Review

Advances in the relationship between Hashimoto's thyroiditis and thyroid cancer

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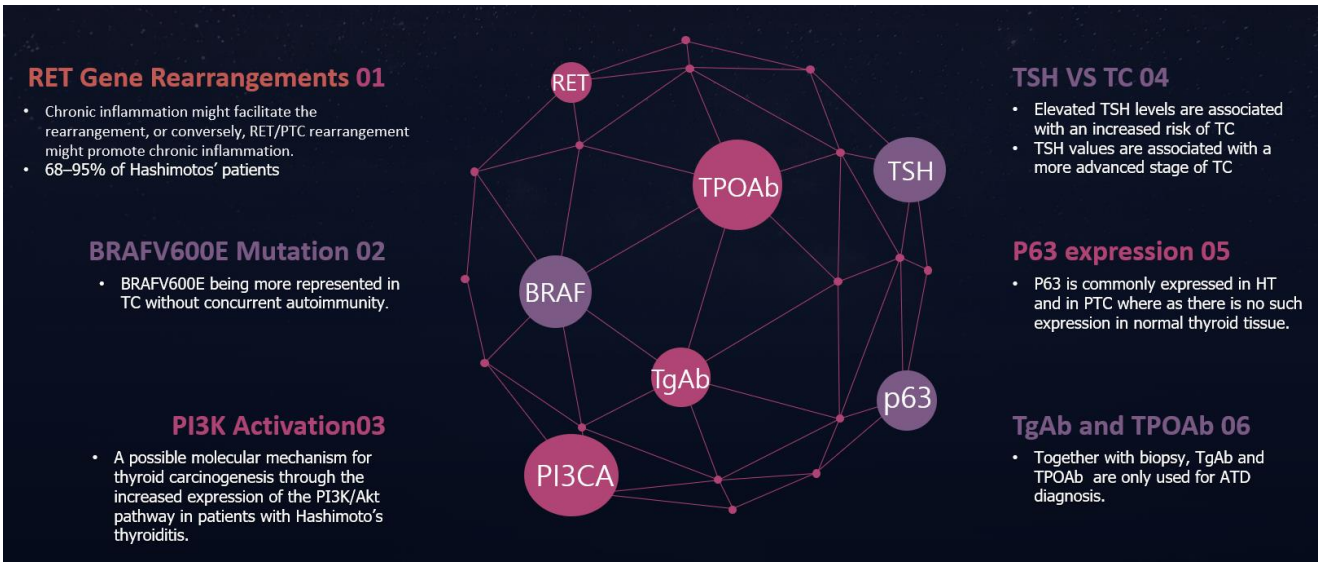
Highlights

In this paper, various factors related to Hashimoto's thyroiditis and thyroid cancer, especially papillary thyroid cancer, morbidity and lymph node metastasis, are reviewed concerning recent literature.

Editor's Summary

In recent decades, it is very high for the incidence of HT and the thyroid cancer rate. This article is more likely that autoimmune thyroid inflammation such as HT is carcinogenic, and thyroid dysfunction related to HT may also promote tumor growth induced by stimulating TSH receptor.



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Abstract

In recent years, the incidence of Hashimoto's thyroiditis and thyroid cancer has shown a rapid growth trend. These two diseases have severely affected the public health. Many epidemiological studies have shown that thyroid cancer is often associated with Hashimoto's thyroiditis. Hashimoto's thyroiditis may promote the occurrence of thyroid cancer, as well as affecting the progression of the tumor, lymph node metastasis, and even the prognosis of patients. In this paper, the relationship between Hashimoto's thyroiditis and thyroid cancer and the pathogenesis of thyroid cancer are reviewed regarding molecular mechanism, clinical pathology, and serology.

Keywords: Hashimoto's thyroiditis, Thyroid cancer, Inflammation, Tumor

摘要

近年来，桥本氏甲状腺炎和甲状腺癌的发病率呈现快速增长趋势。 这两种疾病严重影响了公众健康。 许多流行病学研究表明，甲状腺癌通常与桥本氏甲状腺炎有关。 桥本氏甲状腺炎可能促进甲状腺癌的发生，以及影响肿瘤的进展，淋巴结转移，甚至患者的预后。 本文从分子机制，临床病理学和血清学方面综述了桥本氏甲状腺炎与甲状腺癌的关系及甲状腺癌的发病机制。

关键词：桥本甲状腺炎；甲状腺癌；炎症；肿瘤

Abbreviations: HT, Hashimoto's thyroiditis; PTC, Papillary thyroid cancer; RET, Ret proto-oncogene; T2R38, Taste 2 receptor member 38; CXCL, C-X-C motif chemokine ligand; IL, Interleukin; MAPK, Mitogen-activated protein kinase; FasL, Fas ligand; SNP, single nucleotide polymorphism; TgAb, Thyroglobulin antibody; TPOAb, Thyroid peroxidase antibody; TSH, Thyroid stimulating hormone.

Competing interests: Authors declare that they have no competing interests.

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Introduction

Hashimoto's thyroiditis (HT) is one of the most common autoimmune diseases of the thyroid and is also one of the most common causes of hypothyroidism [1, 2]. The pathogenesis of HT includes humoral immunity (autoantibody), cellular immunity and gene [3]. There is often lymphocytic infiltration in HT, so it is also known as chronic lymphocytic thyroiditis. The infiltrating T cells release cytokines under the stimulation of the thyroid autoantigen, which leads to the apoptosis of thyroid cells, and the antibody relating to thyroid released by humoral immunity promotes the progressive thyroid fibrosis [4]. In recent years, the incidence of HT is consistent growth [5], which may be one of the reasons for the increased incidence of thyroid cancer.

Thyroid nodules are very common. Ultrasonography detects the 30-67% [1, 6] of thyroid nodules. In recent years, the incidence of papillary thyroid carcinoma continues to increase rapidly [7]. According to statistics, from 1974 to 2013, there are 77276 patients in the United States diagnosed with thyroid cancer, with an average annual increase of 3% [8]. In South Korea, thyroid cancer has also become one of the most common malignancies in women [9]. Similarly, the incidence of thyroid cancer in China is also increasing rapidly. On the basis of statistics, the new incidence of thyroid cancer is about 143900 cases in 2013, which the incidence is 10.58/100000, while in 2010 the new incidence of thyroid cancer is only 54175 cases in China [10, 11]. As the incidence of thyroid cancer increasing, Hashimoto's thyroiditis is also booming rapidly.

Chronic inflammation and immune diseases have been confirmed to promote the occurrence of certain cancers, such as the relationship between pelvic inflammation and ovarian cancer, scleroderma and breast cancer, as well as chronic inflammation and lung cancer [12]. Similarly, HT may also be one of the risk factors leading to papillary thyroid cancer (PTC). However, PTC associated with HT is less aggressive and malignant, and the prognosis is better than that of without HT [14].

Molecule mechanism study

Ret proto-oncogene / taste 2 receptor member 38 (RET / T2R38) gene rearrangement

The mechanism of PTC triggered by HT may be related to the role of RET/T2R38 in the immune system [15, 16]. It is reported that RET/T2R38 gene mutates in 68 - 95% of patients with Hashimoto's thyroiditis [17], which also often exists in the PTC [18-20]. A retrospective study also confirmed that the probability of RET/T2R38 gene rearrangement in PTC patients with HT was higher than that in patients without HT. It is also reported that chronic inflammation can cause the conformation of chromatin to become unstable, and then induce the mutation of RET/T2R38 gene [21]. Specifically, this mutation is a gene rearrangement between the RET tyrosine kinase domain and the heterologous gene, which leads to the continuous activation of the RET gene, finally making the oncoprotein dimerization or oligomerization [3]. This gene rearrangement may be one of the reasons that HT promotes the occurrence of PTC.

Besides, RET/T2R38 can also induce a large number of pro-inflammatory factors, such as C-X-C motif chemokine ligand 1 (CXCL 1), CCR-like protein 2, granulocyte-macrophage colony stimulating factor, interleukin (IL)-1α, IL-1β, IL-6, IL-24, prostaglandin E2, MicrosomalprostaglandinEsynthase-1, and cyclooxygenase 2 [3, 22]. Therefore, the RET/T2R38 gene rearrangement also promotes the occurrence of chronic inflammation.

The oncogenes RET/T2R38 can also activate downstream RAF kinase and mitogen-activated protein kinase (MAPK) cascade reaction [16, 23, 24]. Bozec A *et al.* also shows that HT may activate MAPK signaling pathway during the development of PTC [25]. This activated MAPK may be due to long-term HT induced RET/T2R38 gene rearrangement (Figure 1).

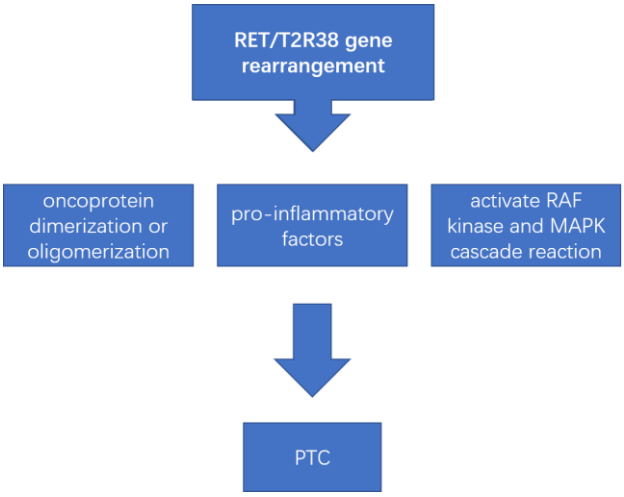

Figure 1 RET/T2R38 gene rearrangement and PTC

B-Raf proto-oncogene V 600E (BRAF V600E) mutation

BRAF V600E is one of the members of the MAPK signaling pathway and is also an essential oncogene in PTC, which is closely related to the increased invasiveness of PTC, while this mutation less appears in the PTC patients with HT [14]. This gene mutation may be one of the reasons for the better prognosis of PTC patients with HT. Although there are many studies on BRAF V600E mutations, it remains further research that the relationship between HT and lymph node metastasis in patients with PTC [26].

RET/T2R38 rearrangement often occurs in PTC with HT, while BRAF V600E mutation is common in PTC without thyroiditis [21]. Recent reports have also confirmed that there is no significant association between BRAF mutation and HT in PTC [27]. However, some studies have shown that the simultaneous expression of RET/T2R38 and BRAF thyroid cells can induce gene expression related to the immune response [3], which leads to the combination of chemokine and its receptor. In particular, chemokine CXCL10 plays a crucial role in the initial lymph node invasion of HT patients [28, 29].

PI3K activation

Concerning the role of HT in promoting the development of thyroid cancer, Larson *et al*. study proposed novel possible molecular mechanism: the activation of the PI3K/Akt signaling pathway in HT patients, and they detected the incremental phosphorylated Akt expression in HT and PTC [30]. Activated Akt also exists in chronic inflammation and thyroid cancer, indicating that it plays a similar role in the occurrence and transformation of HT.

P63 gene

P63 is a member of the P53 gene family [31], which overexpresses in many tumors [32]. The P63 protein is also highly expressed in HT and PTC, but P63 protein is not expressed or low expressed in normal thyroid tissue [33]. PTC with highly expressed P63 has stronger biological invasiveness, in which the central lymph node metastases are more than those of P63 low expression, and P63 may also promote the proliferation and progression of PTC cells. Therefore, P63 is expected to become a predictor of PTC's malignant biological behavior [34]. Because P63 is highly expressed in HT and PTC, some scholars speculate that there are some potential pathological connections between these two diseases. However, the mechanism remains to be further clarified. We make the following two speculations: first, P63 protein is recognized as being able to regulate and maintain the homeostasis of the squamous stem cells and to maintain the intracellular environment. Overexpression of P63 may lead to abnormal cell differentiation and internal environmental disorders [31, 33]. Oncogenes mutations in residual embryonic stem cells with P63 positive may contribute to PTC, or these cells may stimulate some immune responses, leading to the occurrence of Hashimoto's thyroiditis [21].

In addition to the expression of P63 as a predictor of PTC's malignant biological behavior, it can be used to distinguish PTC from other thyroid cancer because of its low expression in the follicular and medullary thyroid carcinoma isoforms [33] (Figure 2).

Fas /Fas Ligand (Fas / FasL) gene

The frequencies of Fas genotype and allele in HT patients were significantly different from those in the normal population. Lymphocytes infiltrated for thyroiditis can express Fas-L. The combination of Fas and Fas-L leads to apoptosis of thyroid cells. The polymorphism of Fas gene and the different frequency of alleles may be important reasons for the apoptosis of thyroid cells caused by autoimmune diseases, but it needs to study further that the reason of HT induces cell apoptosis and causes the destruction of thyroid follicles [35].

Fas/FasL associated inflammation and single nucleotide polymorphisms (SNPs) have been proved to increase the risk of some tumors and poor prognosis of a variety of cancers [36-42]. Recently, a significant difference in the frequency of Fas alleles was found by comparing PTC patients to healthy people, and it was preliminarily demonstrated that the progression of PTC was significantly related to the intron and promoter of the Fas and 30-UTR of SNP [43].

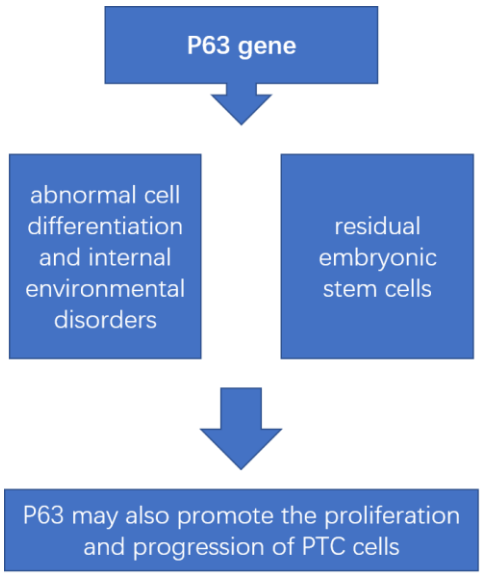

Figure 2 P63 gene and PTC

Clinical pathology study

Histological examination showed that the thyroid gland often had lymphocytic infiltration in thyroid cancer patients. Therefore, it was speculated that there might be a precise relationship between HT and PTC in pathology. Yoon YH and other studies suggest that thyroiditis has some association with PTC in clinicopathology. Compared to patients without thyroiditis, PTC with thyroiditis has smaller age, more women, smaller tumor size, and less probability of extracapsular invasion. Besides, the probability of central lymph node metastasis in PTC patients with thyroiditis is lower than in patients without it [44]. Last year, the literature further suggested that the probability of central and lateral cervical lymph node metastasis in the HT positive group was lower than that of the PTC patients without HT, and the lymph node ratio was lower in the central region [45]. In addition to their research, clinicopathological studies of Lee JH, Jankovic B, and Chen YK also obtained similar results [2, 46, 47]. However, it is worth noting that the association

between HT and thyroid cancer seems to exist only in papillary thyroid carcinoma, while there is no correlation between follicular thyroid carcinoma and HT. Moreover, there is less related research in medullary and undifferentiated cancers.

Serological study

Thyroglobulin antibody and Thyroid peroxidase antibody (TgAb and TPOAb)

Laboratory tests of HT patients often show elevated thyroglobulin, TgAb, and TPOAb titers. The autoantibodies of TPOAb and TgAb have specific complement and cytotoxicity, which can lead to thyroid cell damage. It is believed that the cross-reaction between Tg and TPO contributes to the occurrence of autoimmune thyroid disease [1], which TPOAb is associated with autoimmune lymph nodes [48]. Compared with TgAb, increased TPOAb is more accurate in diagnosing HT and hypothyroidism, while TgAb is more tumor-specific [49]. Korean and Greek scholars retrospectively studied 1171 and 854 cases, of which HT accounted for 365/1171and 246/836 respectively, PTC accounted for 389/836 and /1171 respectively. After data analysis, they came to the same conclusion: increased TgAb is an independent risk factor for PTC, and positively correlated with lymph node metastasis of PTC [1, 49]. After thyroid cancer surgery, the metastasis is often monitored through the TgAb titer, but because TgAb is also associated with lymph node metastasis, it may interfere with the effect of TgAb. Patients with poor primary tumor characteristics often have a high level of serum TgAb before surgery, such as lymph node invasion or metastasis, but it does not make worse prognosis than those with normal TgAb titers [49]. We speculate that a more aggressive treatment plan is adopted because of the poor tumor characteristics (Figure 3).

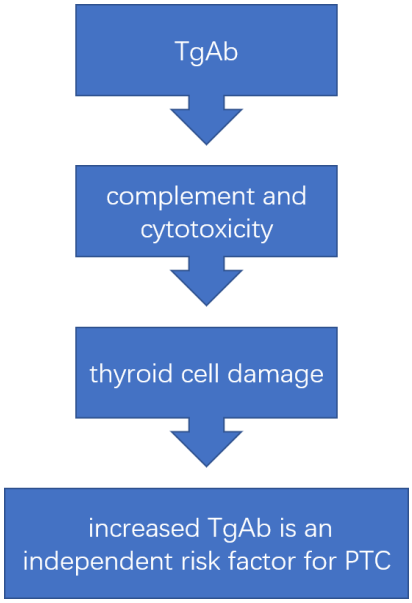

Figure 3 TgAb and PTC

Previous literature has shown that a high titer of TPOAb is a protective factor for thyroid cancer [50]. Some scholars have found that TPOAb shows a moderate degree of antibody-dependent cell-mediated cytotoxicity and anti-proliferative activity in the thyroid cancer cell line [51]. Thus, the increased TPOAb in HT patients seems to prevent the progression of thyroid cancer. However, there is also a different view that TPOAb is a risk factor for malignant thyroid nodules [52]. When TPOAb > 140 IU/mL with HT and PTC, the risk of recurrent PTC is increased, and TPOAb has a significant predictive value for the occurrence of multifocal and central lymph node metastases. Many retrospective studies have found that TPOAb is entirely unrelated to PTC [53, 54]. TPOAb level of malignant thyroid nodules is not higher than benign thyroid nodules [53, 55].

Thyroid stimulating hormone (TSH)

When HT leads to thyroid dysfunction, it may occur in subclinical or clinical hypothyroidism. These two cases all have a high level of serum thyroid stimulating hormone (TSH). The increased TSH promotes the atrophy and hypofunction of the thyroid gland, so the elevated TSH titer is considered to be one of the critical risk factors for differentiated thyroid cancer in some literature [56, 57]. Therefore, the treatment guidelines recommend that all patients with thyroid nodules should detect serum TSH levels [58]. Recently, a further study has pointed out that the risk of PTC increases in women whose serum TSH level below the normal range, while in men whose serum TSH level beyond the normal range [59]. However, more studies still show that a high level of TSH is a risk factor for thyroid cancer [57, 60]. Therefore, thyroid cancer patients usually take levothyroxine (T4) to inhibit the TSH level, standard adjuvant therapy for thyroid cancer [58, 61]. Besides, patients with high TSH level had a larger diameter of malignant thyroid nodules and advanced clinical stage of tumors [56, 60].

Summary

In recent decades, it is very high for the incidence of HT and the thyroid cancer rate, and it showed sustainable growth, which is worthy of our attention and study. This article reviews the relationship between HT and thyroid cancer concerning clinical and pathological aspects. Although there are still some disputes about the relationship, this article is more likely to that autoimmune thyroid inflammation such as HT is carcinogenic, and thyroid dysfunction related to HT may also promote tumor growth induced by stimulating TSH receptor. As the level of TSH and TgAb rise and thyroid nodules with HT, so does the possibility of malignant, yet an independent risk factor, which is of great significance for clinical practice. There are different views, perhaps because of the different race, sex ratio and regional. Also, there are relatively few studies on HT and its related antibodies and lymph node metastasis of thyroid cancer.

Further study is needed to predict the extent of lymph node dissection through the severity of HT or the titer of associated antibodies (Figure 4). This will have important clinical value in the choice of operation method.

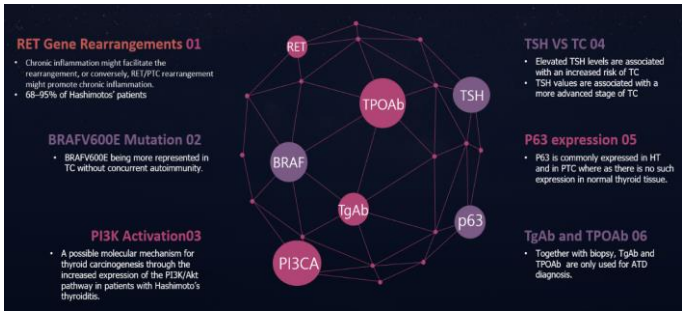

Figure 4 Biomolecular markers have been identified as possibly being involved in the neoplastic transformation from HT to TC.

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