Metabolic Reprogramming in Thyroid Cancer

Subjects: Oncology

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Reprogramming of metabolism is now recognized a hallmark of carcinogenesis as metabolic changes, such as those related to glucose, glutamine and lipids, are tightly related to the proliferation, invasion, migration, radiosensitivity, and chemosensitivity of several tumors, including thyroid cancer.

thyroid cancer metabolism epithelial-mesenchymal transition thyroid cancer progression

1. Introduction

Thyroid cancer (TC) represents the most common endocrine malignancy all over the world, with a steady increase in both the incidence and the mortality rate for the more aggressive forms [1]. According to the most recent epidemiologic studies in United States, TC incidence increased, on average, 3.6% per year during the period 1974–2013, mainly due to an increase in the incidence of papillary thyroid carcinoma (PTC) [1], and it has been estimated that by 2030 TC will be the fourth leading cancer diagnosis in the United States [2]. Accordingly, a recent deep analysis of the Global Burden of Disease 2019 database has calculated that the global incidence of TC has continued to increase in the past three decades [3]. Some of the highest TC incidence worldwide has been reported in Italy where, under the age of 45, TC was the second most common cancer among women (after breast cancer), and the fifth most common among men [4]. The most frequent TC (84% of all TC) is PTC, a differentiated TC (DTC) deriving from epithelial follicular cells. It is generally characterized by an indolent growth and a good prognosis after adjuvant radioiodine (RAI) treatment; the 5-year relative survival rate for patients who had TC diagnosed during the period 2008–2014 was 98%, and it refers mainly to the most prevalent PTC [5]. However, 20–30% of PTC cases show a more aggressive behavior and patients experience relapse/persistence and/or development of lymph node and visceral metastases with consequent increased mortality, despite the use of targeted therapeutic options, such as tyrosine kinase inhibitors (TKI), including sorafenib and lenvatinib [6][7]. During 1994–2013, incidence-based mortality increased 2.9% per year for advanced-stage PTC [1]. Due to the high global incidence of PTCs, the percentage of those RAI-resistant (RAI-R) has a significant impact and it is therefore imperative to find new therapeutic strategies. The aim of our review is to analyze the possibility that the intercross between epithelial-to-mesenchymal transition (EMT) and metabolism could be exploited to find such strategies. These aggressive forms of PTC exhibit loss of differentiation characteristics, including loss of sodium iodine symporter expression/function, resulting in RAI treatment failure and high mortality. At the molecular level, this loss of differentiation is related to the degree of activation of the mitogen-activated protein kinase (MAPK), which is highest in tumors with BRAF mutations [8].

On the other side, anaplastic thyroid carcinoma (ATC), the most undifferentiated TC, is a rare but devastating disease. It accounts for only 2–5% of all TC cases and is associated with a median overall survival (OS), greatly improved in the last years thanks to the targeted therapy, of 15.7 months, a median 1-year survival of 59%, and a median 2-year survival of 42%, despite aggressive multimodal management [9][10][11]. Current management of ATC consists primarily of surgical resection, combined with adjuvant chemoradiation followed by targeted therapy (dabrafenib and trametinib therapy in patients harboring the BRAF V600E mutation) [12]. The pathogenesis of ATC is still debated. Most studies support a gradual dedifferentiation from DTC to poorly differentiated thyroid carcinoma (PDTC), and eventually to ATC, with the progressive accumulation of somatic pro-cancer mutations. This is supported by the fact that 18–37% of ATC cases result from longstanding goiters or DTC lesions, where ATC occurs concurrently in 30–89% of cases, and ATC sometimes develops following treatment failure of DTC and PDTC. Genomic analyses have further demonstrated shared mutations between co-existing ATC and DTC or PDTC lesions, suggesting a common parent cell [13]. Another theory states that ATC could arise from cancer stem cells (CSCs) that are derived from adult stem cells present within a thyroid niche having accumulated genetic mutations that drive the tumor development [14]. For both theories, EMT plays a pivotal role. In fact, a DTC could lead to ATC as a result of either a dedifferentiation process or the development of CSCs, and both depend on EMT. CSCs are in turn the main responsible of cancer resistance [15], and therefore EMT is a cellular process associated with both tumor progression and TC resistance to therapy. Hence, understanding the biology of EMT and the reverse mesenchymal-to-epithelial transition (MET) process should lead to the design of more effective drugs to target cancer cells, including CSCs.

2. The Warburg and Reverse Warburg Effects

Carcinoma cells show preferential use of lactate-generating glycolysis over the more energy-efficient route of oxidative phosphorylation (OXPHOS), which produces more ATP per glucose molecule than glycolysis [16][17][18][19][20]. This altered metabolism, named “Warburg effect”, implies that cancer cells have increased glucose uptake and lactate secretion, and allows cancer cells to gain an advantage in terms of growth and survival, possibly due to increased carbon utilization, hypoxic adaptation, and increased rate of ATP production. More recently, similar metabolic changes have been described in cancer-associated fibroblasts (CAFs) present in the tumor microenvironment (TME), often as a result of oxidative stress induced by hydrogen peroxide secreted by cancer cells. CAFs in turn increase their own production of reactive oxygen species (ROS), resulting in the induction of aerobic glycolysis and consequent production and secretion of lactate and pyruvate. These metabolites are transferred to cancer cells via inflammation, where they are metabolized into mitochondria to generate new ATP, which assists tumor progression. This metabolic interplay between different tumor cell compartments is called “reverse Warburg effect” and facilitates cancer cell anabolism through catabolic reactions pursued by the TME [21][22][23][24][25]. The reverse Warburg effect can occur not only between CAFs and tumor cells but also between different tumor cells, one of which being hypoxic and hypersecreting intermediate catabolites such as lactate and glutamine. Metabolic coupling with glycolysis occurring in some cancer cells and OXPHOS in other cancer cells promotes cell proliferation and survival. In this multi-compartment metabolism, a key role is played by the lactate

monocarboxylate transporters MCT-1 and MCT-4, which mediate the influx into the cell and the efflux from the cell, respectively [26] (**Figure 1**).

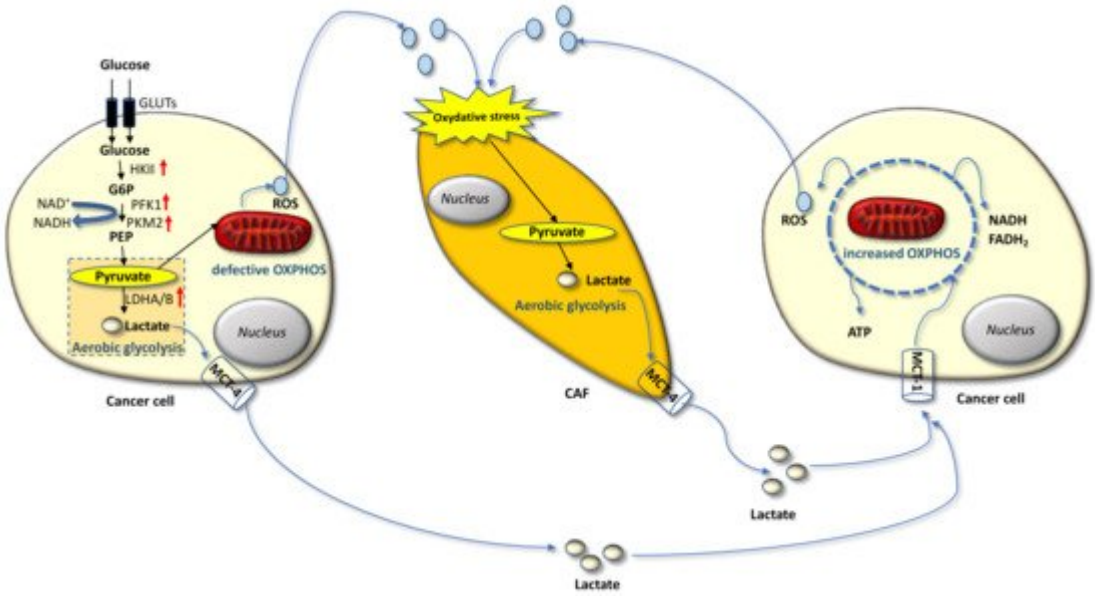

Figure 1. Warburg and reverse Warburg effect. The cancer cell on the left is undergoing the Warburg effect consisting in the metabolic switch from OXPHOS to aerobic glycolysis, which implies increased glucose uptake and secretion of lactate. Cancers cells also establish a metabolic coupling with cancer-associated fibroblasts (CAFs) and other cancer cells: secretion of reactive species, such as hydrogen peroxide in the tumor microenvironment (TME) induces oxidative stress into a neighboring CAF, which hence engages aerobic glycolysis and generates lactate. This in turn is secreted into the TME and fuels OXPHOS in the cancer cell on the right, thus getting efficient ATP production and promoting survival and proliferation. Lactate monocarboxylate transporters mediate efflux (MCT-4) and the influx (MCT-1) of the lactate from and into the cell.

3. Metabolic Reprogramming in Thyroid Cancer

Metabolic rewiring towards an enhanced glycolytic phenotype primarily involves increased glucose uptake and glycolysis flux, mitochondrial dysfunction, and a more acidic TME, playing a critical role in tumor aggressiveness. In other words, malignant tumor cells alter their glucose metabolism to enhance aerobic glycolysis so that they can maintain their metastatic potential.

Amino acids metabolism has a critical role in maintaining cellular metabolic homeostasis. Among all amino acids, glutamine has the greatest consumption during tumor progression and is considered the most important substrate of the cancer cells. It has an essential role in nucleotide and non-essential amino acids synthesis, as well as in providing substrates for the tricarboxylic acid (TCA) cycle, which fuels tumor growth [27]. In particular, TCA cycle is maintained by glutamic acid derived from the conversion of glutamine through the process of glutaminolysis. Consistently, glutamic acid has been found increased in the plasma of patients with thyroid nodules, consisting of 19 PTCs and 16 multinodular goiters, compared to 20 healthy controls [28]. In this pilot study, a panel of significantly

altered metabolites, including some associated with amino acids metabolism, such as cysteine and cystine as well as glutamic acid, was identified by untargeted gas chromatography-mass spectrometry in the plasma of patients with PTC nodules compared to healthy subjects. Differently from glutamic acid, cysteine and cystine were decreased in PTC patients and their levels correlated with the tumor stage [28].

Conversely, in a previous study, cysteine and most amino acids were found significantly up-regulated in PTC tissue (collected from 57 patients) compared to adjacent non-tumor tissue [29]. Cysteine is a precursor for glutathione (GSH) biosynthesis, which plays an essential role in supporting intracellular redox homeostasis by extinguishing ROS from mitochondrial respiration. Cancer cells require exogenous cysteine for GSH synthesis to protect themselves from ROS in order to maintain cell proliferation and resistance to apoptosis [30]. Therefore, decreased plasma levels of cysteine and cystine in patients with thyroid nodules may be explained by the higher consumption of cysteine in the cancer cells. Consistently, in the study by Abooshahab and coworkers, significantly altered metabolites between PTC nodules and healthy persons were also associated with GSH biosynthesis. Overall, they found that the metabolism of about 11 amino acids, including metabolites related to GSH biosynthesis, but also methionine, glycine, serine, threonine, and phenylalanine, had been changed in plasma of patients with PTC nodules compared to healthy subjects. Moreover, the TCA cycle, fatty acids (FA), and purine and pyrimidine metabolism were significantly changed as well [28].

4. Thyroid Cancer Progression and Reciprocal Role of Epithelial-Mesenchymal Transition and Metabolic Rewiring

Activation of EMT, a process by which epithelial cancer cells acquire mesenchymal features, is a key determinant of cancer progression toward an invasive and metastatic phenotype. By acquiring mesenchymal features, cancer cells, in fact, lose cell-to-cell junctions and gain the capacity to migrate and invade the basal lamina thanks to a complex reprogramming of transcription through epigenetic changes. In TC progression, the tumor cells undergo EMT, becoming spindle shaped and invading tumor stroma. Molecular changes include reduced E-cadherin expression levels and increased expression of Snail, Slug, Twist, Paired Related Homeobox 1 (PRRX1), and other EMT-related genes. Hence, first intravasation into the blood and/or lymphatic vessels and then extravasation in distant metastatic sites, such as the lymph nodes and lungs, occur. After a variable time in the quiescence state, the tumor cells are subjected to MET to colonize distant organs forming secondary tumors (**Figure 2**). During this last phase there is a decrease in the expression of Twist and PRRX1 and an increase in the expression of epidermal growth factor (EGFR) and c-Met [15]. Indeed, well-differentiated TC and normal thyroid express high levels of E-cadherin, but do not commonly express Snail and Twist [31]. However, the leading front of PTCs, as well as ATCs, frequently express EMT markers, such as vimentin and Snail, Slug and Twist, but not E-cadherin [15][32][33].

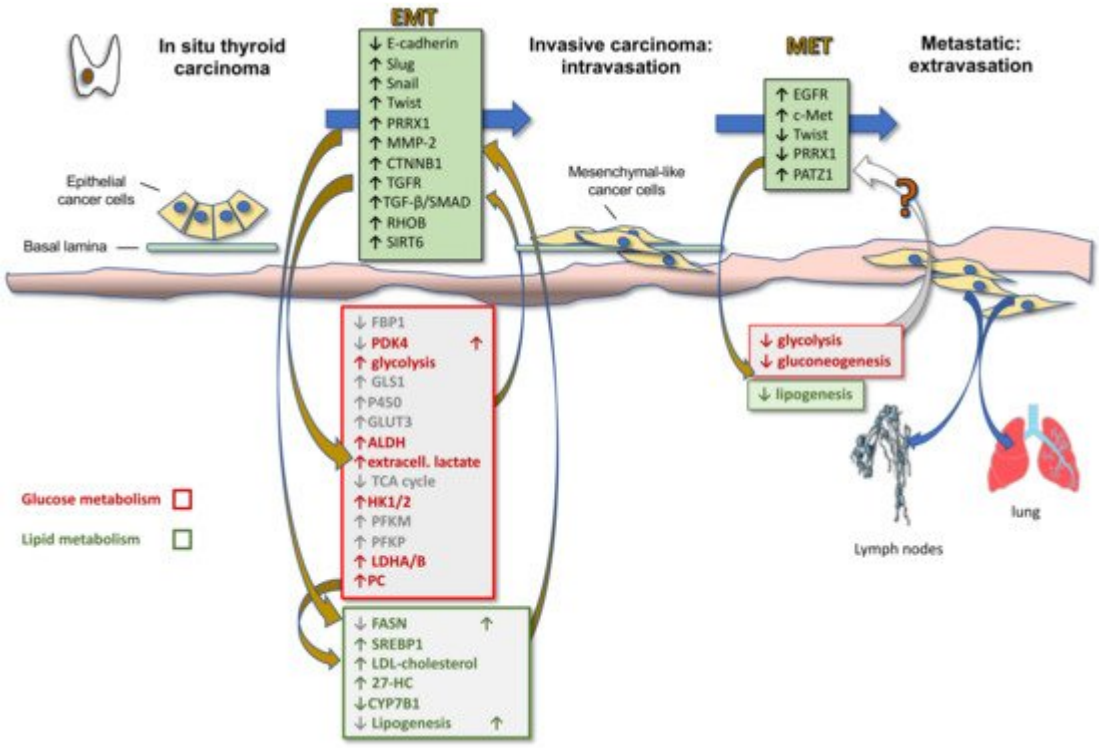

Figure 2. Thyroid cancer progression: reciprocal role of EMT and metabolic reprogramming. The cartoon illustrates the phases of thyroid cancer progression, from in situ to invasive carcinoma and metastatic tumor, highlighting the molecular actors of EMT as well as their reciprocal relationship with metabolic players. Upregulation (arrow up)/downregulation (arrow down) of proteins demonstrated in other cancers but not yet validated in TC is shown in gray.

During EMT cancer cells also acquire stem cell features that allow them to resist to different treatment options. Based on the CSC hypothesis of TC development, normal follicular cells that accumulate errors can give rise to differentiated cancers, which in turn can develop into undifferentiated cancers following the enrichment of CSCs through the EMT process [13]. This is likely the reason why patients with ATCs, which consist of CSCs and non-CSCs, usually have a relapse after surgery and conventional chemotherapy and radio-iodine [15].

More recently, it has become clear that EMT is also involved in metabolic rewiring needed for the increased energetic demand of the mesenchymal cells compared to their epithelial counterparts due to the increased motility and invasion ability. In fact, EMT induction in epithelial mammary cells by Twist expression upregulates the expression of 44 metabolic genes, including dihydropyrimidine dehydrogenase (DPYD), an enzyme involved in pyrimidine catabolism, that in turn upregulates EMT [34]. Therefore, it is likely that metabolic rewiring is required for completeness of EMT. Other metabolic pathways modulated by EMT include glycolysis, lipid metabolism, mitochondrial metabolism and glutaminolysis. Specifically, it has been shown that EMT induction suppresses the expression of multiple metabolic proteins, including fructose-1.6-bisphosphatase 1 (FBP1), thus resulting in increased glycolysis [35], fatty acid synthase (FASN) and ACC, thus resulting in decreased lipogenesis [36], nucleoside transporter [37], and pyruvate dehydrogenase kinase 4 (PDK4) [38], whilst enhancing the expression of glutaminase 1 (GLS1) [39], enzymes of glutathione metabolism, cytochrome P450, aldehyde dehydrogenase, thus

accounting for the increased chemoresistance [40], and GLUT3 [41]. On the other side, these metabolic alterations sustain the Warburg effect and induce EMT by enhancing glycolysis and blocking the TCA cycle. In particular, upregulation of (i) GLUT1 and GLUT3 glucose transporters activates matrix metallopeptidase MMP-2, which in turn induces EMT and invasiveness; (ii) HK1 and HK2 hexokinase, involved in the first step of glycolysis, activates Snail and Slug, which in turn induces EMT; (iii) PFKM and PFKP, rate-limiting enzymes of glycolysis, directly induce EMT; (iv) LDHA and LDHB, associated with enhanced glycolysis and lactate production, as well as extracellular lactate, activate Snail and therefore EMT [42].

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