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Targeting vascular endothelial growth factor (VEGF) pathway in iodine-refractory differentiated thyroid carcinoma (DTC): From bench to bedside

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Abstract

Thyroid cancer is the most common endocrine malignancy, representing 1% of all human malignancies; its incidence has been escalating worldwide during the last decades. In recent years important molecular pathways contributing to tumor progression and worse survival rates have been identified in iodine-refractory differentiated thyroid carcinoma (DTC) with the consequent development of molecular therapeutics to target these specific oncogenic pathways. For example, a positive correlation has been found between expression of vascular endothelial

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growth factor (VEGF) and a more aggressive phenotype of DTC. This has led to the widespread adoption of VEGF-targeted therapeutics in the preclinical and clinical settings. In this review we will provide an overview of the different aspects of the use of VEGF-pathway-oriented treatments in iodine-refractory DTC with particular focus on future prospects.

Keywords: Thyroid carcinoma; Iodine-refractory; Systemic therapy; Sorafenib; Sunitinib; VEGF

1. Introduction

Thyroid cancer is a common endocrine malignancy, the incidence of which shows marked geographic, ethnic and gender variation [1–3]. According to the WHO classification, thyroid carcinoma has been classified into papillary, follicular, medullary and anaplastic thyroid cancer subtypes [4]. These subtypes differ markedly in terms of etiology, biology, clinical presentation, treatment and prognosis [5]. The American Joint Committee on Cancer (AJCC) TNM classification has been widely used worldwide to stage thyroid carcinomas, taking into consideration the primary tumor (T), regional lymph nodes (N) and presence or absence of distant metastases (M).

While the primary treatment for localized differentiated thyroid cancer (DTC) is surgical intervention followed by radioiodine treatment for intermediate- and high-risk patients [6], the situation is more complicated for metastatic disease, with multiple treatment options which include radioiodine therapy, surgery, external-beam radiotherapy and systemic therapy [7]. A long list of systemic agents has been tested for iodine-refractory DTC [8]. This includes cytotoxic chemotherapy agents (including anthracyclines, taxanes and platinum analogs); however, the results for cytotoxics have been largely discouraging [7].

In recent years, important molecular pathways contributing to tumor progression and worse survival have been identified in iodine-refractory DTC, with the consequent development of molecular therapeutics to target these specific oncogenic pathways [9]. The most extensively studied oncogenic pathways and kinases include RET/PTC, VEGF, mTOR and c-MET [10]. In this review we will provide an overview of the different preclinical and clinical aspects of the use of VEGF-pathway-oriented treatments in iodine-refractory DTC with particular focus on their future potential.

2. Understanding the impact of VEGF pathway on carcinogenesis

The vascular endothelial growth factor (VEGF) is the most commonly explored molecular marker in a number of different diseases [11]. The VEGF family comprises seven glycoproteins (VEGF-A, -B, -C, -D, -E and PlGF-1 and -2), as well as three tyrosine kinase receptors (VEGR-1, -2 and -3) [12]. VEGF glycoproteins can be secreted by tumor cells or derived from marrow-derived progenitor cells and inflammatory cells such as activated T cells [13,14].

To understand the intricate network of VEGF in cancer development and progression, mechanisms that lead to either increased or decreased VEGF level have been proposed. First, hypoxia works as the principal stimulant of angiogenesis by inducing the hypoxia-induced factor 1 (HIF-1a) which then translocates to the nucleus where it induces the expression of a number of growth factors, of which VEGF is the most significant [15]. Second, increased production of a number of growth factors – platelet-derived growth factor (PDGF), epidermal growth factor (EGF), insulin-like growth factor 1 (IGF-1), transforming growth factor alfa (TGF-a) and transforming growth factor beta (TGF-b) – may lead also to an increase in VEGF production [16,17].

Once the excessive production of VEGF occurs, angiogenesis ensues with a consequent impact on the enhancement of the invasive and metastatic potential of the cancer cells (i.e., through the increase in neo-vessels in the tumor microenvironment) and the enhancement of immune evasion of the tumor cells [18,19].

3. Pathogenetic role of the VEGF pathway in the development of DTC

VEGF has been suggested as an early pathogenetic event in the development of DTC [20]. However, whether or not VEGF expression promotes DTC progression is not yet fully established. For example, Luo et al. found that the expression of VEGF-C and -D in papillary thyroid carcinoma with lymphatic metastasis was significantly higher than that in papillary thyroid carcinoma without lymphatic metastasis ($P < 0.05$), and they suggested a possible etiologic mechanism between VEGF-C and -D and lymphatic metastasis through the induction of proliferation of lymphatic endothelial cells and development of lymphatic vessels [21]. Additionally, VEGFR-2 was found to form a signaling complex with sphingosine 1-phosphate and to extracellularly regulated kinase 1/2 and protein kinase C-alpha regulating thyroid carcinoma cell migration [22]. Moreover, lymphatic vessel density and VEGF-C expression were found to be significantly different between benign and malignant thyroid lesions [23].

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