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Mitochondrial Energy Metabolism and Thyroid Cancers

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Primary thyroid cancers including papillary, follicular, poorly differentiated, and anaplastic carcinomas show substantial differences in biological and clinical behaviors. Even in the same pathological type, there is wide variability in the clinical course of disease progression. The molecular carcinogenesis of thyroid cancer has advanced tremendously in the last decade. However, specific inhibition of oncogenic pathways did not provide a significant survival benefit in advanced progressive thyroid cancer that is resistant to radioactive iodine therapy. Accumulating evidence clearly shows that cellular energy metabolism, which is controlled by oncogenes and other tumor-related factors, is a critical factor determining the clinical phenotypes of cancer. However, the role and nature of energy metabolism in thyroid cancer remain unclear. In this article, we discuss the role of cellular energy metabolism, particularly mitochondrial energy metabolism, in thyroid cancer. Determining the molecular nature of metabolic remodeling in thyroid cancer may provide new biomarkers and therapeutic targets that may be useful in the management of refractory thyroid cancers.

Keywords: Thyroid neoplasms; Mitochondria; Energy metabolism

INTRODUCTION

Energy metabolism in most cancer cells differs markedly from that in normal cells to meet the energy needs during tumor progression. Currently, thyroid cancer originating from follicular epithelial cells is classified based on pathological features. The four major types of primary thyroid cancers—papillary, follicular, poorly differentiated, and anaplastic carcinomas—show substantial differences in biological and clinical behaviors. Even among the same pathological types, there is wide variability in the clinical course of disease progression. It is clear that cellular energy metabolism, which is controlled by oncogenes and other tumor-related factors, is a critical factor in determining the clinical phenotypes of cancer. The molecular carcinogenesis of thyroid cancer has advanced tremendously in the last decade [1-6]. However, the role and nature of energy metabolism in thyroid cancer remain unclear.

Mitochondria provide 90% of the cellular energy required for various biological functions through oxidative phosphorylation (OxPhos) in the inner mitochondrial membrane [7]. In addition, mitochondria regulate cellular metabolism, including steroid hormone and porphyrin synthesis, the urea cycle, lipid metabolism, and interconversion of amino acids [8]. They also play central roles in apoptosis, cell proliferation, and cellular

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Ca^{2+} homeostasis, which affect numerous other cell signaling pathways [8,9]. Thus, mitochondria play an important role in energy metabolism in the normal thyroid gland as well as in thyroid tumors. The roles of functional and structural alterations in mitochondria in tumorigenesis and tumor progression in the thyroid gland need to be explored. This review article focuses on current knowledge of mitochondrial metabolism and its exploitation by thyroid cancer. We give an overview of metabolic changes, mitochondrial alterations, and the significance of mitochondria in slow-growing and fast-growing thyroid cancers.

MITOCHONDRIAL OxPhos FUNCTION IN THE THYROID GLAND

The thyroid gland is an endocrine organ with a high energy demand, in which oxidative processes are indispensable for thyroid hormone synthesis. It is thought that huge amounts of reactive oxygen species (ROS), which are generated from electron transport within the inner mitochondrial membrane, are produced in the thyroid under physiological conditions. Because of the cellular toxicity of excess amounts of ROS, such as H_2O_2, mitochondria of follicular cells contain various antioxidant defense systems, such as glutathione peroxidase, catalase, superoxide dismutases, and peroxiredoxins, to detoxify H_2O_2 and other ROS. Mitochondrial defense mechanisms against ROS are also important for cell viability [10]. Increased oxidative damage to macromolecules and inactive antioxidant defense systems have been found in thyroid cancers [11]. Oxidative damage to macromolecules may be an early event in thyroid cancer that may affect disease progression. Additionally, whereas antioxidant defense activity increases in differentiated thyroid cancer, decreased expression of antioxidant enzymes was found in advanced thyroid cancer and anaplastic carcinoma.

The primary function of the thyroid gland is the production of thyroid hormone, a process that is regulated by multiple unique cell biological pathways [12]. Although many investigators suggest that oxidative stress and energy depletion might result in thyroid dysfunction, no clear evidence indicates that mitochondrial dysfunction is an immediate cause of thyroid dysfunction. We developed a mouse model of thyroid-specific mitochondrial dysfunction to investigate the role of oxidative function and to identify modifiers in thyroid failure. We showed that a severe mitochondrial OxPhos defect resulted in overt hypothyroidism, with morphological changes characterized by distortion of thyroid follicles (unpublished data).

ENERGY METABOLISM IN THYROID CANCER

Differentiated thyroid cancers (papillary, follicular, and medullary carcinoma) are slow-growing cancers with good prognoses. As previously described, the Warburg effect and aerobic glycolysis were not greatly elevated in slow-growing cancers, but were strongly associated with poorly differentiated fast-growing cancers. Activation of hypoxia-inducible factor 1 (HIF-1), a transcription factor that is stabilized in response to hypoxia, significantly contributes to the conversion of glucose to lactate [13]. The activation of certain oncogenes, such as epidermal growth factor receptor (EGFR) and Src, also stabilizes HIF-1 protein under normoxic conditions, resulting in inhibition of mitochondrial adenosine triphosphate (ATP) production and activation of aerobic glycolytic metabolism [14]. HIF-1 activation is associated with increased proliferation, which is potentially associated with more aggressive tumors and poor prognosis [15].

As well as differences in cancer cell metabolism between fast-growing and slow-growing thyroid cancers, there are also differences in survival rate and prognosis between differentiated and poorly differentiated thyroid cancers. A subgroup of patients with differentiated thyroid cancer showed higher expression of HIF-1, and its expression was associated with advanced stage and unfavorable clinical outcomes. These observations suggest that metabolic alterations, including biased activation of glycolysis, are a prerequisite determining aggressive tumor biology.

Cancer cells show suppression of mitochondrial OxPhos function, and increase aerobic glycolysis to create a more advantageous metabolic state for cancer cell survival. Normal and tumorous human thyroid tissues and human thyroid cancer cell lines are capable of a metabolic switch between aerobic glycolysis and OxPhos depending on the microenvironment [16]. This metabolic flexibility shows that interplay between glycolysis and OxPhos adapt the mechanisms of energy production to microenvironmental changes, as well as differences in tumor energy needs or biosynthetic activity. All these observations indicate the importance of maintaining proper mitochondrial function and active OxPhos metabolism in normal thyroid cancer cells [17].

Benign and well differentiated thyroid tumors retain fludeoxyglucose (FDG) poorly, whereas more malignant tumors

appear to have a higher uptake of FDG. A recent series of the retrospective analyses showed the ability of FDG-positron emission tomography to identify thyroid cancer patients who may have a poor prognosis. It was hypothesized that patients with metastatic lesions that did not concentrate RAI but had high glucose uptake would have reduced survival. These clinical observations indicate that energy production via excessive glucose uptake and glycolysis, resulting from suppressed mitochondrial OxPhos function, is an important phenotypic change determining the clinical behavior of thyroid cancer.

Hürthle cell carcinoma is a relatively rare type of differentiated thyroid cancer. Excess mitochondria are the hallmark of Hürthle cells and oncocytic cells. Gene profiling of thyroid Hürthle cell tumors revealed up-regulation of genes coding for glycolytic, tricarboxylic acid cycle, and OxPhos enzymes, and underexpression of the lactate dehydrogenase A gene. This suggests that thyroid Hürthle cell tumors produce energy through an aerobic pathway because of defective OxPhos in mitochondria [18].

ROLE OF MITOCHONDRIA IN ONCOGENE ACTION IN THYUROID CANCER

Many genetic alterations activating several signal transduction pathways have been identified in thyroid cancers. Activating mutations in the *BRAF* gene are found at high frequency in various human cancers. $BRAF^{V600E}$ is the most common of these activating mutations, especially in papillary thyroid cancer, where its frequency is 40% to 70%. In $BRAF^{V600E}$-positive thyroid cancer cell lines and $BRAF^{V600E}$-transgenic mice, this mutation is responsible for tumor initiation, transformation, growth, proliferation, and dedifferentiation. Research into the molecular mechanisms of $BRAF^{V600E}$-positive tumors has revealed that the missense valine to glutamic acid mutation increases kinase activity, promoting the constitutive activation of mitogen-activated protein kinase kinase (MEK)-extracellular signal-regulated kinase (ERK) signaling and increasing ERK-dependent transcriptional output. However, signaling pathways other than the MEK-ERK pathways that are regulated in $BRAF^{V600E}$-positive tumors are not fully characterized. Moreover, tumor suppressor systems that may be controlled by $BRAF^{V600E}$ in thyroid cancer remain to be identified.

Recently, we explored oncogenic actions of $BRAF^{V600E}$ related to crosstalk with Hippo signaling pathways and mitochondria. We identified novel crosstalk between $BRAF^{V600E}$ and MST1, thereby demonstrating functional activity of the RASSF1A-MST1-FoxO3 tumor suppressor system. In addition, we found that $BRAF^{V600E}$ interacts with mitochondria in a mutation-specific fashion. The mitochondrial localization of $BRAF^{V600E}$ induced anti-apoptotic effects and metabolic changes characterized by decreased O_2 consumption and an increased rate of glucose uptake, suggesting reduced mitochondrial OxPhos. Surprisingly, a well known and clinically used RAF inhibitor had no effect on the crosstalk with Hippo pathways and mitochondrial interactions. These new insights into the mutation-specific roles of $BRAF^{V600E}$ may be important for the development of future therapeutics.

The receptor tyrosine kinase (RTK) genes *EGFR, PDGFRα, PDGFRβ, VEGFR1, VEGFR2, c-MET,* and *c-KIT* encode cell surface receptors for polypeptide growth factors, cytokines, and hormones. RTKs are frequently overexpressed or aberrantly activated in follicular and anaplastic thyroid carcinomas [19]. Recently, RTKs were shown to directly modulate mitochondrial function. EGF stimulation leads to EGFR and c-Src activation. EGFR and c-Src translocate to the mitochondria, and then phosphorylate respiratory chain complex II. These processes lead to the inactivation of respiratory chain complexes, reduced oxidative ATP and free radical production, and an increase in cell viability [20].

The *Ras*-Raf-MEK-ERK/mitogen-activated protein kinase (MAPK) cascade is initiated by ligation of a RTK. Oncogenic *BRAF* mutations in the *Ras*-Raf-MEK-ERK/MAPK pathway occur preferentially in papillary thyroid cancer. Recently, our group demonstrated that $BRAF^{V600E}$ is localized to the outer mitochondrial membrane in thyroid cancer [21].

In cancer cell lines, ERK1 was shown to translocate to mitochondria, where it inhibits apoptosis by binding to several mitochondrial proteins, such as voltage-dependent anion channel [22], and by desensitizing the permeability transition pore (PTP) through inhibition of a signaling axis that involves glycogen synthase kinase-3 (GSK3) and the PTP regulator cyclophilin D [23]. Previous studies performed on $BRAF^{V600E}$-positive melanoma cell lines showed that its anti-apoptotic effects were linked to constitutive MEK-ERK activation. Inhibition of MEK signaling pathways accelerated death in these cells. However, we demonstrated that ERK activation by $BRAF^{V600E}$ may not be a critical factor determining the apoptotic response. Therefore, the anti-apoptotic effects of $BRAF^{V600E}$ are not solely dependent on MEK/ERK activities in thyroid cells [21].

Ras mutations are also common in thyroid tumors, particularly in follicular carcinoma [24], follicular variants of papillary carcinoma [25], and poorly differentiated carcinomas

[26]. By cont t, *Ras* mutations rarely occur in papillary carcinoma [27]. *RAS* mutations constitutively activate the PI3K-Akt pathway in thyroid cancers [28-30]. PI3K stimulation induces rapid accumulation of Akt in mitochondria. Within the mitochondria, Akt phosphorylates the β-subunit of ATP synthase, GSK3β, thereby inactivating it. Phospho-inactivation of GSK3β inhibits apoptosis and serves to promote cell survival [30].

The oncogenic function of *Ras* requires the activation and subsequent translocation to mitochondria of the transcription factor STAT3 [31]. Mitochondrial STAT3 has been suggested to be a modulator of cellular metabolism, including glycolysis and mitochondrial respiration. Recent studies indicate that phospho-S727 STAT3 localizes to mitochondria, where it regulates the activity of complex I/II in OxPhos and ROS production [32,33].

The Wnt-β-catenin signaling pathway regulates cell development. However, its dysregulated activation has emerged as an important player in cancer formation [34]. In thyroid cancer, PI3K/Akt signaling affected Wnt-β-catenin signaling by activating GSK3β, resulting in cytoplasmic retention of β-catenin and reduced expression of its target genes (cyclins). Downstream effectors of Wnt signaling, such as β-catenin and GSK3β, regulate mitochondria-dependent apoptosis and mitochondrial function. These data emphasize the fact that Wnt may regulate mitochondrial function.

The types of mitochondrial dysfunction in cancerous thyroid follicular cells can be classified as follows: (1) defective OxPhos arising from somatic alterations in mitochondrial DNA in Hürthle cell thyroid carcinoma [35] and papillary thyroid carcinoma [36]; (2) mitophagy defects in Hürthle thyroid carcinoma; and (3) increased cytochrome b and cytochrome c oxidase I in papillary thyroid carcinoma [37].

AUTOPHAGY AND MITOPHAGY IN THYROID CANCER

Cargo-specific autophagy is a critical cellular catabolic pathway that performs quality control of cellular organelles, including mitochondria, by recycling dysfunctional cellular components through the autophagosome-lysosome machinery [38]. Autophagy can be considered a double-edged sword in tumorigenesis: it is a context-dependent tumor-suppressing mechanism that can also promote tumor cell survival under certain adverse conditions [39]. Mitophagy serves to degrade damaged or dysfunctional mitochondria to match the metabolic demand and orchestrate mitochondrial quality and quantity control in cellular homeostasis. Recent studies demonstrated that mitophagy also plays a double-faceted role in tumorigenesis. While it serves to remove dysfunctional mitochondria to mitigate oxidative stress and prevent carcinogenesis, it can protect cells from apoptosis or necrosis and promote tumor cell survival under poor nutrient supply and hypoxic stress [40]. Mutation of the PARK2 gene, which is involved in PTEN-induced kinase 1 (PINK1)/Parkin-dependent mitophagy, is the most common cause of early-onset Parkinson's disease. In human cancers, PARK2 mutation-associated mitophagy may contribute to oncogenesis when it is altered in non-neuronal somatic cells [41]. Although autophagy defects are indeed associated with thyroid cancers [42], the relationship between mitophagy defects and thyroid cancer is yet to be established. In one study, we observed a Parkin-associated mitophagy defect in Hürthle cell thyroid tumors that affected tumor pathogenesis (unpublished data).

CONCLUSIONS

Advanced thyroid cancer that is refractory to radioactive iodine is usually intractable to current chemotherapy and conventional radiotherapy. The changes in metabolic phenotypes during tumor progression determine the biological and clinical behavior. Elucidation of the molecular nature of metabolic remodeling in thyroid cancer may provide new biomarkers and therapeutic targets that may be useful in the management of refractory thyroid cancers.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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