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Review Article

Cytokines, thyroid diseases and thyroid cancer

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ABSTRACT

Cytokines are molecules that influence activation, growth, and differentiation of several target cells. They are proinflammatory mediators, regulate the systemic inflammatory response, playing a crucial role in autoimmune thyroid diseases, and modulate development and growth of both normal and neoplastic thyroid cells. In addition cytokines, as well as chemokines, have been shown to generate antitumor response. In patients with thyroid cancer, cytokines are useful as serum biomarkers, and should be a part of multi-analyte assay in the clinical evaluation of patients with indeterminate fine-needle aspiration cytology. Finally, several cytokines, such as interleukin-6 (IL-6), leukemia inhibiting factor (LIF), and thyroid transcription factor-1 (TTF-1) are expressed in thyroid cancer cell lines, and they can be used for evaluating the inhibitory effects of several drugs in redifferentiation therapies. This review reports the latest advances in defining the actions of cytokines, and resumes the relationship between cytokines, thyroid diseases and thyroid cancer.

1. Introduction

Thyroid carcinoma is a rare malignancy, occurring roughly in 1–2% of cancer patients, with an overall incidence of 0.01% per year [1,2]. However, in the United States, the estimated new cases among women were 22,600 in 2006 and 27,200 in 2009, corresponding to 3% and 4% of all female cancers, respectively [3,4]. Thus, the incidence of thyroid cancer is still increasing [5,6].

Adenocarcinoma is the most common histologic type seen in the thyroid gland, and at least 95% of malignant thyroid tumors are differentiated carcinomas, papillary and follicular, both derived from the follicular cells [1,7]. In 5% of patients with papillary thyroid carcinoma a more aggressive familial nonmedullary type of cancer has been shown, with localization of susceptibility genes on chromosomes 1q21, 2q21, and 19p13.2 [1,8].

Ultrasound-guided fine-needle aspiration (FNA) cytology usually represents the first step in the management of thyroid nodule [6,9]. Unfortunately, the FNA cytology reads "follicular neoplasm" or "suspicious" in up to 30% of cases, and most patients with follicular lesions will require surgical management with the aim of having a permanent histologic examination [1,10,11].

In several studies, the detection of oncogene mutations in aspirates has been proposed as a adjunctive evaluation in patients with uncertain FNA cytology [12]. A high prevalence of mutation of BRAF gene, that makes a protein called B-RAF, in patients with papillary thyroid carcinoma has been found, and thus the mutational analysis of BRAF in FNA aspirates should be suggested as a part of the preoperative decision-making of patients with thyroid nodules [13,14].

It has also been hypothesized that the study of a broad set of serum markers, including cytokines, would provide useful information, in conjunction with FNA cytology, with the aim of reducing the need of surgery [15]. In distinguishing between thyroid carcinomas and benign thyroid nodules, a multi-gene approach using a multi-analyte profiling technology analysis of serum cytokines, chemokines, and growth factors was recently reported [9,16].

2. Cytokines and inflammation

Soluble mediators in an immune response include immunoglobulins, antigen-specific proteins made by mature B lymphocytes, usually called antibodies, and cytokines [17].

Cytokines are molecules that influence activation, growth, and differentiation of several target cells, and more than 100 types of cytokines have been identified. They are produced by different types of cells, exhibiting less restricted tissue specificity than hormones [17,18].

Several cytokines, such as interleukin-1 beta (IL-1β), interleukin-6 (IL-6), and interleukin-8 (IL-8) are proinflammatory mediators, inducing a systemic inflammatory response reflected by increased levels of soluble interleukin-2 receptor (sIL-2R),

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Nomenclature

AFP	α-fetoprotein
ATRA	all-*trans*-retinoic acid
bFGF	basic fibroblast growth factor
13-CRA	13-*cis*-retinoic acid
EGF	epidermal growth factor
G-CSF	granulocyte colony-stimulating factor
HGF	hepatocyte growth factor
IGF	insulin-like growth factor
IGF-1	insulin-like growth factor-1
IL-1α	interleukin-1 alpha
IL-1β	interleukin-1 beta
IL-1 RA	interleukin-1 beta receptor antagonist
IL-6	interleukin-6
IL-8	interleukin-8
IL-10	interleukin-10
INF-γ	interferon gamma
LIF	leukemia inhibitory factor
Met	thyrosine kinase receptor for hepatocyte growth factor
NIS	sodium–iodine symporter
PAX-8	paired box gene 8
PTHrP	parathyroid hormone-related protein
RANKL	receptor activator of nuclear factor-κ ligand
Ret	rearranged during transfection
sIL-2R	soluble interleukin-2 receptor
Tg	thyroglobulin
TGF-α	transforming growth factor-alpha
TGF-β	transforming growth factor-beta
TGF-β1	transforming growth factor-beta 1
TGF-β2	transforming growth factor-beta 2
TKR	thyrosine kinase receptor
TNF	tumor necrosis factor
TNF-α	tumor necrosis factor-alpha
TPO	thyroid peroxidase
Trk	tropomyosin-related kinase
TSH	thyroid-stimulating hormone (thyrotropin)
TSH-R	thyroid-stimulating hormone-receptor
TTF-1	thyroid transcription factor-1

neopterin, or tumor necrosis factor-alpha (TNF-α), while other cytokines, such as interleukin-10 (IL-10), and interleukin-1 beta receptor antagonist (IL-1RA) are involved in systemic inflammatory response [18].

Cytokines are mainly produced from immune cells, but are also secreted by the thyroid follicular cells as well as by the inflammatory cells [19].They upregulate the inflammatory reaction through stimulation of T and B lymphocytes, resulting in antibody production and tissue injury, and play a crucial role in autoimmune thyroid diseases [19,20].

Activation of receptor activator of nuclear factor-κ ligand (RANKL), produced by either cells of immune system, stromal cells or tumor cells on response to interleukins or parathyroid hormone-related protein (PTHrP), represents the key process in a paraneoplastic cancer-induced hypercalcemic syndrome [21]. RANKL activates osteoclast precursors and subsequent bone osteolysis, leading to the release of several bone-derived growth factors, including insulin-like growth factor-1 (IGF1), and transforming growth factor-beta (TGF-β) [22]. An abnormal activation of RANKL is induced by several circulating cytokines, such as interleukin-1 alpha (IL-1α), IL-6, TNF-α and TGF-β, and a specific TNF family protein binds to RANKL and promotes apoptosis of osteoclasts, blocking bone resorption [23–25]. As possible pharmacological intervention, both the human monoclonal antibody denosumab, which is able to interfere with RANKL-RANK pathways, and humanized anti PTHrP antibody, have been suggested [26,27].

3. Cytokines, thyroid function and autoimmunity

Cytokines play a role in the pathogenesis of several autoimmune thyroid diseases. They affect the autoimmune process by (1) recruitment of inflammatory cells, (2) upregulating molecules able to perpetuate the inflammatory response, and (3) interfering with thyroid hormone synthesis [28].

Normal thyroid follicular cell lines produce high levels of IL-6 and IL-8, while TGF-α is not expressed in normal thyroid tissues, but it may inhibit the growth of most epithelial cells [29]. Moreover, the extracellular matrix and extracellular matrix-bound cytokines modulate the expression of cell-surface molecules in their ability to induce local immune-cell activation on target malignant cells [30]. Finally, both in benign and in malignant thyroid diseases, the serum cytokines profile is related to inflammatory disregulation, which may be reflected in specific cytokine alterations [9].

The active transport of iodine into the thyroid cell is mediated by an intrinsic membrane protein called sodium–iodine symporter (NIS), that plays key role in thyroid pathophysiology [31,32]. Cytokines, including IL-1α, IL-1β, IL-6, TNF-α, and TGF-β2, have an inhibitory role in NIS protein expression and NIS gene transcription [19,33].

Both in Graves' disease and in Hashimoto's thyroiditis, thyroid cells are exposed to complement attack, with subsequent release of prostaglandin E2, IL-1α, and IL-6, which promote infiltration of lymphocytes leading to cell destruction [34,35]. In Grave's disease, inflammatory mediators, such as interleukins and TNF-α, stimulate the production of external thyroid-stimulating antibodies that bind the thyroid-stimulating hormone (TSH) receptors (TSH-R). Both IL-6 and TNF-α regulate type 2 iodothyronine 5′-deiodinase in the anterior pituitary, affecting TSH releasing, and contribute to nonthyroidal illness syndrome [36,37].

4. Cytokines and thyroid cancer

It has long been found that there are several growth factors stimulating growth of normal thyroid epithelial cells, and that cultured normal thyroid follicular cells are able to produce high levels of IL-6 and IL-8 [38]. More recently, reduced IL-6 expression was found in anaplastic thyroid carcinoma cell lines, while overexpression of TGF-α was demonstrated in several thyroid tumors [29]. On the other hand, TGF-β inhibits the growth of most epithelial cells, including cancer cells [29,39]. TGF-β and activin A are the most important growth inhibitors of thyroid follicular cells, and a relationship between p53 over-expression and epidermal growth factor (EGF) receptor rate was found [23,40].

Thyroid cell lines originating from papillary, follicular and Hürthle cell carcinomas express thyroid differentiation markers, such as thyroid peroxidase (TPO), thyroglobulin (Tg), and TSH-R, while those originated from undifferentiated carcinomas express cytokines (i.e. IL-6, leukemia inhibiting factor [LIF], thyroid transcription factor-1 [TTF-1], and paired box gene 8 [PAX-8]), and other markers such as granulocyte colony-stimulating factor (G-CSF), and PTHrP [41]. PAX-8 is a gene that encodes proteins involved in thyroid follicular cell development, while IL-6, hepatocyte growth factor (HGF) and Met protein (a thyroisine kinase