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# Current status and perspectives of TMIGD2-targeted therapy in thyroid cancer

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**Abstract:**

In recent studies, TMIGD2 has found that it may play an important role in a new therapeutic target in the process of accurate tumor treatment. High expression of TMIGD2 in HCC and glioma cancer can be used as a potential therapeutic target, and some studies showed that the expression level of TMIGD2 in thyroid cancer tissue is also higher than that in normal thyroid tissue, and its expression level is correlated with the malignancy and poor prognosis of tumors. These more cutting-edge findings suggest that TMIGD2 may be used as a potential target for the treatment of thyroid cancer for precise treatment. This article will introduce the current situation and development trend of TMIGD2 in the clinical precision treatment of thyroid cancer.

**Keywords:** HHLA 2, TMIGD2, thyroid cancer, therapeutic target

## 1 Introduction

The study data suggest that the overall 5-year survival rate of undifferentiated thyroid carcinoma is very low. Previous studies have found that TMIGD2 can benefit patients through the HHLA2 pathway in HCC, glioma cancer, and other tumors. The high expression of HHLA2 and TMIGD2 makes it possible to predict molecular markers for long-term prognosis. If TMIGD2 is used as a therapeutic target for thyroid cancer in precision medicine, it can expand the approach to targeted therapy, fill the gap in therapeutic targets for thyroid cancer, and is of great value in broadening therapeutic strategies and guiding the research and development of new drugs. With the study of immune mechanisms, HHLA2 will have great prospects in immunotherapy, and TMIGD2, as one of the recipients of HHLA2, will also be a potential therapeutic target in solid tumors. Currently, researchers are using TMIGD2 for the treatment of thyroid cancer and constantly advancing the research process. Current studies have focused on its relationship with biological behaviors such as tumor cell proliferation, invasion, and metastasis.

## 2 Current status of thyroid cancer treatment

The data suggest that the overall 5-year survival rate of undifferentiated thyroid cancer is only 7%. Previous studies have found that TMIGD2 can benefit patients through the HHLA2 pathway. Globally, with the development of medical technology, the diagnosis rate of thyroid cancer is increasing rapidly, and the mortality rate of undifferentiated thyroid cancer is also rising.

Although the approval of thyroid cancer drugs Vandertanib and anlotinib has made significant progress in targeted therapy, surgical treatment, especially endoscopic thyroid surgery (ETS), remains the main treatment method. Moreover, following the advent of HD cavity lenses and robot auxiliary systems, the clinical application of ETS is becoming increasingly extensive. However, this technique often causes compensatory sweating (excessive sweating in a large area or the entire body), serious irreversible side effects such as hypotension, arrhythmia, and intolerance to high temperatures. Therefore, it is particularly important to find suitable therapeutic targets for targeted therapy. As a treatment method that accurately targets cancer cells, targeted therapy has high efficiency, small side effects, and convenient drug administration. It points the way for the targeted treatment of thyroid cancer and can more accurately identify cancer treatment methods.

Malignant thyroid tumors, a serious and potentially life-threatening condition, are initially treated with a combination of surgery and radioiodine therapy. Recent advances in the understanding of thyroid carcinogenesis have aided in the development of new treatments and drugs, which is a significant step towards improving the quality of life for patients. Ultrasound-based risk stratification systems and therapies such as surgery, chemotherapy,

radiation, and radioiodine are considered standard treatments for malignant thyroid tumors. However, novel treatments, such as polytyrosine kinase inhibitors or immune checkpoint inhibitors used in conjunction with multi-kinase inhibitors (MKI), have shown promise in controlling the progression of differentiated thyroid cancer (DTC), medullary thyroid carcinoma, and anaplastic thyroid cancer (ATC). The combination therapy of mitogen-activated protein kinase and phosphoinositide 3-kinase inhibitors is highly recommended as a strategy to enhance treatment efficacy. Recent studies have pointed to targetable alternative pathways that could help overcome resistance to existing treatments. In recent years, targeted therapy and immunotherapy have made significant advancements in the treatment of ATC. Genetic mutations have been identified in ATC cells, involving different molecular pathways. New therapies acting on these pathways are currently being studied, with the aim of improving patients' quality of life. Recent clinical trials and meta-analyses have shown that new molecular targeting drugs have significant efficacy in thyroid cancer.

The discovery and confirmation of MIGD 2 as a potential therapeutic target is the first step in the development of new drugs, providing a more accurate treatment direction. This has the potential to enhance the efficiency of cancer treatment, save lives, and improve social well-being.

## 3 TMIGD2

TMIGD2 is a transmembrane protein, a member of the immunoglobulin superfamily. As a co-stimulating immune receptor, TMIGD2 participates in regulating the activation and function of T cells, is expressed in a variety of immune cells, and has the function of regulating the immune function of these cells.

TMIGD2 A recently discovered costimulatory immune receptor, aberrantly expressed on human AML cells, TMIGD2 plays an extremely important role in the development and maintenance of ALL, especially during the self-renewal and differentiation of LSCs. The expression of TMIGD2 is not associated with normal hematopoiesis, which means that precise targeted therapy of tumors with TMIGD2 may have little impact on normal cells, thus having high therapeutic safety and research value. In the face of the current situation of few studies in TMIGD2 rethyroid cancer, Information can be initially obtained by collecting data, Then immune tissue staining was used to verify that TMIGD2 protein was upregulated in infiltrating immune cells and tumor cells, Then, gene set enrichment analysis was used to verify the significantly enriched patient signal pathways with low TMIGD2 expression. Finally, the abundance of immune cell subsets was tested to verify that TMIGD2 expression was positively correlated with anti-tumor immune cell infiltration, And negatively associated with tumor-promoting immune cell subsets, The feasibility of TMIGD2 as the target treatment in thyroid cancer. TMIGD2 The therapeutic target of thyroid cancer can make up for the gap in the therapeutic target of thyroid cancer and expand new targeted therapeutic approaches, so as to find the best treatment method, promote the research and development of new drugs, and improve the survival rate of patients.

However, the current research on TMIGD2 targeted therapy is still in the laboratory stage and has not entered clinical trials. Nonetheless, these studies provide insight for TMIGD2 as a target for cancer treatment.

## 4 HHLA2

HHLA2 is a new type of immune checkpoint molecule found in recent years that can be used for precise treatment.HHLA2 binds to different receptors in different sites. HHLA 2 weakens the body's antitumor immune response by inhibiting the activation and proliferation of T cells, as well as by regulating the secretion of immune factors. Because of its expression in various tumor tissues, HHLA 2 is considered a potential target for tumor immunotherapy. In recent years, monoclonal antibodies (mAbs) against HHLA 2 and vaccines have been advanced in experimental studies, and some HHLA 2-based vaccines have also shown certain antitumor effects in animal models.

As a novel immune checkpoint molecule, HHLA 2 also has some potential in the field of thyroid cancer therapy. HHLA 2 expression was found to be high in thyroid cancer tissues and was associated with aggressive and poor prognosis in thyroid cancer. This suggests that HHLA2 has the potential to work with TMIGD2 in the treatment of thyroid cancer.

## 5 TMIGD2 in thyroid cancer

Regarding the potential of TMIGD2 as a therapeutic target in accurate cancer treatment, there is currently less research in thyroid cancer, It is often used only for the treatment target research of liver cancer, glioma, etc., and mainly focuses on its relationship with biological behaviors such as tumor cell proliferation, invasion and metastasis. By retrieving data from multiple databases, it was found that the expression level of TMIGD2 as a therapeutic target in thyroid cancer tissue is higher than that in normal thyroid tissue, and its expression level affects the malignancy of thyroid tumors and even reduces its adverse prognosis.

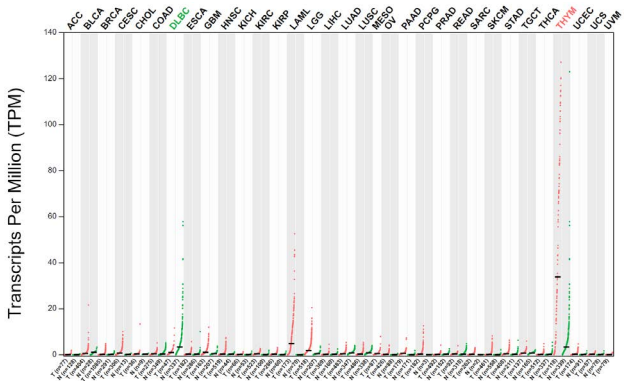


**FIGURE 1. Overview of gene expression of all tumor samples and paired normal tissues. ( Point chart) Each point represents the expression of the sample. It can be found that the expression level of thyroid cancer is abnormally elevated.**

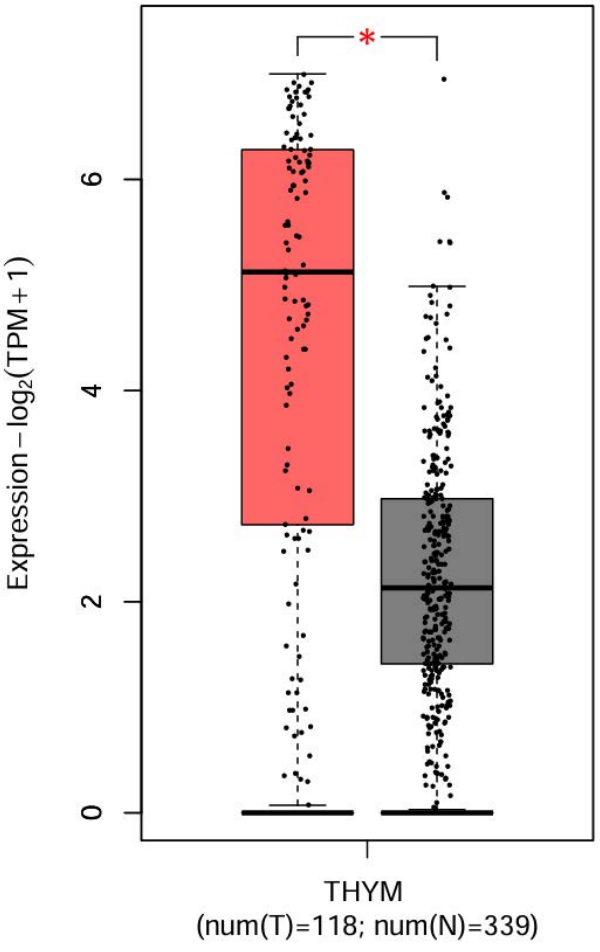


**FIGURE 2. The results show the expression level of TMIGD2 between thyroid tumors and normal samples based on The Cancer Genome Atlas (TCGA) database.**

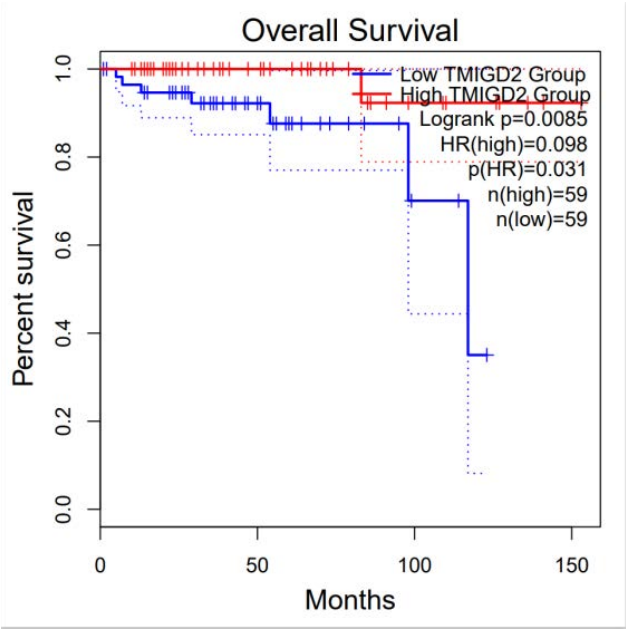


**FIGURE 3. According to the expression of TMIGD2 in the thyroid tumor microenvironment, the total survival rate of the GEPIA2 cohort.**

According to the database data and the performance of TMIGD2 in cancer treatment, it can be observed that TMIGD2 increases significantly in thyroid cancer and is significantly associated with the prognosis of thyroid cancer, potentially prolonging the survival time of patients.

TMIGD2 is aberrantly expressed in thyroid cancer tissue, whereas its expression is low in normal thyroid tissue. Due to its high selectivity, it has less impact on normal thyroid tissue, thereby reducing the potential side effects of compensatory sweating (large area or excessive sweating of the body), hypotension, and arrhythmia compared to traditional treatment. As an immune regulator, TMIGD2 participates in regulating the function of immune cells, enhancing the anti-tumor immune response. Monoclonal antibodies targeting TMIGD2 can significantly reduce the self-renewal capacity of thyroid cancer stem cells (CSCs) and reduce tumor burden in thyroid cancer patient-derived xenograft (PDX) models. This indicates a potential antitumor effect of targeting TMIGD2. By examining the expression of TMIGD2 in thyroid cancer, the risk of recurrence can be predicted, and therapeutic measures can be taken accordingly. Given the characteristics of TMIGD2 precision treatment, it can be tailored to the specific conditions of patients to achieve individualized treatment.

In the current application of TMIGD2 in the targeted treatment of thyroid cancer, the research primarily focuses on monoclonal antibody therapy, immunotherapy, CAR-T cell therapy, and so on. Monoclonal antibodies targeting TMIGD2 were developed to block the interaction between TMIGD2 and its receptors, relieving the inhibition of TMIGD2 on T cell function and enhancing the anti-tumor immune response. Combining monoclonal antibodies targeting TMIGD2 with other immunotherapies may produce a stronger anti-tumor immune response. Researchers found that the modification of T cells can enhance anti-tumor ability, so that T cells can express chimeric antigen receptors against TMIGD2 on the surface, and enable T cells to specifically identify and attack TMIGD2 positive thyroid cancer cells.

Although the research on the target treatment of TMIGD2 in thyroid cancer is still in the preliminary stage. However, the data indicated that the expression of TMIGD2 was high in thyroid cancer tissues was high and associated with aggressive and poor prognosis of thyroid cancer. These findings about differences in expression levels suggest that the precise treatment of TMIGD2 for thyroid cancer may help inhibit the growth and metastasis of tumors, provide certain insights for thyroid potential pathological mechanism and valuable indicators, help to further enrich the thyroid cancer treatment target, expand the treatment way, has important value to guide new drug development, and the discovery of TMIGD2 drug targets can avoid the irreversible side effects of traditional surgical treatment, help find the best treatment, thus get the best treatment to improve treatment effect, improve patient survival rate.

## 6 Summary

To clarify the expression characteristics of TMIGD2 in thyroid cancer, strengthen the understanding of the therapeutic targets of thyroid cancer, improve the targeted treatment methods of thyroid cancer, avoid accidental injury to normal cells and reduce side effects, and find that TMIGD2 may serve as a new target for the precise treatment of thyroid cancer. It not only provides guiding suggestions for the efficient and accurate treatment of thyroid cancer in the era of precision medicine, but also provides innovative opinions for the research and development of new drugs in the era of rapid technological development, so as to improve social happiness by improving the survival rate of cancer patients.

Based on the current TMIGD2 is often used for liver cancer, glioma, colorectal cancer and endometrial cancer treatment targets, can by immunohistochemical study of patients with thyroid cancer samples, by immunostain evaluation of TMIGD2 staining positive cells in thyroid tumor cells and immune cells, immune cell abundance identifier and gene set enrichment analysis, further study whether TMIGD2 as a therapeutic target of thyroid cancer.

However, it should be noted that although TMIGD2 may be therapeutical in thyroid cancer, more energy needs to be invested in the study of targeted precision treatment and clinical trials of thyroid cancer to prove its feasibility and safety. Moreover, targeted therapy may also develop resistance, therefore, long-term therapeutic effects also need to be further observed.

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