumor thyrocytes and nodular goiter samples [11]. The fibroblasts around the adenoma and throughout the rest of the gland showed low MCT4 staining. In one case, MCT4 was elevated around the adenoma, but negative throughout the rest of the gland [11].

Papillary Thyroid Cancer (PTC)

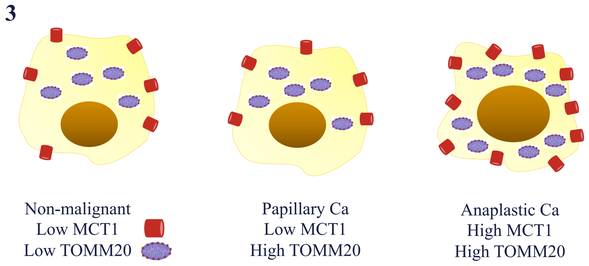
All PTC thyrocytes from patients with and without advanced disease showed homogeneously high expression of TOMM20 throughout the tumor. Of note, there was a difference between intensity of staining between non-advanced and advanced PTC specimens, but this was not statistically significant (p=0.36) [11]. Specimens from the PTC group with advanced disease demonstrated higher MCT4 staining in the CAFs compared to PTC without advanced disease group; this difference was statistically significant (p < 0.01). MCT1 expression was low in PTC specimens (p < 0.001).

Anaplastic Thyroid Cancer (ATC)

There was significantly more TOMM20 staining in ATC compared to NCT (p < 0.05) [12], and majority of samples also showed robust MCT1 expression.

	NCT/NG	FA	PTC	ATC
TOMM20 (in thyrocytes)	–	+	+	+
MCT4 (in CAFs/stroma)	–	–	+	
MCT1 (in thyrocytes)	–		–	+

Figure 3



Conclusions

We present a review of the current knowledge of metabolism in thyroid cancer, integrating our recent discoveries on the role of transmembrane lactate transporters MCT1 and MCT4, and a translocase of the outer mitochondrial membrane TOMM20. PTC samples exhibited TOMM20 and MCT4 positivity, whereas the more aggressive ATC demonstrated robust TOMM20 and MCT1 positivity. This contrasts non-cancerous and nodular goiter thyroid tissue, which were negative for all three biomarkers. Our characterization of the multiple metabolic compartments in thyroid cancer subtypes opens up avenues for therapy by intervening in the pathway to ATP generation with mitochondrial inhibitors like metformin.

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