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Targeted therapy and immunotherapy in thyroid cancer

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Abstract. Thyroid cancer is among the most prevalent endocrine-related malignancies, with a significant rise in incidence observed in recent years. Based on the 2022 version of the thyroid cancer diagnosis and treatment guidelines, some treatment methods for thyroid cancer include surgery, radiotherapy, chemotherapy, immunotherapy, and molecular targeted therapy. Surgical intervention remains effective for most cases of well-differentiated thyroid cancer, and postoperative radioiodine therapy enhances overall survival in high-risk patients; however, surgical options for advanced thyroid cancer are limited, and radioactive iodine therapy is ineffective for iodine-refractory cases. Consequently, targeted therapy and immunotherapy present promising alternative treatment strategies. Both targeted therapy and immunotherapy are rooted in a comprehensive understanding of the molecular mechanisms underlying thyroid cancer, with recent developments focusing on inhibiting well-characterized oncogenic pathways such as the MAPK pathway, the PI3K/Akt-mTOR pathway, and VEGF signaling. Although much progress has been made in the molecular pathogenesis of thyroid cancer in recent years, effective treatments for advanced and metastatic iodine-resistant thyroid cancer are still lacking. This review aims to summarize the molecular mechanisms implicated in thyroid cancer, explore current drug-dependent therapeutic pathways, and discuss the latest advancements in targeted therapy and immunotherapy, while also outlining future directions for research and clinical application.

Keywords: Targeted therapy, Immunotherapy, Thyroid cancer, Molecular mechanism, Drug mechanism.

1. Introduction

In the past two decades, the incidence of thyroid cancer in China has increased annually, with the standardized incidence rising from 1.4 per 100,000 person-years in 1990 to 14.65 per 100,000 person-years in 2016, making it the seventh most common malignant tumor in the country [1]. This increase is particularly pronounced among women, whose incidence rankings rose from seventh to third place between the 2012 and 2016 national cancer epidemiology statistics. From 2000 to 2016, the incidence of thyroid cancer in women increased nearly tenfold, with women aged 15 to 45 being most susceptible. The incidence among women is three to four times higher than that among men. Current theories suggest that this heightened incidence may be linked to estrogen levels and reproductive factors, although the underlying mechanisms remain unclear. Estrogen's ability to promote the self-renewal of stem cells suggests it could play a role in tumor development, and the higher rates of thyroid dysfunction in women may also be attributed to sex differences in immune function.

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The global incidence of thyroid cancer has also risen sharply since 2000 [2]. According to the American Cancer Society, there were an estimated 44,280 new cases of thyroid cancer and 2,200 deaths in the United States in 2021. This surge in incidence is largely attributed to the overdiagnosis of differentiated thyroid cancer (DTC), while the rates of medullary thyroid carcinoma (MTC), follicular thyroid carcinoma (FTC), and undifferentiated thyroid carcinoma (ATC) have remained stable during the same period.

Thyroid cancer, originating from either follicular epithelial cells or parafollicular C cells, is among the most common endocrine malignancies. The classification of thyroid cancer derived from follicular cells encompasses four main histological types: papillary thyroid carcinoma (PTC), which constitutes 80-85% of cases; FTC, accounting for 10-15%; poorly differentiated thyroid carcinoma (PDTC), less than 2%; and ATC, also less than 2%. Among these, PTC and FTC are grouped together as well-differentiated thyroid carcinomas (WDTC) and represent the majority of cases [3, 4].

Among them, ATC is a very challenging one. ATC accounts for 1.7% of all thyroid cancer cases. ATC progresses rapidly, with distant metastases occurring in 75% of patients. ATC has a poor prognosis, accounting for 20-50% of all thyroid cancer deaths and a median survival of 3-6 months. ATC does not respond to current conventional treatment with radioactive iodine ablation and chemotherapy. It is recognized as one of the most aggressive malignancies, with a cancer-specific mortality rate of 98-99%, making it a leading cause of mortality related to thyroid cancer each year. Currently, there are no effective treatment options for ATC, and the urgent development of new therapies is critical.

Despite ATC being the most aggressive subtype of thyroid cancer, the majority of thyroid cancer-related deaths arise from the progression of radioiodine-resistant WDTC. For both types, surgical options are limited, particularly in cases of locally advanced thyroid cancer, which involves significant invasion of surrounding structures, inadequate surgical conditions, and poor prognostic outcomes. Iodine-resistant thyroid cancer is characterized by inherent resistance to iodine therapy, leading to a low five-year survival rate of 66% and only 10% at ten years. The low survival rates among patients with advanced thyroid cancer highlight the pressing need for effective treatment strategies, where targeted therapy and immunotherapy may provide viable clinical options for managing both ATC and WDTC [5, 6].

At present, surgical intervention is still the main treatment method for thyroid cancer, supplemented by endocrine therapy (TSH suppression), radionuclide therapy (RAI), radiotherapy, and targeted therapy. The current standard treatment of surgical resection and radioactive iodine ablation, which are mainstream, is also difficult to be effective. They fail in 10% of DTCS and all ATCs. The efficacy of multimodal treatment is also very limited. Recent advancements in understanding the molecular characteristics of thyroid cancer have significantly expanded the application of targeted therapies for advanced cancers. Currently in use are tyrosine kinase inhibitors, anti-angiogenic drugs, among others. Lately, several new medications targeting cell proliferation, angiogenesis, apoptosis, immunosuppression, metabolic reprogramming, and epigenetic modifications have been explored. Challenges associated with thyroid cancer include postoperative recurrence, tumor metastasis, and the prevalence of radioactive iodine-resistant DTC (RR-DTC) and ATC mutations. The possibilities of targeted therapy and immunotherapy require more research [7].

Recent years have seen major breakthroughs in understanding the potential carcinogenic molecular pathways associated with thyroid cancer, with the MAPK signaling pathway being one of the most extensively studied [8]. Additionally, inhibitors targeting the PI3K/Akt pathway have demonstrated promising antitumor activity in vitro and in vivo against thyroid cancer cells. Multikinase inhibitors (MKIs) have also been shown to exert antitumor effects in radioiodine-refractory metastatic thyroid cancer primarily through their antiangiogenic properties [9].

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2. Targeted therapy

2.1. Targeted therapy for the MAPK pathway

The MAPK pathway includes the RAS-RAF-MAPK kinase (MEK) -Extracellular signal-associated kinase (ERK) pathway [10]. RAF kinase is a major mediator of the MAPK pathway and is responsible for the continuous activation of downstream targets such as MEK and transcription factor ERK. They control many cellular and physiological processes, including biological development, cell cycle control, cell proliferation and differentiation, and cell survival and death. This pathway is associated with the development of cancer.

Thyroid cancers frequently exhibit genetic alterations that activate the MAPK pathway, including mutations in BRAF, RAS, and RET/PTC translocations [11]. The potential of these mutations as therapeutic targets for advanced thyroid cancer has been thoroughly investigated. Vemurafenib and dabrafenib, which are inhibitors of BRAFV600E, function as competitive ATP inhibitors. Notably, vemurafenib exhibits greater selectivity for mutant BRAF compared to wild-type BRAF. Clinical studies have indicated that vemurafenib exhibits antitumor effects in patients with progressive BRAFV600E-positive, radioactive iodine-refractory thyroid cancer, particularly those who have not previously been treated with multiple kinase inhibitors [12].

2.2. Targeted therapy for the PI3K/Akt pathway

Abnormal activation of PI3K/AKT/mTOR pathway plays a big part in carcinogenesis. The PI3K/Akt pathway plays a crucial role in thyroid cancer, affecting cell dedifferentiation, invasion, and metastasis. This pathway primarily consists of PI3K, Akt, and mTOR. In advanced differentiated thyroid cancer, especially in follicular thyroid cancer and ATC, mutations and copy number gains in the gene encoding the catalytic subunit of PI3K (PIK3CA) have been observed. Additionally, inactivating mutations and hypermethylation of the tumor suppressor gene PTEN have been identified.

These genetic and epigenetic alterations contribute to angiogenesis, drug resistance, and the progression and metastasis of thyroid cancer. Targeting the PI3K/Akt/mTOR pathway has become a significant focus of cancer research, with several inhibitors demonstrating promising antitumor activity in vitro and in vivo. Clinical studies have shown that everolimus exhibits moderate antitumor activity and can stabilize the disease; however, trials have not established a correlation between tumor mutation status and drug response in patients with advanced thyroid cancer [13].

2.3. Anti-angiogenic TKIs

The most widely used anti-angiogenic drugs include monoclonal antibodies and tyrosine kinase inhibitors (TKI) that target the vascular endothelial growth factor (VEGF) pathway [14]. However, the clinical benefits of this approach remain limited due to a number of shortcomings such as adverse events, acquired resistance, tumor recurrence, and lack of proven biomarkers, prompting further research into tumor angiogenesis mechanisms, multi-drug development, and combination therapies to figure out how to improve treatment effectiveness. Sorafenib is a multikinase inhibitor that targets VEGFR1-3, RET, FLT3, c-Kit, BRAF, and BRAFV600E. Studies assessing the efficacy of sorafenib in advanced thyroid cancer have shown that patients with radioactive iodine-refractory thyroid cancer treated with sorafenib experience significant improvements in progression-free survival (PFS) [15]. Sorafenib was approved by the FDA in 2013 for the treatment of locally recurrent or metastatic, progressive differentiated, iodine-refractory thyroid cancer. However, serious adverse events were reported in 37% of patients in the sorafenib treatment group. Lenvatinib, another multikinase inhibitor targeting VEGFR1-3, FGFR, PDGFR, RET, and KIT, received FDA approval in 2013 for the treatment of advanced, progressive differentiated, iodine-resistant thyroid cancer [16, 17]

3. Immunotherapy

The interaction between the tumor microenvironment (TME) and cancer cells plays a crucial role in cancer progression. Recent discoveries regarding the mechanisms by which cancer cells evade immune

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surveillance have positioned the immune system as a promising therapeutic target in oncology. In thyroid cancer, the TME comprises cancer-associated fibroblasts (CAFs) and various immune cells, which can be categorized as tumor-associated myeloid cells (TAMC) or lymphocytes (TALC). TAMC includes macrophages (tumor-associated macrophages, TAM), myeloid-derived suppressor cells (MDSC), neutrophils (TAN), and dendritic cells (TADC), while TALC encompasses T cells and natural killer (NK) cells. Genomic analyses reveal that ATC exhibits a higher level of immune infiltration in the TME compared to DTC and PDTC, particularly characterized by type 2 TAM and dysfunctional or depleted T and NK cells. Additionally, ATC demonstrates elevated expression of PD-L1 relative to other TC subtypes. Given this altered immune profile, ATC tumors may benefit from immune checkpoint inhibitor (ICI) therapy, adoptive T and NK cell therapies, and strategies targeting the TAM population [18, 19].

Immunoscore, a method for assessing cancer patient prognosis based on the presence of immune cells infiltrating the tumor, has shown a significant negative correlation between thyroid differentiation scores and immunosuppressive markers. Increased PD-L1 expression is noted in several solid tumors and is associated with poor prognosis. Tumor cells expressing PD-L1 inhibit T cell activation within the TME, thus protecting tumor cells from immune responses. Analysis of the prognostic potential of PD-L1 in 185 PTCs and 66 benign nodules revealed that elevated PD-L1 expression in thyroid cancer correlates with a higher risk of recurrence and shorter disease-free survival (DFS). These findings indicate that targeting PD-L1 could represent an effective treatment strategy for advanced thyroid cancer. Clinical trials with the PD-1 antibody pembrolizumab have demonstrated that targeting PD-1 is a viable treatment approach for advanced thyroid cancer.

Moreover, preclinical models of ATC indicate that the combination of PLX4720 (a BRAFV600E inhibitor) with anti-PD-L1/PD-1 antibodies reduce tumor growth while increasing the presence of CD8+ cytotoxic T cells, FoxP3+ regulatory T cells (Tregs), and NK cells in the tumor. This suggests an induction of an immunosuppressive TME. Collectively, these findings propose that combination therapy using BRAFV600E inhibitors and anti-PD-1/PD-L1 antibodies is a promising treatment strategy for metastatic thyroid cancer.

MTC is a rare malignancy, and the treatment of metastatic MTC poses significant challenges. CD276 is a common target across various cancers, and studies have identified it as a potential immunotherapy target in MTC. Notably, CD276 expression in MTC cells is three times higher than in normal tissues. Targeting this immune checkpoint molecule may offer a promising strategy for treating MTC.

Interdisciplinary research is also focusing on the diagnosis and management of TC, with nanoscience presenting potential benefits for patients with drug-resistant forms of TC. For instance, nanodelivery systems have been developed to deliver siRNA that inhibits BRAF expression, significantly reducing tumor growth and metastasis in in situ ATC mouse models. Rajendran et al. demonstrated the use of extracellular vesicles (EVs) to deliver TKIs to restore iodine sensitivity in radioiodine-resistant TC cells. These studies underscore the need to clarify whether advanced nanoplatforms that enable targeted delivery of MKIs, non-coding RNAs, or mRNAs for precise tumor site release can help reduce adverse effects and enhance drug efficacy [20].

4. Conclusion

mRNA cancer vaccines represent a significant advancement in personalized cancer immunotherapy. This review summarizes the molecular pathogenesis of thyroid cancer and the current landscape of targeted therapy and immunotherapy. The treatment of advanced and metastatic iodine-resistant thyroid cancer remains a significant challenge, with only four drugs currently approved for differentiated thyroid cancer and MTC. Key unmet needs are emerging in scientific discussions, including issues of resistance, off-target effects that may diminish efficacy, and the potential for combination therapies informed by molecular insights. We aim to explore contemporary molecular prospects and therapeutic strategies for thyroid cancer, highlighting ongoing clinical and translational research focused on novel drugs and combinations that enhance inhibition of driver mutations such as BRAF and RET.

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Additionally, we consider how systemic therapies, including immunotherapy and peptide receptor radionuclide therapy, may contribute to the future management of advanced thyroid cancer.

Significant advancements in understanding the molecular pathogenesis of thyroid cancer have led to notable improvements in treating aggressive tumors. Preclinical and clinical research on targeted therapies and immunotherapies has demonstrated substantial clinical benefits, providing new avenues for treating advanced patients who are unsuitable for surgical resection and resistant to iodine therapy. Continued research is essential to refine these treatment strategies and improve outcomes for patients with advanced and metastatic thyroid cancer.

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