ADVANCES IN TUMOR MARKERS FOR THE EARLY DIAGNOSIS OF PAPILLARY THYROID CARCINOMA

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ABSTRACT

Papillary Thyroid Carcinoma (PTC) is a common endocrine malignancy and mostly is found in women. Different pathological types of PTC have different biological behaviors. The hidden onset results in difficulties to diagnose the early PTC. With the development of the molecular biology, increasing the number of researchers is a focus on tumor markers. The sensitivity and specificity of these tumor markers are helpful for early diagnosis and therapy of PTC. This review is oriented towards the finding of the potent thyroid cancer markers have enhanced sensitivity and specificity, with diagnostic, prognostic and therapeutic efficiency.

Keywords: Papillary thyroid carcinoma, Tumor markers, Galectin-3, Ki67, HBME-1, CK19, VEGF-C, Claudin-1

INTRODUCTION

Thyroid carcinoma is the most frequent endocrine cancer in the last 30 y; the incidence of thyroid carcinoma has been increasing rapidly, which has caused a wide attention. The new cases of thyroid carcinoma account for 1%-5% of all cancer, particularly in women [1]. Rahib L [2] shows that by 2030, the incidence of thyroid carcinoma will rise to a fourth of malignant tumors. In 2010, the average annual percentage change (AAPC) of men and women were 5.4 and 6.5; the number of thyroid cancer cases of men and women were 11000 and 34000, and it would be increased to 39000 and 144000 cases [2-4].

In addition to the medullary carcinoma, the vast majority of thyroid carcinoma originated in follicular epithelial cells. Thyroid carcinoma can be classified according to their histopathological characteristics, such as, PTC, follicular thyroid cancer (FTC), medullary thyroid cancer (MTC), anaplastic thyroid cancer (ATC), poorly differentiated thyroid cancer, thyroid lymphoma, squamous cell thyroid carcinoma and sarcoma of thyroid. Among them, PTC and FTC belong to differentiated thyroid carcinoma (DTC), PTC is the most common thyroid tumor accounts for 79%-94% of total thyroid tumor followed by FTC (15%), MTC (5%) and ATC (1%) tumor (ATC is primarily rare and highly aggressive subsets), which is generally treated by surgical resection and radio-iodine therapy [5].

Thyroid cancer is as aggressive in nature as other cancers, where complete remission can be achieved by early diagnosis and proper treatment. For the majority of thyroid cancer patients with good prognosis, the 5, 10 and 30-year survival rates were approximately 98%, 93% and 76% [6]. In the early stage, differentiated thyroid cancer (PTC and FTC) shows better prognosis with 95% 5-year survival rate in all the stages and 100% mortality. Therefore, more attention should be paid to its early diagnosis.

The majority of the PTC are being diagnosed by palpation, ultrasound, scintigraphy, fine needle aspiration biopsy (FNAC), histology, immunohistochemistry (IHC), imaging modalities like X-ray, and computed tomography (CT) in clinical. However, these methods can not distinguish between benign and malignant nodules conditions; and has certain limitations. Just like variants of papillary and follicular cancer creates confusion among pathologists, where the morphological features are indistinguishable. In order to address this problem, several tumor markers are proposed and their efficiency in thyroid cancer diagnosis, treatment and prognosis are being evaluated which look forward to apply to early diagnosis of PTC or prognostic prediction in PTC patients, such as Galectin-3 (GAL-3), Hector battenia mesothelial epitope-1 (HBME-1), cytokeratin-19 (CK19), Ki67, vascular endothelial growth factor-C (VEGF-C) and Claudin-1 [9]. They were first preferred in many hospitals for their ease of use.

In this article, we have reviewed their recent development and the prospective value of the combination of multiple tumor markers in thyroid cancer, which may be helpful for the early diagnosis and the prognostic monitoring of patients with PTC.

The most common of the aggressive variant of PTC is the tall cell variant. PTC can be onset in any age, which is more common in children or younger female. (Some patients had done neck-X-ray therapy in childhood). PTC grow slowly, could be confined to the Thyroid for several years. The lesion could spread to other parts of thyroid and neck lymph node from the primary site through lymphatic vessel within the thyroid. Moreover, it could be confined for several years, therefore, it is easy to overlook. Extra-thyroid extension, late regional metastases, and distant metastases may be risk factors for early death from PTC [10]. In summary, the incidence tendency of PTC is increasing year by year, and now finding some biomarkers to assist diagnosis of PTC has become a hotspot.

Galectin-3

Galectin family members show altered expression at the mRNA level in PTC. Significant expression differences in all tested galectin family members (1, 2, 3, 4, 7, 8, 9, 10 and 12) were noted for mRNA in PTC, with and without lymph node metastasis. Overexpression of galectin-1 and 3 proteins were noted in PTC with lymph node metastasis. Galectin-1 protein was more strongly expressed than galectin-3 protein in PTC. Galectin-3 is a β-galactoside binding animal lectin which participates in cell-cell and cell-matrix adhesion, cell growth and cell cycle regulation, neoplastic transformation, metastasis, cellular damage reparation and apoptosis [11]. It has been noted to be expressed in PTC and transformed thyroid cell lines but not in normal thyroid cells. It
positive (4/4, 3/3, 2/2; 100% respectively). Tall cell and solid PTC variants showed the diversity of staining (2/3; 66.67% and 13/23; 56.52% respectively), high expression of this protein predicts the aggressive behavior of PTC and can help in the identification of a particular subgroup of PTC patients with a potentially worse prognosis. Furthermore, CK19 could be played a role in extrathyroid tumor spread [25].

Other potential PTC markers

With high sensitivity and specificity, positive staining panel of Galectin-3, Ki67, HBME-1, CK19, VEGF-C have been proved to be the most promising and most frequently used molecular markers in identifying PTC, including both the classic (CPTC) and the follicular variant (FVPTC). However, there are some other biomarkers also have potential in accurate diagnosis and prognosis of thyroid carcinoma and have been reported. Efforts have been made to discover new tissue biomarkers and molecules measurable in body fluids with high sensitivity and specificity. Table 1 summarizes some of the most relevant molecular markers that can be used in the context of PTC.
The evaluation of MMP-2 in thyroid PTC appears to be a borderline correlation was found between the positive reaction of tumor cells with the presence of vascular invasion. Beclin1 is a more specific marker than HBME-1 in PTC and has a higher correlation with Ki-67, and it may play a role in tumorogenesis and lymph node metastasis in PTC. NGAL were positive in most PTC, but were negative or showed focal weak staining in control.

**Table 1: Emerging biomarkers for diagnosis, prognosis, and prediction of PTC**

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Characterization</th>
<th>Observation in PTC</th>
<th>Use</th>
<th>Detection</th>
<th>Reference</th>
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<tr>
<td>matrix metalloproteinases-2 (MMP-2)</td>
<td>The MMPs play an important role in tissue remodeling associated with various physiological or pathological processes. MMP-2 is thought to be important in metastasis.</td>
<td>The evaluation of MMP-2 in thyroid PTC appears to be a borderline correlation was found between the positive reaction of tumor cells with the presence of vascular invasion. Beclin1 is a more specific marker than HBME-1 in PTC and has a higher correlation with Ki-67, and it may play a role in tumorogenesis and lymph node metastasis in PTC. NGAL were positive in most PTC, but were negative or showed focal weak staining in control.</td>
<td>Diagnostic</td>
<td>Tissue vascular</td>
<td>[26] Wu G, et al., 2013;</td>
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<td>Beclin-1</td>
<td>Beclin-1 participates in the regulation of autophagy and has an important role in development, tumorigenesis, and neurodegeneration. A small molecular weight secreted protein which was originally found in activated neutrophils.</td>
<td>The evaluation of Beclin1 in PTC appears to be a borderline correlation was found between the positive reaction of tumor cells with the presence of vascular invasion. Beclin1 is a more specific marker than HBME-1 in PTC and has a higher correlation with Ki-67, and it may play a role in tumorogenesis and lymph node metastasis in PTC. NGAL were positive in most PTC, but were negative or showed focal weak staining in control.</td>
<td>Diagnostic</td>
<td>Tissue</td>
<td>[27] Yesil C, et al., 2015;</td>
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<td>neutrophil gelatinase-associated lipocalin (NGAL)</td>
<td>Claudin-1 plays a major role in tight junctions-specific obliteration of the intercellular space, through calcium-independent cell adhesion activity.</td>
<td>High claudin-1 protein expression is specific for PTC and its regional lymph node metastases</td>
<td>Diagnostic</td>
<td>Tissue</td>
<td>[28] Barresi V, et al., 2012;</td>
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<td>p16</td>
<td>p16 is a tumor suppressor protein, that in humans is encoded by the CDKN2A gene.</td>
<td>p16 gene alterations are common and correlate with histological features and biological aggressiveness in PTC.</td>
<td>Diagnostic</td>
<td>Cell Blood</td>
<td>[30] Do SI, et al., 2015;</td>
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<tr>
<td>p53</td>
<td>p53 has a role in conserving stability by preventing genome mutation, it is a tumor suppressor protein.</td>
<td>P53 is valuable to distinguish PTC from other benign thyroid lesions, but there is no correlation between p53 protein overexpression and clinical pathologic features.</td>
<td>Diagnostic</td>
<td>Cell Blood</td>
<td>[31] Huang Y, et al., 2014;</td>
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<td>p63</td>
<td>Tumor protein p63 is a member of the p53 family of transcription factors. Ras protein family members belong to a class of protein called small GTPase, and are involved in transmitting signals within cells. The functions of TFF3 are not defined, but they may protect the mucosa from insults, stabilize the mucus layer and affect healing of the epithelium. The high expression of TFF3 in PTC is correlated with carcinogenesis and progression, may play a significant role in evaluating the malignancy degree and progression of PTC. The evaluation of active MMP-9 by immunohistochemistry and determination of its activation ratio by gelatin zymography may be a useful adjunct to the known clinicopathological factors in predicting tumor behavior.</td>
<td>Abnormal expression of p63 may be important to promote the progression and metastasis of PTC. RAS-positive PTC was commonly follicular variant, with infrequent extrathyroidal extension and lymph node metastasis. The functions of TFF5 are not defined, but they may protect the mucosa from insults, stabilize the mucus layer and affect healing of the epithelium. The high expression of TFF3 in PTC is correlated with carcinogenesis and progression, may play a significant role in evaluating the malignancy degree and progression of PTC. The evaluation of active MMP-9 by immunohistochemistry and determination of its activation ratio by gelatin zymography may be a useful adjunct to the known clinicopathological factors in predicting tumor behavior.</td>
<td>Diagnostic</td>
<td>Tissue Blood</td>
<td>[32] Hao Y, et al., 2013;</td>
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<tr>
<td>Ras</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>[33] Yip L, et al., 2015;</td>
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<td>trefoil factor-3(TFF3)</td>
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<td>Tissue Blood</td>
<td>[34] Xue G, et al., 2014;</td>
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<td>matrix metalloproteinases-9 (MMP-9)</td>
<td>The MMPs play an important role in tissue remodeling associated with various physiological or pathological processes. MMP-9 is thought to be important in metastasis.</td>
<td>The evaluation of MMP-9 in thyroid PTC appears to be a borderline correlation was found between the positive reaction of tumor cells with the presence of vascular invasion. Beclin1 is a more specific marker than HBME-1 in PTC and has a higher correlation with Ki-67, and it may play a role in tumorogenesis and lymph node metastasis in PTC. NGAL were positive in most PTC, but were negative or showed focal weak staining in control.</td>
<td>Diagnostic</td>
<td>Tissue</td>
<td>[35] Marecko I, et al., 2014;</td>
</tr>
<tr>
<td>matrix metalloproteinases-13 (MMP-13)</td>
<td>MMP-13 is a recently identified member of the MMPs, with broad substrate specificity, and a potential role in tumor metastasis and invasion has been proposed.</td>
<td>The evaluation of MMP-13 appears to be a borderline correlation was found between the positive reaction of tumor cells with the presence of vascular invasion. Beclin1 is a more specific marker than HBME-1 in PTC and has a higher correlation with Ki-67, and it may play a role in tumorogenesis and lymph node metastasis in PTC. NGAL were positive in most PTC, but were negative or showed focal weak staining in control.</td>
<td>Diagnostic</td>
<td>Tissue</td>
<td>[36] Wang JR, et al., 2013;</td>
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<td>v-raf murine sarcoma viral oncogene homolog B1 (BRAF V600E)</td>
<td>The B-Raf protein is involved in sending signals inside cells, which are involved in directing cell growth.</td>
<td>The evaluation of B-Raf protein appears to be a borderline correlation was found between the positive reaction of tumor cells with the presence of vascular invasion. Beclin1 is a more specific marker than HBME-1 in PTC and has a higher correlation with Ki-67, and it may play a role in tumorogenesis and lymph node metastasis in PTC. NGAL were positive in most PTC, but were negative or showed focal weak staining in control.</td>
<td>Diagnostic</td>
<td>Tissue</td>
<td>[37] Rossi ED, et al., 2015;</td>
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<tr>
<td>E-cadherin</td>
<td>The E-cadherin plays a key role in cellular adhesion; loss of this function has been associated with greater tumor metastasis.</td>
<td>The evaluation of E-cadherin appears to be a borderline correlation was found between the positive reaction of tumor cells with the presence of vascular invasion. Beclin1 is a more specific marker than HBME-1 in PTC and has a higher correlation with Ki-67, and it may play a role in tumorogenesis and lymph node metastasis in PTC. NGAL were positive in most PTC, but were negative or showed focal weak staining in control.</td>
<td>Diagnostic</td>
<td>Tissue</td>
<td>[38] Cheng Y, et al., 2015;</td>
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<td>rearranged during transfection(RET)/PTC</td>
<td>RET is a tyrosine kinase receptor whose ligands are neurotrophic factors of the glial-cell line derived neurotrophic factor family, including neurturin, artemin and persefin. RET activation is mediated via different glycosyl phosphatidylinositol-linked GRF receptors.</td>
<td>The current understanding of the clinicopathologic role of RET/PTC fusion proteins in PTC development and progression and the molecular mechanisms by which RET/PTCs exert their oncogenic effects on the thyroid epithelium</td>
<td>Diagnostic</td>
<td>Tissue</td>
<td>[39] Prescott JD, et al., 2015;</td>
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CONCLUSION
In summary, each tumor markers in the diagnosis of PTC have a certain role, whereas there are some limitations of any single biomarker cannot be used as PTC diagnostic criteria. However, combined targeted therapeutic approach against different thyroid cancer biomarkers can reduce the side effect, improve therapeutic efficiency, and improve PTC diagnostic accuracy, which has been confirmed by many studies. Despite the recent positive progress observed in PTC incidence and mortality rates, efforts have to be made to achieve a better understanding of PTC precancerous lesions and of the factors triggering PTC development. This comprehension would enable a more proactive action against PTC progression. With the development of molecular biology techniques, the researches of PTC-associated tumor markers have been gradually deepened.

The exploration of molecular targets and interactions for PTC treatment has been surprisingly rewarding and promising, with several benefits achieved in blocking progression and causing regression of metastases. Therefore, there are still exist problems about the biomarkers of PTC, such as, poor sensitivity and specificity in clinical. Looking for biomarkers of PTC with high sensitivity and specificity remains to be done.

CONFLICT OF INTERESTS
Declared none

REFERENCES
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