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Review

Bridging hypoxia, inflammation and estrogen receptors in thyroid cancer progression

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ABSTRACT

Thyroid cancer is a common endocrine-related cancer with a higher incidence in women than in men. Thyroid tumors are classified on the basis of their histopathology as papillary, follicular, medullary, and undifferentiated or anaplastic. Epidemiological and *in vitro* or *in vivo* studies have suggested a correlation between incidence of thyroid malignancies and hormones. In particular, growing evidence indicates a role of estrogens and estrogen receptors (ERs) in thyroid tumorigenesis, reprogramming and progression. In this scenario, estrogens are hypothesized to contribute to the observed female predominance of thyroid cancer in reproductive years. However, the precise contribution of estrogens in thyroid proliferative disease initiation and progression is not well understood. HIF-1α and NF-κB are two transcription factors very frequently activated in tumors and involved in tumor growth, progression and resistance to chemotherapy. In fact, HIF-1α and NF-κB together regulate transcription of over a thousand genes that, in turn, control vital cellular processes such as adaptation to the hypoxia, metabolic and differentiation reprogramming, inflammatory-reparative response, extracellular matrix digestion, migration and invasion, adhesion, etc. Because of this wide involvement, they could control in an integrated manner the origin of the malignant phenotype. Interestingly, hypoxia and inflammation have been sequentially bridged in tumors by the discovery that alarmin receptors genes such as RAGE, P2X7 and some TLRs are activated by HIF-1α; and that, in turn, alarmin receptors strongly activate NF-κB and proinflammatory gene expression, evidencing all the hallmarks of the malignant phenotype. Recently, a large number of drugs have been identified that inhibit one or both transcription factors with promising results in terms of controlling tumor progression. In addition, many of these inhibitors are natural compounds or off-label drugs already used to cure other pathologies. Some of them are undergoing clinical trials and soon they will be used alone or in combination with standard anti-tumoral agents to achieve a better treatment of tumors to achieve a reduction of metastasis formation and, more importantly, a net increase in survival. This review highlights the central role of HIF-1α activated in hypoxic regions of the tumor, of NF-κB activation and proinflammatory gene expression in transformed thyroid cells to understand their progression toward malignancy. The role of ER-α will be underlined, considering also its role in reprogramming cancer cells.

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Contents

1. Introduction: transformation and progression of thyroid cancer

Thyroid cancer accounts for more than 95% of endocrine malignancy. It includes differentiated thyroid carcinomas (DTCs) of papillary (PTC) and follicular (FTC) type, and undifferentiated thyroid cancer (UTC), all arising from a cell of the follicular epithelial lineage, and medullary thyroid carcinoma (MTC), originating from parafollicular or C cell lineage. DTCs represent approximately 93% of all thyroid cancers, with papillary cancer accounting for the majority (80–85%) of histological subtypes. Papillary thyroid cancers (PTC) occur mainly in premenopausal women with a predominance peak at puberty. Follicular thyroid carcinoma (FTC), the second most frequent subtype, accounts for 10–15% of all thyroid cancers, occurs also more frequently in women aged 40 to 60 years. This gender difference suggests that growth and progression of thyroid cancer may be influenced by female sex hormones, particularly estrogens [1,2].

Over the last decade, tumor-initiating genetic events have been a major focus in thyroid cancer initiation. Point mutations in the BRAF (especially $BRAF^{V600E}$) and RAS genes as well as RET/PTC and PAX8/PPARγ chromosomal rearrangements, are found frequently in papillary and follicular thyroid cancer[3–5]. Genetic alterations activate intracellular signaling pathways such as the mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) pathway [6,7], PI3K-Akt and β-catenin signaling cascade [8], which all have been implicated in thyroid tumor cells survival and proliferation.

More recently, accumulating lines of clinical and experimental evidence suggest that the classical multistep carcinogenesis model, involving sequential accumulation of genetic mutations during proliferation of mature thyroid follicular cells, should be revised. [9–11].

New insights have been gained with the recent identification and characterization, in the thyroid gland, of normal and malignant thyroid stem cells [12]. This has lead to the formulation of cancer stem cells hypothesis, which proposes that thyroid cancer originates from progenitor/stem cells. This hypothesis accounts for the functional diversity commonly found in thyroid tumors.

At the same time, an interesting advance in cancer biology has been the appreciation that the phenotypic characteristics of cancer are defined not by the genetics of the tumor cells alone but by the their interaction with surrounding milieu. Abnormal microenvironment conditions, such as hypoxia, extensive cell death, inflammation, DNA-damage, oxidative stress are now recognized as hallmarks of all solid cancers, including thyroid tumors, suggesting that thyroid tumor microenvironment is critically important for transformation, progression, metastasis and drug resistance [13].

Furthermore, growing evidence indicates a role of estrogens and estrogen receptors (ERs) in thyroid tumorigenesis and progression [14]. Estrogens are hypothesized to contribute to the observed female predominance of thyroid cancer in reproductive years, and *in vitro* studies have demonstrated that estradiol (E_2) stimulates the proliferation of papillary thyroid cancer (PTC) cells [15]. The biological effects of estrogen are mediated by two related but distinct isoforms of receptors: estrogen receptor alpha (ER-α) and estrogen receptor beta (ER-β). The two isoforms appear to mediate different effects on tumoral cells, ER-α having a proliferative and anti-apoptotic activity, while ER-β displaying differentiative and proapoptotic effects [16].

Therefore, in addition to the above mentioned signaling pathways, involved in thyroid tumorigenesis, the HIF-1α, NF-κB and ERs pathways have been implicated in the development of both less aggressive thyroid cancers, papillary and follicular adenocarcinomas, and progression to aggressive thyroid cancers, such as anaplastic adenocarcinomas.

In the present review, we will focus on the role of hypoxia, inflammation and estrogen receptors in thyroid cancer and provide novel insights into ERs cross-talk with HIF-1α and NF-κB cellular signaling pathways in thyroid cancer cells.

2. Role of hypoxia and HIF-1α dependent genes in thyroid cancer progression

A characteristic feature of human solid tumors, such as thyroid carcinomas, is the presence of hypoxic areas often surrounding areas of necrosis. Necrosis and hypoxic regions are the result of the progressively increasing distance between cells and blood vessels as the tumor is growing, as well as of the abnormal new vasculature. Adaptation of cancer cells to their hypoxic microenvironment is one critical point in the progression of solid malignant tumors [17]. This adaptive process is regulated primarily by the hypoxia-inducible factor-1 (HIF-1), DNA-binding transcription factor [13].

HIF-1 is a heterodimeric protein that is composed of a constitutively expressed HIF-1β subunit and an O_2-regulated HIF-1α subunit. Under normoxia, HIF-1α is hydroxylated by prolyl-hydroxylase domain (PHDs)-containing enzymes. Hydroxy-HIF-1α is recognized by the pVHL ubiquitin ligase complex and is subsequently ubiquitylated and degradated by the 26S proteasome. Hydroxylation of HIF-1α is abrogated under low oxygen tensions (hypoxia), allowing HIF-1α to escape degradation. Stabilized HIF-1α dimerizes with nuclear HIF-1β and the heterodimer HIF-1, initiates the transcription of a myriad of genes involved in angiogenesis (VEGFA, SDF1 and PDGFB), glucose metabolism (SLC2A1, GLUT1, GLUT3), erytropoiesis (EPO), apoptosis resistance, inflammation (NF-κB), invasion and metastasis (MMP2, MMP9 and LOX) promoting tumor progression [13].

Recently, several studies and our, have shown that in thyroid carcinomas HIF-1α protein is over-expressed and activated compared to normal thyroid tissue. Interestingly, HIF expression was highest in the most aggressive thyroid carcinomas and associated with increased resistance to both radiotherapy and chemotherapy [18].

HIF-1 promotes angiogenesis by increasing vascular endothelial growth factor (VEGF) transcription. Thyroid tumors are more vascular than normal thyroid tissue, and there is a clear correlation between increased VEGF expression and more aggressive thyroid