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REVIEW

The Blood Biomarkers of Thyroid Cancer

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Introduction: With the gradual increase in the incidence of thyroid cancer, people's attention to thyroid cancer has also gradually increased. Although the prognosis of thyroid cancer is rather mild compared to other cancers, it will still bring a heavy psychological burden on people who have been diagnosed. At present, the diagnosis of thyroid cancer mainly depends on ultrasound and percutaneous fine needle aspiration (pFNA). Due to the unsatisfactory accuracy of the diagnosis methods we use now, there are still some thyroid nodules that cannot be clearly diagnosed before surgery.

Methods: In this article, we have searched for relevant research on blood markers of thyroid cancer in the past five years and categoried them into four groups.

Discussion: Though we have not found a biomarker which can diagnose thyroid cancer both sensitively and specifically, we do found many substances that are related to it, and have the potential to recognize it and help the diagnosis. And perhaps combined models can do it better.

Keywords: thyroid neoplasms, blood biomarkers, diagnosis

Introduction

In the past ten years, the incidence of thyroid cancer has been increasing yearly, and it has become the fourth highest in women;[1] Part of the reason might due to the rapid development of imaging detection technologies and continuously increasing awareness of people's health. But at the same time, data show that the incidence of advanced thyroid cancer and the diagnosis of low-risk thyroid cancer are also rising, so this phenomenon cannot be explained only by overdiagnosis.[2] Current initial diagnostic methods mainly rely on ultrasound, and the gold standard for screening benign and malignant thyroid nodules is percutaneous fine needle puncture biopsy (pFNA) or intraoperative frozen pathological results.[3] But in view of the limited accuracy of ultrasound diagnosis, and the defect that pFNA depends too much on the diagnostic level of the pathology department of the medical institution and due to the small sample size, some specimens cannot be diagnosed, repeated puncture or intraoperative frozen pathology should be done to make the diagnosis, we need to find a biomarker to assist or even replace existing diagnostic methods.[4]

Blood is the most convenient and difficult-to-contaminate body fluid in the diagnosis of diseases, and various tumor markers in blood have been widely used in the diagnostic procedures, which confirmed its value in the diagnosis of tumors. As an important endocrine organ in the body, the thyroid has a wide range of effects on the human body, and its canceration will undoubtedly be reflected in the blood.

Biomarkers for thyroid cancer have been studied for more than 50 years.[5–7] Many people have made in this regard with a lot of results. This article reviews the

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results of tumor markers in the blood of thyroid cancer patients by categories in order to help find potential blood markers for thyroid cancer.

Testing Methods and Means

The determination of substances in blood is often combined with a variety of substance separation and analysis methods, such as nuclear magnetic resonance spectroscopy (MRI), mass spectrometry (MS), gas chromatography (GC), liquid chromatography (LC) and photoacoustic imaging etc. Through the combination of multiple technologies, the possible content that changes a lot in blood can be separated. Besides, for some markers, such as melatonin, they are mainly identified by enzyme-linked immunosorbent assay (ELISA).

Blood Markers

Markers That Related to Metabolism

As an organ participates in energy metabolism, the thyroid gland plays an important role in it. At the same time, tumor cells also show their unique metabolic characteristics in the human body, mainly as follows: cancer cells prefers to use glycolysis rather than aerobic cycle even in an aerobic environment, namely the Warburg effect;[8] The main pathways involved in human metabolism include energy metabolism (glucose metabolism, lipid metabolism and TCA), protein transcription and synthesis, and synthesis of nucleic acids and phosphatidylcholines.

In a study by Wojtowicz et al, the serum and urine samples of healthy people and patients with thyroid disease were compared, and it was suggested that serum is more suitable as diagnostic material than urine. Compared with healthy people, the levels of valine, alanine, creatine, and tyrosine in the serum of patients with papillary thyroid carcinoma have decreased; compared with patients with benign nodules, the serum valine and lactic acid also have a significant decrease in content, while compared to patients with thyroid adenoma, only lactic acid levels decreases.[9]

Farrokhi Yekta et al utilized non-targeted 1H-NMR to detect the blood of 17 patients with multiple goiter, 17 with thyroid papillary cancer and 20 healthy volunteers. Compared to healthy volunteers, there are quite obvious variation in the level of myo-inositol, shark-inositol, tryptophan, alanine, lactic acid, homocysteine, 3-methylglutaric acid, asparagine, and aspartate in serum samples from patients with PTC. The content of aspartic acid, choline, and acetamide has also changed significantly. Compared with patients with multiple goiter, changes in citric acid, acetylcarnitine, glutamine, homoserine, glutathione, kynurenine, niacin, hippuric acid, tyrosine, tryptophan, β-alanine, and xanthine were more pronounced.[10]

Huang et al performed a metabonomic analysis of thyroid nodules from 1540 serum-plasma matches and 114 tissue samples. In this analysis, Huang et al found that there is a significant difference in metabolic phenotypes in blood between healthy people and patients with thyroid nodules. The metabolic disordered pathways identified from serum include glycerophospholipid metabolism, arachidonic acid metabolism, linoleic acid metabolism, alanine, aspartic and glutamic acid metabolism and D-glutamine metabolism. Different metabolic pathways identified from plasma include alanine, aspartic acid, and glutamic acid metabolism, aminoacyl-tRNA biosynthesis, cysteine and methionine metabolism, and taurine-subtaurine metabolism and selenium amino acid metabolism. However, in Huang's study, the metabolic profiles between benign nodules and PTC overlapped completely. Therefore, non-invasive blood tests based on metabolomics are not suitable for their differential diagnosis.[11]

But Wojakowska's and Guo's research has yielded different results. Wojakowska's[12] research using tissues as the material, reached similar conclusions as Guo's[13] which used serum and tissue as the material. They both have confirmed the diagnostic significance of phosphatidylcholines (34:1) phosphatidic acids (36:3) and sphingomyelins (34:1). Phosphatidylcholines (34:1) can distinguish nodular patients from healthy people, while phosphatidic acids (36:3) and sphingomyelins (34:1) can distinguish benign and malignant nodules. Therefore, Guo et al believe that a tool combining the three may be able to distinguish benign and malignant thyroid nodules from healthy people.

Lee et al used nanoflow ultrahigh performance liquid chromatography-electrospray ionization-tandem mass spectrometry (nUHPLC-ESI-MS/MS) technology to analyze the lipid profiling that may occur in five types of cancer. Compared with healthy people, it is found that the lipid profiling of patients with thyroid cancer often shows a different trend from other cancers, and the increase in lysophosphatidylinositols (18:0 and 18:1) and lysophosphatidylethanolamine (18:1 and 18:2) might can be a sign of distinguishing thyroid cancer.[14]

At the same time, Lu's study based on proteomics also believes that people with papillary thyroid cancer (PTC) can be identified by establishing a model of peptide ions.

Lu et al collected blood samples from 88 patients with PTC, 31 patients with benign nodules, and 49 healthy individuals. They found that a model based on 6 peptide ions can be used as a biomarker to identify PTC. At the same time, fibrinogen α and complement C4A/B are considered potential markers for diagnosis of PTC.[15]

Markers Related to Thyroid Function

Thyroglobulin is a large glycoprotein found in thyroid cells and glia. However, because it is also derived from normal thyroid tissue and cells, it cannot be used as a basis for diagnosing thyroid cancer. However, after total thyroidectomy and ablation treatment, the level of serum thyroglobulin can be used for long-term monitoring and accessing the risk of recurrence. However, it should be noted that the presence of TgAb may interfere with the measurement of Tg during the detection process, resulting in erroneous results.[16] Although thyroglobulin does not distinguish thyroid cancer from normal thyroid tissue, some studies[17,18] have shown that preoperative detection of thyroglobulin may help predict the tumor burden and lymph node metastasis of patients. A study in South Korea[19] believes that patients with preoperative thyroid globulin above 13.15ng/mL can be considered to have ipsilateral cervical lymph node metastasis, while above 30.05ng/mL may also have contralateral cervical lymph node metastasis, if higher than 62.9 ng/mL is at risk for distant metastases. Therefore, although thyroglobulin cannot be used as a marker for the diagnosis of thyroid cancer, it has a pivotal position in the management of thyroid cancer.

Calcitonin, a peptide hormone secreted by thyroid follicular cells, has been widely used in the diagnosis of medullary thyroid cancer (MTC) and postoperative follow-up,[3] but its role in the diagnosis of all types of thyroid cancer has always existed disputes. In their study, Unluhizarci et al suggested that although the mechanism is not clear, in addition to MTC, other types of thyroid diseases, including methylene inflammation and Hashimoto's thyroiditis, may also elevate serum calcitonin.[20] Although in 2009, someone[21] also claimed that follicular and papillary cancer cells can release substances that have paracrine stimulating effects on C cells, and ultimately increase serum calcitonin levels. However, related research is not sufficient, and its diagnostic significance is not clear.

There have been conflicting reports on the relationship between serum selenium, copper, and magnesium levels and thyroid cancer. In 2015, Shen et al conducted a meta-analysis on this issue and finally showed that there was a significant correlation between serum selenium, copper, and magnesium levels and thyroid cancer.[22] Serum selenium concentration was negatively correlated with the stage of thyroid cancer. In addition, serum copper levels in patients with thyroid cancer were higher than those in healthy controls, and low levels of serum magnesium were associated with thyroid cancer. Although geography and detection methods may affect experimental results.[23] Although most studies support a decrease in serum selenium levels in patients with thyroid cancer, and supplementation with selenium may reduce the risk of certain diseases, the decline is not specific, except for thyroid cancer, including infections, many diseases, including Parkinson's, can cause selenium levels to decline.[24]

The significance of vitamin D in the diagnosis and prognosis of thyroid cancer is also conflicted, although in 2016 and 2017, Choi[25] and Danilovic[26] denied serum 25 (OH) D_3's role in determining the risk of thyroid cancer in their studies respectively. But in 2018, Zhang et al found that the content of 1,25 $(OH)_2$ D_3 in the serum of patients with PTC is significantly lower than that of healthy people, so maybe 1,25 $(OH)_2$ D_3 can become a potential diagnostic marker for PTC.[27] Hu's[28] and Zhao's[29] further studies suggest that 25 (OH) D_3 and vitamin D binding protein may even be protective factors for thyroid cancer and vitamin D deficiency may be a risk factor for thyroid cancer.

Related Hormones as Markers

As we all know, the incidence of thyroid cancer has a very clear and obvious gender difference, which is easily reminiscent of the effects of sex-related hormones. However, the expression of estrogen receptors in thyroid tissue has many different and even some contradictory results. And because sex-related hormones, such as estradiol, are affected by numerous factors, they are not very sensitive and specific. Therefore, despite the fact that many studies have shown that there are multiple ERs in thyroid tissue,[30,31] and played an important role in the pathophysiology of thyroid cancer, but it may not be suitable as a diagnostic marker.

There is another important hormone that cannot be avoided in the occurrence and development of thyroid cancer, which is thyroid stimulating hormone (TSH). As the main growth factor of thyroid cells, TSH is a regulator of thyroid function, and its importance as a predictor of thyroid cancer risk has been widely recognized. At

present, TSH inhibition therapy is widely used in clinical patients after surgery to reduce thyroid cancer recurrence rate and improve patient survival.[3] Although there is some evidence that TSH levels in patients with thyroid cancer will increase, the cutoff is difficult to determine, so based on TSH alone cannot make diagnosis.[32] And about whether the TSH level rises in thyroid cancer patients before surgery is actually still controversial. In Huang's study, it was suggested that TSH levels showed opposite effects in different genders, and were also affected by various pathological subtypes of thyroid cancer.[33]

Tumor-Related Markers

As we all know, chronic inflammation is related to the occurrence of cancer, and calprotectin is involved in the occurrence and development of various inflammations. Tabur et al found that the concentration of calprotectin in the serum of PTC patients increased significantly, and then decreased significantly after total thyroidectomy, besides, the level was similar to that of healthy people. Therefore, perhaps an increase in calprotectin may be a potential marker for oxidative stress in thyroid cancer. But again, the increase in calprotectin can occur in many diseases, so its specificity is not satisfactory.[34] Besides, Argyris summarized some searches and found that only malignant thyroid cancer which has aggressive characteristics would has increased calprotectin level. In addition to anaplastic thyroid carcinoma, it has no significant role in non-neoplastic thyroid tissue and well-differentiated thyroid tumors.[35]

And as an important proinflammatory factor, platelets have also been studied as a biomarker. It will be rather convenient if the platelets could be the marker, since the test of it is such regular. However, the results are totally different and contradictory. The study by Baldane et al in 2015 included 98 people shows the mean platelet volume (MPV) is higher in PTC patients, and gave a cut-off value as 7.81fl.[36] Yu et al investigated 280 people in 2017 attained a complete opposite result with PTC patients have lower MPV and higher platelet distribution width (PDW).[37] While in Dincel's study there's no significant difference in MPV, but PDW is lower and plateletcrit is higher in PTC patients.[38]

For patients with tumor diseases, intact tumor cells and cell-free nucleic acids (cfDNA/cfRNA and circulating miRNA) can all appear in peripheral blood.[39] And given the tissue-specific expression pattern and stability of miRNAs, circulating miRNAs have become ideal biomarkers for many cancers. Among the most often mentioned and proven circulating substances in PTC patients are cf-DNA,[40,41] lnc-RNAs[42] and various miRNAs. Among them, levels of miR-146, miR-221, miR-222 and let-7 were higher than those of the healthy control group[43–48] and miR-222 and miR-146b can distinguish between PTC and benign nodules. What's more, high-mobility group box-1 has also been proposed to be a marker,[49] and as Mardente studied, its interact with RAGE enhances the level of miR221/222 that in turn inhibits tumor suppressor gene PTEN.[50]

Midkine is a pleiotropic growth factor that is significantly expressed during embryogenesis and regulates cell growth, survival, migration, angiogenesis, and anti-apoptotic activities, but usually has low expression levels in adulthood. Some studies have shown that midkine expression in PTC is strong, and it is related to the clinicopathological characteristics and metastasis of PTC.[51,52] Meng[53] and Li[54] have successively confirmed midkine's potential as a marker of thyroid cancer. Moreover, Meng et al used 323.12 pg/mL as the cutoff value to distinguish benign and malignant thyroid nodules and obtained its sensitivity, specificity, and diagnostic accuracy rates of 75.70%, 75.00%, and 75.31%, respectively. But in fact, it has increased in more than 20 tumor diseases, so it needs to be assisted by other means.

Interleukin (IL) is a small protein signal molecule mainly synthesized by T cells, monocytes, macrophages and endothelial cells. It plays an important role in promoting communication between immune system cells, regulating transcription factors, controlling inflammation, differentiation, proliferation, and secreting antibodies etc. Various interleukins have been widely recognized as diagnostic, prognostic indicators and treatment methods. In a validation test by Martins et al, the levels of IL-6, IL-8, and IL-10 were higher in patients with thyroid nodules than in healthy people, but they could not distinguish between benign and malignant nodules. In addition to the sensitivity of IL-2 reaching 98%, the others' sensitivity and specificity are not ideal.[55]

Matrix metalloproteinase (MMP) is a zinc-dependent endopeptidase, which has the function of digesting gelatin and a variety of collagens, and is involved in the development of many tumors. Shi et al affirmed its value as a diagnostic marker of thyroid cancer in their research. The serum MMP-2 concentration of PTC patients is greater than of healthy people, and its level can be reduced after surgery. In addition, it may also have significant effects in prognostic evaluation and treatment.[56] Zhang et al also

affirmed the role of MMP-2 in their research. At the same time, they also proposed that MMP-9 and TIMP-1, and TIMP-2 may have analogous effects, and the imbalance between MMP and TIMP may cause tumor progression.[57]

Vascular adhesion protein-1 (VAP-1) is an endothelial cell adhesion molecule that is involved in the process of leukocyte rolling, adhesion and transfer to inflammatory sites. Hu et al measured serum levels of VAP-1 in patients with thyroid cancer and benign thyroid adenomas, and found that serum VAP-1 levels in the thyroid cancer group were significantly lower than those in the healthy control group and the benign nodule group. And it negatively correlated with serum thyroglobulin concentration in patients with thyroid cancer. The optimal cutoff value of VAP-1 for diagnosis of thyroid cancer was 456.6ng/mL, with a specificity of 77.4% and a sensitivity of 66.7%.[58] Meanwhile, Baki's research in 2019 also confirmed its value as a potential marker.[59]

Galectin-3 is a protein that binds to β-galactosyl residues of cell surface glycoproteins. Many studies have shown that its expression levels are different in benign and malignant thyroid tissues.[60–62] The study of Saussez in 2008 showed that the level of Galectin-3 in the serum of patients with thyroid disease is higher than that of healthy people.[63] Yilmaz's research in 2015 affirmed the statistical value of the difference, but in view of the inadequacy of existing studies, it was considered that it can only be used as a method of auxiliary diagnosis.[64]

β-2 microglobulin is the light chain of human leukocyte antigen (HLA). Studies by Adil et al suggest that after excluding the deposition of β-2 microglobulin in the blood due to renal insufficiency, β-2 microglobulin elevated concentrations in serum can also be used as auxiliary diagnostic markers of thyroid cancer.[65]

CYFRA21-1 is a fragment of CK19, whose washout fluid shows great potential in diagnose the metastatic lymph nodes of DTC when combined with FNA.[66] Though its concentration in serum presents good value in diagnosing head and neck cancer, including oral, oropharyngeal, hypopharyngeal, and laryngeal cancers,[67] it do not perform well in discerning benign and malignant thyroid nodules. Early to 2008 and 2010, someone has claimed that its level has no manifested difference between benign and malignant thyroid nodules. But like Tg, it may help in predicting the prognosis.[68] Besides, the higher level of it may indicate the poorly differentiated and anaplastic thyroid carcinoma, and worse prognosis of DTC.

Discussion

As an important endocrine organ of the human body, the thyroid gland plays an important role in the growth and development of the human body and normal physiological activities, and involves in various physiological processes. Because of this, the mechanism of the occurrence and development of thyroid disease seems to be particularly complicated. The incidence of thyroid disease is increasing year by year, and the largest part of it is PTC. Although with the increasingly standardized treatment of thyroid cancer patients, the 5-year survival rate of patients with thyroid cancer has reached 99.4%,[1] but there are also questions about overdiagnosis and overtreatment. We have to admit that surgery is the cornerstone of not only DTC but almost all kinds of thyroid cancers. However, due to the inaccurate diagnosis, we may do some unnecessary surgeries, which also means some unnecessary risks, like the injury of parathyroid or recurrent laryngeal nerve, which may cannot be prevented.[69]

Given that the blood test and ultrasound have become the regular examinations when patients come to hospital for thyroid disease. This article summarizes potential markers in the blood of patients with PTC, hoping to find a marker that can sensitively and specifically diagnose PTC without adding another examination for patients.

We have listed plenty of biomarkers in categories, but as we can see, most of them are general markers for many cancers. And unfortunately, even the substances related to thyroid function, except calcitonin for medullary thyroid cancer, have not shown enough value in diagnosis, for their undefinite cut-off value. But the markers which have definite changes, like miR-221, miR-222 or midkine etc., between malignant and benign nodules may can help in confirming the existence of cancer, although they may not have satisfactory specificity. But combining different kinds of marker as a panel may have some help. Though the changes on metabolic profiles and circulatory system nucleic acids are rather complicated, but in my opinion, they do show a hopeful prospect compared to other markers. We may have some hope to find a substance in them that can balance sensitivity and specificity to help diagnose thyroid cancer in the future.

The biomarkers can discern the malignant nodules with benign ones can help us avoid the unnecessary surgeries. What's more, if they can predict the aggressiveness of the cancer, it may also help to decide the surgical method, for

the extent of lymph node clearance is controversy for years, especially about the preventive clearance. For some poorly differentiated cancer or ATC, some paper proposed the combined treatment might improve the survival, but is better in early stage.[70] So it is quite important to find a biomarker for ATC, like CYFRA21-1 and calprotectin might have the potential, in order to make the early diagnosis.

In summary, for more than 40 years, people have made many efforts in the search for thyroid cancer markers, but have not yet found a substance that can accurately diagnose PTC. Most of the substances above correspond to multiple diseases at the same time, thus cannot rely on a single one to diagnose thyroid cancer, but perhaps combined with several models can better distinguish patients with thyroid cancer.

Disclosure

The authors report no conflicts of interest in this work.

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